ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 48, Number 4
July | August
2022

Volume 48, Number 4 July | August 2022

HIGHLIGHT

SBPT consensus on sleep-disordered breathing

Use of anticoagulants in patients with COVID-19

Incidental chest findings on coronary CT (angiography)

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

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 4, July/August 2022

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Expediente

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

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
Circulation: 4.000 copies
Distribution: Free to members of the BTS and libraries
Printed on acid-free paper

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. 4, July/August 2022

Contents

ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 4, July/August 2022

Contents

J Bras Pneumol. 2022;48(4):e20220220
https://dx.doi.org/10.36416/1806-3756/e20220220

Traction bronchiectasis: is it as benign as we think?

Amina Bekki[1], Thais Beauperthuy[1], Miguel Ángel Martínez-García[1,2]

Recently, a group of experts from around the world defined bronchiectasis as a dilation of the airway lumen mainly produced by the destruction of the bronchial wall, secondary to the action of various proteolytic substances from local inflammation—usually neutrophilic inflammation,[1] although sometimes also eosinophilic inflammation,[2-4] and even with a systemic component[5,6]—and/or secondary bacterial products (usually as a chronic infection).[7-9] Furthermore, this radiological finding must be accompanied by symptoms related to it, especially productive cough (usually with a purulent component), with or without exacerbations.[10-12] Therefore, the definition of bronchiectasis must meet not only radiological criteria but also clinical criteria.[1,13] As a consequence, traction bronchiectasis (TBE) has been systematically excluded from diagnostic, prognostic, and therapeutic studies of bronchiectasis because it is not usually associated with a secondary clinical picture of airway inflammation or infection.[14]

It is true that TBE is usually due to dilation of the bronchial lumen caused by the destruction of the surrounding lung parenchyma. TBE is not usually accompanied by bronchial wall thickening related to excessive bronchial inflammation, and the probability of chronic infection with potentially pathogenic microorganisms is low. TBE is frequently observed in the context of advanced fibrotic processes secondary to interstitial diseases, after extensive infections or pulmonary emphysema, and, in general, after processes involving destruction of the lung parenchyma.[15]

In recent years, the presence of TBE has generated some particularly interesting questions about its ability to influence the prognosis of the underlying disease. Is TBE really as benign as we think? Could the presence of TBE influence the prognosis of patients, regardless of the usually associated interstitial pattern? Should the progression of TBE be monitored when it appears? Although the name bronchiectasis is still used for etymological reasons (*bronkos* = bronchus and *ectasis* = dilation), there is still no answer to these questions, since TBE has been systematically excluded, as mentioned above, from bronchiectasis studies of all types.

Recently, however, a study[16] involving 5,295 individuals with COPD (mean age = 59 years) seems to have indicated that the presence of TBE is not trivial at all and that TBE is capable of negatively impacting various important outcomes of COPD. In that study, Hata et al.[16] identified a subgroup of patients (n = 582) presenting interstitial abnormalities on CT scans. Those with associated TBE (n = 105) showed an adjusted linear correlation between greater radiological severity of TBE and poorer quality of life. Moreover, the patients with TBE presented an adjusted risk of death 3.8 times higher (95% CI: 2.6-5.6; $p < 0.001$) than did those without it.

These findings on the relationship between the presence of TBE and a poorer prognosis for the underlying disease are not new, having previously been described for various interstitial lung diseases such as idiopathic pulmonary fibrosis,[17] hypersensitivity pneumonitis,[18] and chronic eosinophilic pneumonia.[19] It is also a noteworthy fact that TBE has been shown to progress in most patients, resulting in a progressively worsening prognosis and greater severity of the underlying disease. The presence of TBE could therefore serve as a marker of the severity of interstitial diseases of any origin, which suggests—as it is already known—that early, intensified anti-inflammatory treatment during the inflammatory phase of the underlying disease is essential, before it progresses to an interstitial lesion and, consequently, to TBE. In fact, some authors have suggested the use of a TBE index[16,20] whose validity is distinguished by, among other things, excellent interobserver agreement for the diagnosis of TBE by chest CT (kappa index around 0.75). The TBE index classifies patients into four groups, according to the presence and type of TBE found in the interstitial process: type 1: no TBE; type 2: presence of bronchiolectasis; type 3: moderate TBE; and type 4: severe TBE. This classification system was used in the study by Hata et al,[16], as well as in another population-based study conducted in Iceland.[20] In the latter study, CT scanning was performed at baseline and 5 years after the inclusion of 3,167 participants in the study, 327 of whom had some type of interstitial alteration. The authors observed not only that TBE progressed in most individuals over time, but also that this progression was associated with an increased probability of death (hazard ratio = 1.68; 95% CI: 1.21-2.34; $p < 0.001$), adjusted for age, sex, BMI, and smoking habit after 11.5-14.0 years of follow-up.

All of these findings open up a timely topic of great relevance related to sequelae in the lung parenchyma of patients who have had SARS-CoV-2-related pneumonia. Various follow-up studies based on CT data have shown that a high proportion of such patients have suffered from chronic interstitial damage (especially after having severe pneumonia), often associated with TBE.[21,22] Will TBE even further worsen the prognosis or clinical severity in patients with interstitial alterations, in comparison with those without TBE? The answer to this question is still unknown, but it should certainly be a subject for research because an early aggressive treatment during

1. Departamento de Neumología. Hospital Universitario y Politécnico La Fe, Valencia, España.
2. Centro de Investigación Biomédica En Red de Enfermedades Respiratorias – CIBERES – Instituto de Salud Carlos III, Madrid, España.

the inflammatory phase of the disease would probably be the best option to prevent interstitial sequelae and the subsequent appearance of TBE. Moreover, it is also unknown whether, in addition to TBE, clinically active bronchiectasis might result in chronic infection with pathogenic microorganisms as a consequence of a vicious circle of excessive inflammation/infection over time. This situation cannot be ruled out since it is known that one of the most common etiologies of symptomatic bronchiectasis is after an infection, including viral infections.

In short, the supposed benignity attributed to TBE as part of an interstitial process within different underlying lung diseases (including both interstitial and non-interstitial disorders) does not seem to be confirmed in the literature. The presence of TBE could in fact worsen the prognosis and the clinical severity of the underlying disease responsible for it, over and above the prognosis resulting from the interstitial alteration itself. Another very important question remains to be clarified, which has already been generating a field of research of great interest: what will be the future impact of bronchiectasis associated with interstitial patterns in patients who have overcome COVID-19 pneumonia? There is still no answer to this question, but the data available so far indicate that a long-term follow-up period is required for such patients; if necessary, imaging techniques and even clinical monitoring should be used, including microbiological data, wherever possible.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Aliberti S, Goeminne PC, O'Donnell AE, Aksamit TR, Al-Jahdali H, Barker AF, et al. Criteria and definitions for the radiological and clinical diagnosis of bronchiectasis in adults for use in clinical trials: international consensus recommendations. Lancet Respir Med. 2022;10(3):298-306. https://doi.org/10.1016/S2213-2600(21)00277-0
2. Martínez-García MÁ. Bronchiectasis and Eosinophils. Arch Bronconeumol. 2021;57(11):671-672. https://doi.org/10.1016/j.arbres.2021.08.001
3. Shoemark A, Shteinberg M, De Soyza A, Haworth CS, Richardson H, Gao Y, et al. Characterization of Eosinophilic Bronchiectasis: A European Multicohort Study. Am J Respir Crit Care Med. 2022;205(8):894-902. https://doi.org/10.1164/rccm.202108-1889OC
4. Martinez-Garcia MA, Posadas T, Sotgiu G, Blasi F, Saderi L, Aliberti S. Repeteability of Circulating Eosinophil Measures and Inhaled Corticosteroids Effect in Bronchiectasis. A Post Hoc Analysis of a Randomized Clinical Trial. Arch Bronconeumol (Engl Ed). 2020;56(10):681-683. https://doi.org/10.1016/j.arbr.2020.06.003
5. Saleh AD, Chalmers JD, De Soyza A, Fardon TC, Koustas SO, Scott J, et al. The heterogeneity of systemic inflammation in bronchiectasis. Respir Med. 2017;127:33-39. https://doi.org/10.1016/j.rmed.2017.04.009
6. Posadas T, Oscullo G, Zaldivar E, Villa C, Dobarganes Y, Girón R, et al. C-Reactive Protein Concentration in Steady-State Bronchiectasis: Prognostic Value of Future Severe Exacerbations. Data From the Spanish Registry of Bronchiectasis (RIBRON). Arch Bronconeumol (Engl Ed). 2021;57(1):21-27. https://doi.org/10.1016/j.arbr.2019.12.022
7. de la Rosa Carrillo D, López-Campos JL, Alcázar Navarrete B, Calle Rubio M, Cantón Moreno R, García-Rivero JL, et al. Consensus Document on the Diagnosis and Treatment of Chronic Bronchial Infection in Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (Engl Ed). 2020;56(10):651-664. https://doi.org/10.1016/j.arbr.2020.08.006
8. Figueiredo MR, Lomonaco I, Araújo AS, Lundgren F, Pereira EDB. Isolation of and risk factors for airway infection with Pseudomonas aeruginosa in patients with non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2021;47(3):e20210017. https://doi.org/10.36416/1806-3756/e20210017
9. Monsó E. Look at the wood and not at the tree: The Microbiome in Chronic Obstructive Lung Disease and Cystic Fibrosis. Arch Bronconeumol (Engl Ed). 2020;56(1):5-6. https://doi.org/10.1016/j.arbr.2019.04.014
10. Martinez-García MA, Villa C, Dobarganes Y, Girón R, Maíz L, García-Clemente M, et al. RIBRON: The spanish Online Bronchiectasis Registry. Characterization of the First 1912 Patients. Arch Bronconeumol (Engl Ed). 2021;57(1):28-35. https://doi.org/10.1016/j.arbr.2020.11.010
11. Amati F, Simonetta E, Gramegna A, Tarsia P, Contarini M, Blasi F, et al. The biology of pulmonary exacerbations in bronchiectasis. Eur Respir Rev. 2019 Nov 20;28(154):190055. https://doi.org/10.1183/16000617.0055-2019
12. Chen CL, Huang Y, Yuan JJ, Li HM, Han XR, Martinez-Garcia MA, et al. The Roles of Bacteria and Viruses in Bronchiectasis Exacerbation: A Prospective Study. Arch Bronconeumol (Engl Ed). 2020;56(10):621-629. https://doi.org/10.1016/j.arbr.2019.12.014
13. Nucci MCNM, Fernandes FLA, Salge JM, Stelmach R, Cukier A, Athanazio R. Characterization of the severity of dyspnea in patients with bronchiectasis: correlation with clinical, functional, and tomographic aspects. J Bras Pneumol. 2020;46(5):e20190162. https://doi.org/10.36416/1806-3756/e20190162
14. Crichton ML, Aliberti S, Chalmers JD. A systematic review of pharmacotherapeutic clinical trial end-points for bronchiectasis in adults. Eur Respir Rev. 2019;28(151):180108. https://doi.org/10.1183/16000617.0108-2018
15. Piciucchi S, Tomassetti S, Ravaglia C, Gurioli C, Gurioli C, Dubini A, et al. From "traction bronchiectasis" to honeycombing in idiopathic pulmonary fibrosis: A spectrum of bronchiolar remodeling also in radiology?. BMC Pulm Med. 2016;16(1):87. https://doi.org/10.1186/s12890-016-0245-x
16. Hata A, Hino T, Putman RK, Yanagawa M, Hida T, Menon AA. Traction Bronchiectasis/Bronchiolectasis on CT Scans in Relationship to Clinical Outcomes and Mortality: The COPDGene Study [published online ahead of print, 2022 May 31]. Radiology. 2022;212584. https://doi.org/10.1148/radiol.212584
17. Desai SR, Wells AU, Rubens MB, du Bois RM, Hansell DM. Traction bronchiectasis in cryptogenic fibrosing alveolitis: associated computed tomographic features and physiological significance. Eur Radiol. 2003;13(8):1801-1808. https://doi.org/10.1007/s00330-002-1779-2
18. Jacob J, Bartholmai BJ, Egashira R, Brun AL, Rajagopalan S, Karwoski R, et al. Chronic hypersensitivity pneumonitis: identification of key prognostic determinants using automated CT analysis. BMC Pulm Med. 2017;17(1):81. https://doi.org/10.1186/s12890-017-0418-2
19. Takei R, Arita M, Kumagai S, Ito Y, Takaiwa T, Tokioka F, et al. Traction bronchiectasis on high-resolution computed tomography may predict fatal acute eosinophilic pneumonia. Respir Investig. 2019;57(1):67-72. https://doi.org/10.1016/j.resinv.2018.09.005
20. Hino T, Hida T, Nishino M, Lu J, Putman RK, Gudmundsson EF, et al. Progression of traction bronchiectasis/bronchiolectasis in interstitial lung abnormalities is associated with increased all-cause mortality: Age Gene/Environment Susceptibility-Reykjavik Study. Eur J Radiol Open. 2021;8:100334. https://doi.org/10.1016/j.ejro.2021.100334
21. Martinez-Garcia MA, Aksamit TR, Aliberti S. Bronchiectasis as a Long-Term Consequence of SARS-COVID-19 Pneumonia: Future Studies are Needed. Arch Bronconeumol. 2021;57(12):739-740. https://doi.org/10.1016/j.arbres.2021.04.021
22. Ding X, Xu J, Zhou J, Long Q. Chest CT findings of COVID-19 pneumonia by duration of symptoms. Eur J Radiol. 2020;127:109009. https://doi.org/10.1016/j.ejrad.2020.109009

PET/CT and interstitial lung disease

Marcio Valente Yamada Sawamura[1], Ronaldo Adib Kairalla[2], Carlos Alberto Buchpigel[1]

The combination of PET with CT enabled the acquisition of functional anatomical images with high resolution. PET/CT requires the administration of a radiotracer, ^{18}F-FDG being the most commonly used nowadays. ^{18}F-FDG is a glucose analog capable of demonstrating metabolic activity in organs and lesions on PET/CT. The major clinical application of ^{18}F-FDG PET/CT is in oncology, especially in tumor detection, staging, and diagnosis of residual or recurrent cancer, but it can also be used in order to evaluate cardiovascular diseases, brain disorders, and systemic diseases, such as inflammatory, vascular, and infectious diseases.[1,2]

In the present issue of the *Jornal Brasileiro de Pneumologia*, Bastos et al.[3] investigated the correlation of ^{18}F-FDG PET/CT with HRCT and inflammatory serological markers in patients with systemic sclerosis-associated interstitial lung disease (ILD) in a cross-sectional study involving 23 patients. Although the authors were unable to demonstrate significant differences in metabolic activity between inflammatory and fibrotic areas in the lungs of these patients, they shed a light on the use of PET/CT in ILD. In their study, both ground-glass opacities (GGO) and honeycomb areas on HRCT had a remarkable metabolic activity on ^{18}F-FDG PET/CT.[3] GGO is a challenging finding on HRCT, because it can represent partial filling of airspaces, interstitial thickening (due to fluid, cells, and/or fibrosis), partial collapse of alveoli, increased capillary blood volume, or a combination of these.[4] In the context of ILDs, one of the big questions regarding imaging is whether GGO represents inflammatory (and potential reversible) changes or early interstitial fibrosis; this could be valuable information for the management of these patients. One interesting result is that Bastos et al.[3] found a correlation between GGO on HRCT and serum levels of CCL2, an inflammatory mediator, known to stimulate inflammation and collagen production, which results in fibroblast proliferation and fibrosis. This finding corroborates the fact that GGO may indicate early fibrotic activity in such cases. The drawbacks of the data obtained from Bastos et al.[3] are that all patients had advanced ILD and the majority (17 out of 23) were being treated with prednisone, azathioprine, or methotrexate, which could influence cytokine levels and ^{18}F-FDG uptake on PET/CT.

The results of Bastos et al.[3] agree with those of other authors that investigated the use of ^{18}F-FDG PET/CT in idiopathic pulmonary fibrosis (IPF),[5] in the differentiation of IPF from a non-IPF IPD,[6] and in other ILDs.[7] As suggested by these studies,[5-7] ^{18}F-FDG PET/CT could not differentiate inflammatory and fibrotic changes in lung parenchyma but may have a role in the prognosis and follow-up of these patients. In sarcoidosis, several studies demonstrated the usefulness of ^{18}F-FDG PET/CT in staging, evaluating disease activity, and monitoring treatment response.[8]

Currently, specific biomarkers for PET/CT are increasingly being developed. One of them, ^{68}gallium-fibroblast activation protein inhibitor (^{68}Ga-FAPI) binds to fibroblast activation protein alpha, which is present in active fibroblasts but is negligible or absent in resting fibroblasts.[9] Although ^{68}Ga-FAPI is still in an initial research phase, this radiotracer might be a promising imaging agent for the evaluation of ILD progression and treatment response on PET/CT.

REFERENCES

1. Jones T, Townsend D. History and future technical innovation in positron emission tomography. J Med Imaging (Bellingham). 2017;4(1):011013. https://doi.org/10.1117/1.JMI.4.1.011013
2. Townsend DW. Combined positron emission tomography-computed tomography: the historical perspective. Semin Ultrasound CT MR. 2008;29(4):232-235. https://doi.org/10.1053/j.sult.2008.05.006
3. Bastos AL, Ferreira GA, Mamede M, Mancuzo EV, Teixeira MM, Santos FPST, et al. PET/CT and inflammatory mediators in systemic sclerosis-associated interstitial lung disease. J Bras Pneumol. 2022;48(4):e20210329.
4. Hochhegger B, Marchiori E, Rodrigues R, Mançano A, Jasinowodolinski D, Chate RC, et al. Consensus statement on thoracic radiology terminology in Portuguese used in Brazil and in Portugal [published correction appears in J Bras Pneumol. 2022 Jan 10;47(6):e20200595errata]. J Bras Pneumol. 2021;47(5):e20200595. https://doi.org/10.36416/1806-3756/e20200587
5. Meissner HH, Soo Hoo GW, Khonsary SA, Mandelkern M, Brown CV, Santiago SM. Idiopathic pulmonary fibrosis: evaluation with positron emission tomography. Respiration. 2006;73(2):197-202. https://doi.org/10.1159/000088062
6. Nusair S, Rubinstein R, Freedman NM, Amir G, Bogot NR, Izhar U, et al. Positron emission tomography in interstitial lung disease. Respirology. 2007;12(6):843-847. https://doi.org/10.1111/j.1440-1843.2007.01143.x
7. Nabashi T, Kubo T, Nakamoto Y, Handa T, Koyasu S, Ishimori T, et al. 18F-FDG Uptake in Less Affected Lung Field Provides Prognostic Stratification in Patients with Interstitial Lung Disease. J Nucl Med. 2016;57(12):1899-1904. https://doi.org/10.2967/jnumed.116.174946
8. Treglia G, Annunziata S, Sobic-Saranovic D, Bertagna F, Caldarella C, Giovanella L. The role of 18F-FDG-PET and PET/CT in patients with sarcoidosis: an updated evidence-based review. Acad Radiol. 2014;21(5):675-684. https://doi.org/10.1016/j.acra.2014.01.008
9. Bergmann C, Distler JHW, Treutlein C, Tascilar K, Müller AT, Atzinger A, et al. 68Ga-FAPI-04 PET-CT for molecular assessment of fibroblast activation and risk evaluation in systemic sclerosis-associated interstitial lung disease: a single-centre, pilot study. Lancet Rheumat. 2021;3(3):E185-E194. https://doi.org/10.1016/S2665-9913(20)30421-5

1. Departamento de Radiologia e Oncologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Divisão de Pneumologia, Instituto do Coração, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

J Bras Pneumol. 2022;48(4):e20220300
https://dx.doi.org/10.36416/1806-3756/e20220300

EDITORIAL

Hospital physiotherapy practice in times of COVID-19—lessons to advance

Caio C A Morais[1,2], Shirley L Campos[1], Armèle Dornelas de Andrade[1]

Cardiorespiratory and intensive care physiotherapy are well-established hospital specialties that have two major aims: 1) preventing and mitigating adverse effects related to prolonged bed rest; and 2) maintaining and improving respiratory function. As an emerging specialty, recommendations for respiratory and physical interventions for hospitalized patients have been continuously developed following the growth of scientific evidence.[1,2]

Recently, the waves of COVID-19 infection and the increase in the number of hospitalized patients with severe disease have challenged physiotherapists worldwide. As a result, specialized societies have released recommendations to guide physiotherapists.[3,4] However, as of now, we are unaware of how physiotherapists have provided care to hospitalized patients with COVID-19.

In the current issue of the *Jornal Brasileiro de Pneumologia*, Dias et al.[5] described data regarding the referral and physiotherapy practice for patients with COVID-19 admitted to both the ICU and the ward for the first time. The study has many provocative results and reflections on post-pandemic professional practice.

During five months in 2021, the investigators collected data using a 50-item self-administered survey, obtaining 485 completed questionnaires (completion rate of 76%). The respondents represented all regions in Brazil, mostly from the southeast (61%) and the northeast (21%). Most respondents (80%) had some sort of a specialization degree in in-hospital physiotherapy. However, only 13% were board-certified specialists by the Brazilian Federal Council of Physical Therapy and Occupational Therapy.

The authors found that the main reason for indication of physiotherapy in the ICU and in the ward was oxygenation improvement (> 80%), whereas avoidance of physical deconditioning was the least common reason (< 65%) for both mechanically ventilated patients and spontaneously breathing patients. The indication of mobilization for COVID-19 patients was remarkably lower when compared with that in a previous prospective study,[6] which showed that approximately 90% of critically ill patients treated in Brazilian ICUs received mobilization therapy. The severity of respiratory symptoms in patients with COVID-19 might partially explain the lower number of indications for mobilization in order to prioritize respiratory assistance.

Another possible barrier to mobilization noted in the study by Dias et al.[5] was the limited staff, because physiotherapists treated a median of 10 patients in a six-hour shift. Although this number follows the minimum number recommended by the current Brazilian national legislation,[7] we believe that delivering complete respiratory and mobilization treatment with this professional-to-patient ratio is difficult.

As Dias et al.[5] stated, caring for 10 patients in a 6-h shift means that the physiotherapist had approximately only 30 minutes per patient. Therefore, the limited time of care may potentially affect the patient's therapeutic plan. The priority of treatments associated with the maintenance of life (e.g., respiratory support) is insufficient for improving survival and functionality, which encompass passive mobilization, strength training of upper and lower limbs, transferring the patient to a chair, walking, and functional activities.

Indeed, a survey from members of the Acute Care Section of the American Physical Therapy Association reported that insufficient staffing and training were the main barrier to providing ICU rehabilitation.[8] Moreover, there is evidence demonstrating that the number of patients per physiotherapist is an independent predictor of out-of-bed exercising,[6] and that a greater availability of physiotherapists (12 h/day vs. 24 h/day) may reduce the length of ICU stay and ICU costs.[9]

Another striking result in the study by Dias et al.[5] was that the choice of respiratory interventions largely varied when compared with mobilization therapies. Even though important advances have been made in respiratory care, the rate of adherence to respiratory treatment considered effective was low. For instance, only 25% of the physiotherapists reported using "expiratory flow bias", a well-studied intervention for secretion removal in patients on mechanical ventilation.[10-12] This fact may indicate that having a specialization degree did not prevent the underutilization of effective techniques.

This thought-provoking study[5] revealed that physiotherapists on the front line in caring for patients with COVID-19 will most likely remain in the care of critically ill patients in the ICU and in the ward in Brazil. The need to standardize respiratory physiotherapy treatment and to revise work conditions is urged. Furthermore, physiotherapists should receive more stimuli to becoming board-certified specialists. Finally, professional associations, health managers, universities, and research institutions should discuss these results and take the next steps to dial in the evidence to improve patient treatment and outcomes.

1. Departamento de Fisioterapia, Universidade Federal de Pernambuco, Recife (PE) Brasil.
2. Laboratório de Investigação Médica em Pneumologia (LIM 09), Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ISSN 1806-3756

REFERENCES

1. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med. 2008;34(7):1188-1199. https://doi.org/10.1007/s00134-008-1026-7
2. França EÉ, Ferrari F, Fernandes P, Cavalcanti R, Duarte A, Martinez BP, et al. Physical therapy in critically ill adult patients: recommendations from the Brazilian Association of Intensive Care Medicine Department of Physical Therapy. Rev Bras Ter Intensiva. 2012;24(1):6-22. https://doi.org/10.1590/S0103-507X2012000100003
3. Felten-Barentsz KM, van Oorsouw R, Klooster E, Koenders N, Driehuis F, Hulzebos EHJ, et al. Recommendations for Hospital-Based Physical Therapists Managing Patients With COVID-19. Phys Ther. 2020;100(9):1444-1457. https://doi.org/10.1093/ptj/pzaa114
4. Musumeci MM, Martinez BP, Nogueira IC, Alcanfor T. Physiotherapy techniques used in the intensive care unit for the assessment and treatment of respiratory problems in patients with COVID-19. Assobrafir Ciencia. 2020;11(1):73-86. https://doi.org/10.47066/2177-9333.AC20.covid19.007
5. Dias LMS, Guimaraes FS, Leite CF, Paro FM, Annoni R, Oliveira ACO, et al. Physiotherapy practice for hospitalized patients with COVID-19. J Bras Pneumol. 2022;48(4):e20220121.
6. Timenetsky KT, Neto AS, Assunção MSC, Taniguchi L, Eid RAC, Corrêa TD, et al. Mobilization practices in the ICU: A nationwide 1-day point- prevalence study in Brazil. PLoS One. 2020;15(4):e0230971. https://doi.org/10.1371/journal.pone.0230971
7. Brazil. Ministry of Health. National Health Surveillance Agency. Resolution-RDC No. 7, of February 24, 2010. Diário Oficial da União No. 37 of February 25, 2010.
8. Malone D, Ridgeway K, Nordon-Craft A, Moss P, Schenkman M, Moss M. Physical Therapist Practice in the Intensive Care Unit: Results of a National Survey. Phys Ther. 2015;95(10):1335-1344. https://doi.org/10.2522/ptj.20140417
9. Rotta BP, Silva JMD, Fu C, Goulardins JB, Pires-Neto RC, Tanaka C. Relationship between availability of physiotherapy services and ICU costs. J Bras Pneumol. 2018;44(3):184-189. https://doi.org/10.1590/s1806-37562017000000196
10. Volpe MS, Adams AB, Amato MB, Marini JJ. Ventilation patterns influence airway secretion movement. Respir Care. 2008;53(10):1287-1294.
11. Li Bassi G, Saucedo L, Marti JD, Rigol M, Esperatti M, Luque N, et al. Effects of duty cycle and positive end-expiratory pressure on mucus clearance during mechanical ventilation. Crit Care Med. 2012;40(3):895-902. https://doi.org/10.1097/CCM.0b013e318236efb5
12. Volpe MS, Guimarães FS, Morais CC. Airway Clearance Techniques for Mechanically Ventilated Patients: Insights for Optimization. Respir Care. 2020;65(8):1174-1188. https://doi.org/10.4187/respcare.07904

Diffuse thickening of the tracheal wall, with calcifications

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

Male patient, 58 years old, complaining of dyspnea on exertion accompanied by irritative cough. He received a diagnosis of bronchial asthma 14 years before, denied any symptoms during childhood, and was using bronchodilators and inhaled corticosteroids, with little improvement. A chest computed tomography (CT) showed diffuse thickening of the tracheal wall with small foci of parietal calcification (Figure 1).

Diffuse thickening of the tracheal wall can be determined by several diseases (amyloidosis; relapsing polychondritis; tracheobronchopathia osteochondroplastica (TO); infections such as tuberculosis, paracoccidioidomycosis, and rhinoscleroma; granulomatosis with polyangiitis; sarcoidosis, and lymphomas, among others). Some imaging features can help narrow the differential diagnosis, such as the presence of calcifications in the tracheal wall, and define whether the entire circumference of the trachea is affected or if the lesion preserves the posterior membranous wall, affecting only the cartilaginous portion. In the case presented herein, the CT scan shows that the parietal thickening involves the entire tracheal circumference, with small foci of calcification.

Tracheal wall calcifications can be seen under normal conditions, being related to senility. However, calcifications associated with parietal thickening can be found in amyloidosis, TO, and relapsing polychondritis. TO is a disease of unknown etiology characterized by the formation of small submucosal nodules, which are usually calcified, protruding into the tracheal lumen. This disease is restricted to the tracheobronchial tree. Affected individuals may be asymptomatic or present with cough, dyspnea, wheezing, or, eventually, hemoptysis. Relapsing polychondritis is characterized by recurrent episodes of inflammation in cartilaginous tissue, including the cartilage of the ears, nose, peripheral joints, and the cartilage of the tracheobronchial tree. In amyloidosis, the involvement of the tracheal wall is circumferential and also includes the posterior membranous wall, as observed in the patient analyzed herein.[1,2]

Amyloidosis is characterized by the deposition, either local or systemic, of abnormal amyloid material in extracellular tissue, which may involve multiple organs, including the heart, kidneys, and gastrointestinal tract, among others. Primary respiratory amyloidosis has three characteristic forms: nodular, diffuse parenchymal, and tracheobronchial, the latter being the most common. Tracheobronchial involvement by amyloidosis can determine parietal thickening, luminal narrowing, and consequent airway obstruction, in addition to consolidations, atelectasis, air trapping, and bronchiectasis. Patients are generally asymptomatic but may present with hemoptysis, stridor, cough, hoarseness, dyspnea or wheezing, and recurrent pneumonia.[1,2] Based on these tomographic findings, the diagnosis of amyloidosis was suspected and was confirmed by anatomopathological analysis.

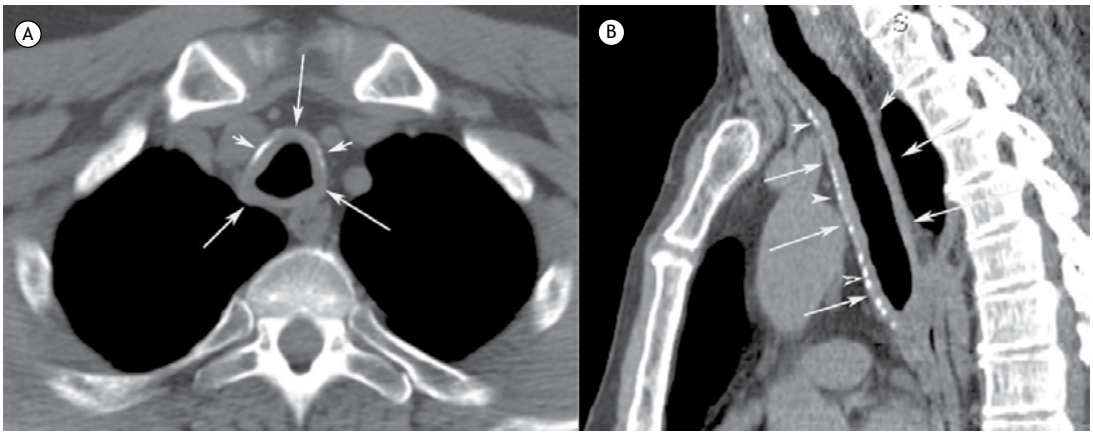


Figure 1. Axial CT (A) and sagittal reconstruction (B) showing concentric thickening of the trachea wall (arrows), with small foci of calcification (arrowheads). Note that the posterior wall (membranous) is also thickened.

REFERENCES

1. Torres PPTES, Rabahi M, Pinto SA, Curado KCMA, Rabahi MF. Primary tracheobronchial amyloidosis. Radiol Bras. 2017;50(4):267-8. https://doi.org/10.1590/0100-3984.2015.0177.
2. de Almeida RR, Zanetti G, Pereira E Silva JL, Neto CA, Gomes AC, Meirelles GS, et al. Respiratory Tract Amyloidosis. State-of-the-Art Review with a Focus on Pulmonary Involvement. Lung. 2015;193(6):875-883. https://doi.org/10.1007/s00408-015-9791-x.

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.

ISSN 1806-3756

Intercurrent events in clinical research: the norm, not the exception

L. Paloma Rojas-Saunero[1,2], Cecilia María Patino[1,3], Juliana Carvalho Ferreira[1,4]

PRACTICAL SCENARIO

A pulmonary and critical care team designed a randomized controlled clinical trial (RCT) to evaluate the efficacy and safety of a new drug vs. standard of care on reducing the number of hospitalizations due to COPD exacerbations within one year among adult patients. Both interventions (new drug and standard of care) required daily inhaler use throughout the follow-up period; therefore, daily adherence was monitored. Importantly, researchers anticipated a nonpreventable problem related to longitudinal studies: participants could die due to common comorbidities, which constitutes an intercurrent event.

INTERCURRENT EVENTS

In RCTs, intercurrent events are defined as events that occur after treatment initiation and either affect the ability to measure the intervention of interest or prevent the occurrence of an outcome over follow-up (Figure 1). Adverse events that lead to study arm crossover or discontinuation of the assigned treatment are considered intercurrent events, because they prevent the continuation of the assigned intervention. Since these events impact the interpretation of study results, we must consider them when defining the research question, study design, and analysis.

COMPETING EVENTS—WHEN THE OUTCOME CANNOT OCCUR

Competing events are a particular type of intercurrent events; they prevent the study outcome from occurring.[1] In our example, participants who died due to other reasons and prior to a hospitalization due to a COPD exacerbation could no longer experience the study outcome. Consequently, death determines that the risk of a COPD exacerbation-related hospitalization for these participants is zero. Therefore, when calculating the measure of effect, such as risk difference or risk ratio between the two study arms, we must be careful when interpreting the results, because part of the effect of the new intervention when compared with the existing one may be explained by how and/or if the intervention affected the competing event.

CENSORING EVENTS—WHEN THE OUTCOME CANNOT BE MEASURED

Competing events can also be defined as a censoring event in some settings. Censoring events are those that may prevent investigators from measuring the outcome, as opposed to preventing it from happening. For example, when participants move to another geographical area and follow-up is interrupted, investigators cannot determine whether those participants were hospitalized, died for other reasons, or remained outcome-free. Censoring

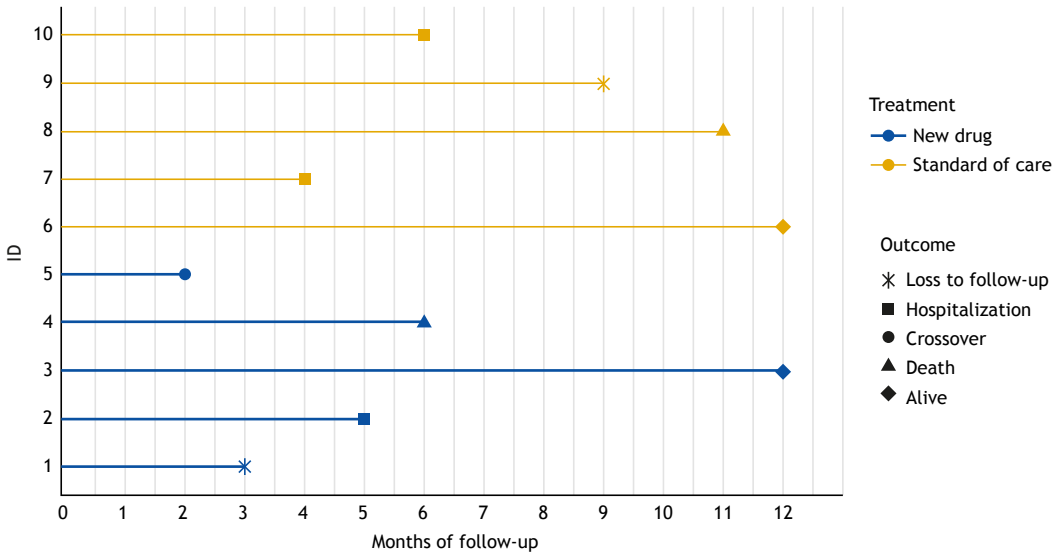


Figure 1. Illustration of different intercurrent events that may happen over follow-up in a controlled trial (or in an observational study). Each identification (ID) represents the path followed by a different participant.

1. Methods in Epidemiologic, Clinical, and Operations Research–MECOR–program, American Thoracic Society/Asociación Latinoamericana del Tórax, Montevideo, Uruguay.
2. Department of Epidemiology, University of California Los Angeles, Los Angeles (CA) USA.
3. Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles (CA) USA.
4. Divisão de Pneumologia, Instituto do Coração, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

relies on the assumption that participants who were lost to follow up (censored) share similar measured and unmeasured demographic and clinical characteristics with those who remained in the study. This assumption is called the "independent censoring assumption", and it requires extensive expertise on the topic of interest to evoke it.[1]

In our example, defining death due to other causes as a censoring event would require that we conceptualized this event as preventable by study design (just as loss to follow-up) and assumed that those who died are demographically and clinically comparable to those who remained in the study. Similarly, having a lung transplant could be considered a competing event, because lung transplant patients no longer have COPD and thus cannot be hospitalized for COPD exacerbations. However, treating lung transplant as a censoring event could be reasonable in some settings.[2]

Careful consideration of the impact of intercurrent events on study results is necessary when designing analytical approaches in order to provide accurate and reliable results to inform patient care and health policies.

KEY POINTS

- Identify all potential intercurrent events that can occur over follow-up when designing RCTs or longitudinal observational studies
- Clear definitions of intercurrent events help
  - refine research questions
  - identify data that need to be collected longitudinally to account for intercurrent events
  - facilitate result interpretation and implications
- Report frequency (absolute and relative numbers) of intercurrent events across the variable
- Consult with an expert when conducting longitudinal studies with competing events

REFERENCES

1. Geskus RB. Data Analysis with Competing Risks and Intermediate States. 1st ed. Boca Raton (FL): Chapman & Hall/CRC Biostatistics Series; 2016.
2. van Geloven N, le Cessie S, Dekker FW, Putter H. Transplant as a competing risk in the analysis of dialysis patients. Nephrol Dial Transplant. 2017;32(suppl_2):ii53-ii59. https://doi.org/10.1093/ndt/gfx012

Managing breathlessness in end-stage COPD: a neural respiratory drive approach

Neeraj M Shah[1,2], Nicholas Hart[1,2], Georgios Kaltsakas[1,2]

BACKGROUND

Management options for patients with COPD with persistent breathlessness can range from non-pharmacological, to pharmacological, to mechanical interventions. This case discusses a patient with severe COPD who was referred for lung transplantation; however, he was eventually managed with daytime non-invasive ventilation (NIV).

CASE HISTORY

A 47-year-old gentleman with severe bullous emphysema (FEV_1: 0.48 L; 11% of predicted; FVC: 1.71 L; 32% of predicted) was referred by his respiratory team for consideration for lung transplantation. He had a smoking history of 30 pack-years including heavy cannabis use in the past. He had suffered from four exacerbations requiring hospitalisation in the past twelve months. He was alpha-1 antitrypsin negative. He also suffered from osteoporosis and chronic hip pain. He had experienced pathological rib fractures secondary to coughing. At the time of referral he was using inhaled long-acting β_2-agonist+corticosteroid, an inhaled long-acting muscarinic antagonist, amitriptyline, regular morphine and breakthrough morphine for breathlessness. He used nocturnal NIV. Baseline arterial blood gas analysis revealed pH = 7.38; PaO_2 = 9 kPa; $PaCO_2$ = 7.1 kPa; and HCO_3^- = 31 mmol/L. He had severely impaired mobility and is a nursing home resident at this writing. The transplant team felt that, considering his poor nutritional state, deconditioning and lack of social support, he was unlikely to have a positive outcome after lung transplantation. He was referred by the transplant team to the regional ventilation centre for consideration of high-flow nasal cannula (HFNC) therapy for management of breathlessness. He underwent a clinical respiratory physiology assessment.

CLINICAL RESPIRATORY PHYSIOLOGY ASSESSMENT

The patient was seen in our ventilation centre for consideration of HFNC therapy. He underwent a full respiratory physiology assessment including measurement of spirometry, respiratory muscle strength and parasternal electromyogram, a surrogate biomarker of neural respiratory drive.[1] The neural respiratory drive index (NRDI) is the product of the neural respiratory drive and the respiratory rate. In this patient, NRDI was increased at baseline (normal value: 74 [46-144] %breaths/min).[2] He was assessed during quiet breathing, and then initiated on HFNC at 20 L/min. This was increased to 60 L/min in increments of 10 L/min. He was then assessed on NIV. The patient's parasternal electromyogram was recorded throughout this titration, and he was asked to score his dyspnoea using the modified Borg Dyspnoea Scale. Breath-by-breath analysis of the parasternal electromyogram was performed. ANOVA followed by Tukey's post hoc test demonstrated that NRDI significantly decreased at each HFNC flow except at 20 L/min. NRDI was significantly reduced on NIV compared with any HFNC flow (Figure 1). Interestingly, the modified Borg Dyspnoea Scale score was 1 at baseline and at each HFNC flow, but 0 with the use of NIV.

DISCUSSION

In patients with end-stage COPD, in whom lung transplantation is not a viable option, the clinical priority is

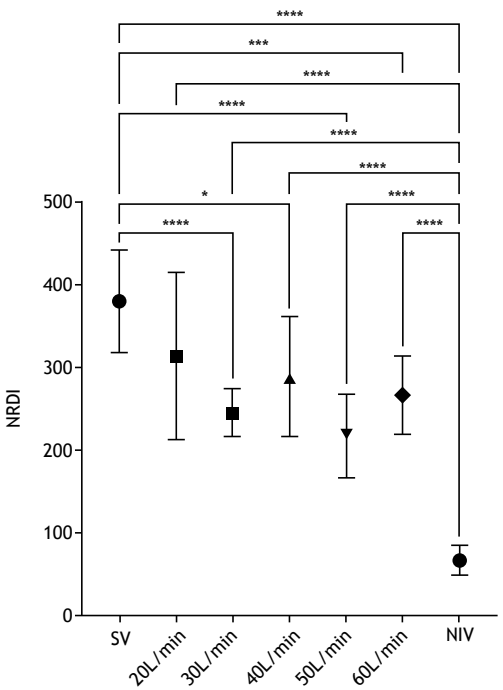


Figure 1. Neural respiratory drive index (NRDI) displayed during spontaneous ventilation (SV), at increasing flows of high flow nasal cannula (from 20 L/min to 60 L/min) and during non-invasive ventilation (NIV). For each setting, breath-by-breath data from one minute of stable parasternal electromyogram is displayed, as mean ± SD. *p < 0.05; ***p < 0.001; ****p < 0.0001.

1. Lane Fox Clinical Respiratory Physiology Centre, Guy's and St Thomas' NHS Foundation Trust, London, United Kingdom.
2. Centre for Human and Applied Physiological Sciences–CHAPS–King's College London, London, United Kingdom.

to manage breathlessness and prevent hospitalisations. Patients often remain breathless despite opiate use. HFNC, an increasingly available intervention, has been recommended for treatment of breathlessness, but the evidence to support this in end-stage hypercapnic COPD patients is limited.[3] Increased neural respiratory drive has been associated with an increased perception of breathlessness,[4] and so interventions that lower neural respiratory drive may be useful in treating breathlessness. Parasternal electromyogram is a useful, non-invasive biomarker of neural respiratory drive.[1] Despite increasing flows on HFNC, NRDI did not change. On daytime NIV, his NRDI decreased considerably, and this was associated with a decrease in subjective breathlessness. Although HFNC has many potential applications in both hypoxic and hypercapnic respiratory failure, in this case, it failed to improve NRDI, suggesting that it does not have an impact on offloading the respiratory muscles. In contrast, NIV has been demonstrated to offload respiratory muscles; thus, reducing the work of breathing.[5] This is the likely explanation for the improvement in breathing after initiation of NIV in this patient.

CLINICAL MESSAGE

Assessment of neural respiratory drive can be a useful tool in clinical practice. Non-pharmacological interventions in combination with standard pharmacological therapy may decrease neural respiratory drive and improve symptoms in patients with end-stage chronic respiratory disease. Clinicians should consider using daytime NIV and HFNC in patients with refractory breathlessness, utilizing their positive impact on neural respiratory drive at rest.

AUTHOR CONTRIBUTIONS

Each author contributed equally to study conception, study design, data collection, data analysis, data synthesis and writing of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Murphy PB, Kumar A, Reilly C, Jolley C, Walterspacher S, Fedele F, et al. Neural respiratory drive as a physiological biomarker to monitor change during acute exacerbations of COPD. Thorax. 2011;66(7):602-608. https://doi.org/10.1136/thx.2010.151332
2. MacBean V, Hughes C, Nicol G, Reilly CC, Rafferty GF. Measurement of neural respiratory drive via parasternal intercostal electromyography in healthy adult subjects. Physiol Meas. 2016;37(11):2050-2063. https://doi.org/10.1088/0967-3334/37/11/2050
3. D'Cruz RF, Hart N, Kaltsakas G. High-flow therapy: physiological effects and clinical applications. Breathe (Sheff). 2020;16(4):200224. https://doi.org/10.1183/20734735.0224-2020
4. Jolley CJ, Luo YM, Steier J, Rafferty GF, Polkey MI, Moxham J. Neural respiratory drive and breathlessness in COPD. Eur Respir J. 2015;45(2):355-364. https://doi.org/10.1183/09031936.00063014
5. Khilnani GC, Banga A. Noninvasive ventilation in patients with chronic obstructive airway disease. Int J Chron Obstruct Pulmon Dis. 2008;3(3):351-357. https://doi.org/10.2147/copd.s946

J Bras Pneumol. 2022;48(4):e20220103
https://dx.doi.org/10.36416/1806-3756/e20220103

EBUS-TBNA versus mediastinoscopy for mediastinal staging of lung cancer: a cost-minimization analysis

João Pedro Steinhauser Motta[1], José Roberto Lapa e Silva[1], Amir Szklo[1], Ricardo E. Steffen[2]

1. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. Instituto de Medicina Social, Universidade Estadual do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

Submitted: 25 March 2022.
Accepted: 21 June 2022.

Study carried out at the Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

ABSTRACT

Objective: To assess cost differences between EBUS-TBNA and mediastinoscopy for mediastinal staging of non-small cell lung cancer (NSCLC). **Methods:** This was an economic evaluation study with a cost-minimization analysis. We used a decision analysis software program to construct a decision tree model to compare the downstream costs of mediastinoscopy, EBUS-TBNA without surgical confirmation of negative results, and EBUS-TBNA with surgical confirmation of negative results for the mediastinal staging of NSCLC. The study was conducted from the perspective of the Brazilian public health care system. Only direct medical costs were considered. Results are shown in Brazilian currency (Real; R$) and in International Dollars (I$). **Results:** For the base-case analysis, initial evaluation with EBUS-TBNA without surgical confirmation of negative results was found to be the least costly strategy (R$1,254/I$2,961) in comparison with mediastinoscopy (R$3,255/I$7,688) and EBUS-TBNA with surgical confirmation of negative results (R$3,688/I$8,711). The sensitivity analyses also showed that EBUS-TBNA without surgical confirmation of negative results was the least costly strategy. Mediastinoscopy would become the least costly strategy if the costs for hospital supplies for EBUS-TBNA increased by more than 300%. EBUS-TBNA with surgical confirmation of negative results, in comparison with mediastinoscopy, will be less costly if the prevalence of mediastinal lymph node metastasis is ≥ 38%. **Conclusions:** This study has demonstrated that EBUS-TBNA is the least costly strategy for invasive mediastinal staging of NSCLC in the Brazilian public health care system.

Keywords: Lung Neoplasms; Neoplasm Staging; Costs and cost analysis; Bronchoscopy; Mediastinoscopy.

INTRODUCTION

Lung cancer is a major health problem, being the second most frequent cause of cancer in the world population and the leading cause of cancer mortality, accounting for about 1,800,000 (or 18% of) annual deaths from malignant neoplasms worldwide.[1] Mediastinal staging has a major role in the definition of the therapeutic strategy in early-stage, locally-advanced non-small cell lung cancer (NSCLC), since upfront surgery is the mainstay of treatment in stages I and II, and induction or definitive chemotherapy and radiochemotherapy are indicated in the treatment of stage III tumors.[2] Although chest CT and PET-CT are the most commonly used noninvasive mediastinal staging modalities of the mediastinum, they cannot always reliably differentiate between benign and malignant mediastinal nodes, because enlarged or PET-CT-positive lymph nodes may also be inflammatory, whereas normal-sized or PET-CT-negative lymph nodes may be malignant. Current guidelines recommend invasive staging in patients with clinical N1 to N3 disease, centrally located tumors, or those larger than 3 cm.[3,4] Mediastinoscopy and video-assisted mediastinoscopy have been considered the gold standard technique for invasive mediastinal staging of lung cancer for a long time. However, the emergence of EBUS-TBNA,[1] a minimally invasive procedure capable of providing valuable information for primary tumor diagnosis and mediastinal staging,[2-4] significantly changed the approach to staging lung cancer, becoming the method of choice for invasive mediastinal evaluation of lung cancer in developed countries.[5-10] In fact, two recent systematic reviews and meta-analyses of randomized controlled trials and observational studies comparing EBUS with mediastinoscopy/video-assisted mediastinoscopy suggested that the two procedures for mediastinal staging of lung cancer are equivalent, with a lower complication rate favoring the endosonographic approach.[11,12]

As a new method being incorporated by different health care systems, the use of EBUS may lead to

Correspondence to:
João Pedro Steinhauser Motta. Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rua Prof. Rodolpho Paulo Rocco, 255, Sala 01D 58/60, Cidade Universitária, CEP 21941-913, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 3938-2887. E-mail: joaosteinhauser@gmail.com

Financial support: This study received financial support from the *Programa de Excelência Acadêmica da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (PROEX/CAPES, Academic Excellence Program of the Office for the Advancement of Higher Education, grant n. 061/2018), the Fundação de Amparo à Pesquisa do Estado do Rio de Janeiro* (FAPERJ, Foundation for the Support of Research in the State of Rio de Janeiro; CNE/FAPERJ E_26/202.866/2018 and E_26/201-061/2022), and the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Finance code 001)

a shift in clinical outcomes and costs. Our group, in a recent systematic review,[13] compared the economic evaluation regarding the use of EBUS vs. mediastinoscopy for mediastinal staging of lung cancer and found that the costs of strategies using EBUS-TBNA were lower than those using mediastinoscopy. Two of the best quality scored studies demonstrated that the mediastinoscopy strategy is less cost-effective than the EBUS-TBNA strategy.[14,15] We found no studies from Latin America or Africa that fulfilled the inclusion criteria in that systematic review,[13] reinforcing the importance of conducting economic evaluation studies in these settings, especially because of the unfavorable economic conditions and the differentiated prevalence of infectious diseases, such as tuberculosis, which can alter mediastinal findings in patients with suspected lung cancer.[7,16] In Brazil, the most populous country in Latin America, lung cancer is also the main cause of cancer mortality.[17] The EBUS-TBNA technique, although used in referral centers for the diagnosis of lung cancer, has not been incorporated in the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System), hindering access to the procedure. This economic evaluation aims to assess cost differences between EBUS-TBNA and mediastinoscopy for mediastinal staging of lung cancer from the perspective of the Brazilian public health care system, that is, the SUS.

METHODS

A cost-minimization analysis model was built. We chose this model since the effectiveness of EBUS-TBNA and mediastinoscopy for mediastinal staging of lung cancer, based on the results of systematic reviews and meta-analyses comparing both techniques, is similar.[11,12] Additionally, the long-term outcomes (measures of effectiveness) of all patients with stage III disease are similar regardless of how invasive the mediastinal staging technique is. Decision analysis software (TreeAge Pro 2020; TreeAge Software, Williamstown, MA, USA) was used in order to construct a decision tree model to compare the downstream costs of mediastinoscopy, EBUS-TBNA without surgical confirmation of negative results, and EBUS-TBNA with surgical confirmation of negative results for the mediastinal staging of NSCLC (Figure 1).

Patient model

The model comprised of a hypothetical population with a diagnosis or diagnostic suspicion of NSCLC after chest CT and/or PET-CT and indication for invasive mediastinal lymph node investigation according to the American College of Chest Physicians guidelines for staging NSCLC.[3]

Assumptions

The model is based on the following assumptions:

1. Patients referred for EBUS or mediastinoscopy are clinically similar.
2. All patients have clinical conditions to undergo surgical resection.
3. Patients with N2/N3 mediastinal disease identified by EBUS or mediastinoscopy will undergo multimodal treatment.
4. Patients without N2/N3 mediastinal disease will undergo surgical resection (consider lobectomy and lymphadenectomy as optimal procedures).
5. The specificity of invasive methods (EBUS and mediastinoscopy) is 100%.

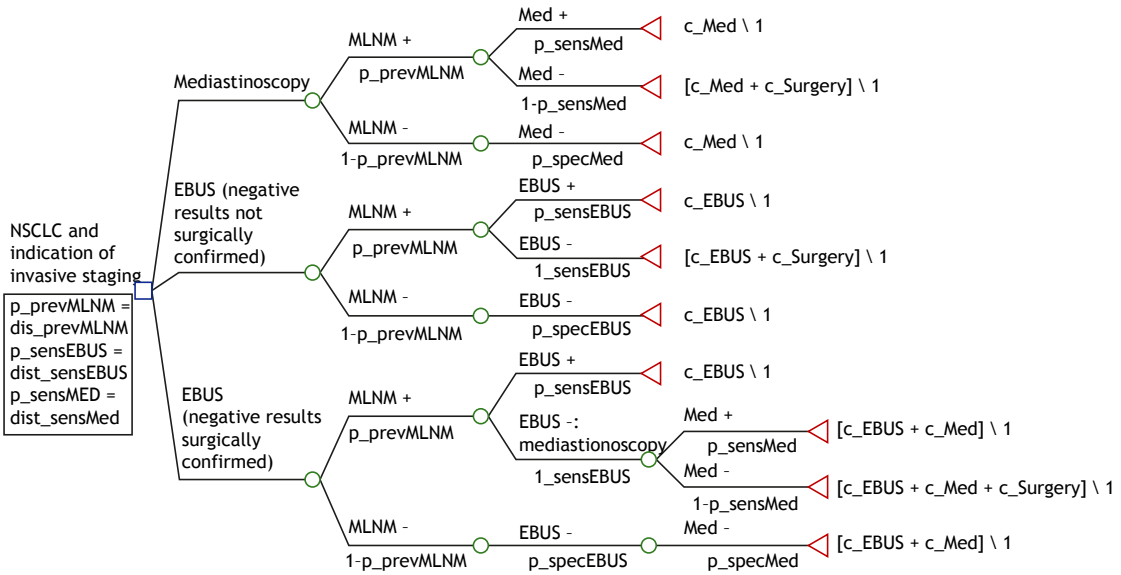


Figure 1. Decision tree model: EBUS-TBNA vs. mediastinoscopy (Med) for mediastinal staging of non-small cell lung cancer (NSCLC). p_prev: prevalence of; MLNM: mediastinal lymph node metastasis; dist_prev: distribution of prevalence (probabilistic sensitivity analysis);+: positive result; −: negative result, p_prev: prevalence of; p_sens: sensitivity; dist_sens: distribution of sensitivity; +: positive result; −: negative result; p_spec: specificity; and c_: total costs; and dist_prev: distribution of prevalence (probabilistic sensitivity analysis).

6. The sensitivity and specificity of thoracotomy and lymph node dissection for the detection of N2/3 metastases are 100%.
7. Pathology costs are identical regardless of the method of acquisition of tissue.
8. The sensitivity and specificity of EBUS are the same whether performed under moderate sedation or general anesthesia.
9. The sensitivity and specificity of EBUS are the same whether performed in the bronchoscopy suite or in the operating room.

Baseline costs

The study was conducted from the perspective of the SUS. Only direct medical costs were considered. The results are shown in Brazilian currency, that is, Real (R$), and in International Dollars (I$). The conversion to I$ was made using the purchasing power parity (PPP) conversion factor of the World Bank (https://data.worldbank.org/). PPP is a spatial price deflator and currency converter that controls for price level differences between countries, thereby allowing volume comparisons of gross domestic product and its expenditure components. The PPP calculated for Brazil in 2020 was 2.362. Since there are no costing estimates for the EBUS-TBNA procedure in the SUS, a micro-costing analysis was conducted, taking as an example four SUS-affiliated referral hospitals associated with the Brazilian public health care network where EBUS-TBNA and/or mediastinoscopy were available (*Hospital Universitário Clementino Fraga Filho*, *Hospital Universitário Pedro Ernesto*, *Hospital Universitário Antonio Pedro*, and *Instituto Nacional do Câncer*, all located in the state of Rio de Janeiro). The first step of the micro-costing analysis was to create an Excel spreadsheet to collect information related to EBUS-TBNA and mediastinoscopy procedures on hospital admission regime, procedure location (bronchoscopy suite or operating room), participating health professionals, type of anesthesia, permanent equipment used, hospital supplies, and medications. This spreadsheet was submitted to and completed by pulmonologists (bronchoscopists) and thoracic surgeons from the four hospitals listed above. Based on the information obtained from the professionals of the four hospitals, a cost survey was carried out in the SUS online systems for values related to daily hospital stays and hospital supplies. Brazilian federal government staff costs were used to calculate the hour value for each health professional, such as physicians (bronchoscopists, surgeons, and pathologists), nurses, and nursing technicians. Surgery costs were based on the SUS reimbursement table for pulmonary lobectomy adjusted by the costs defined by the micro-costing analysis. The costs related to complications were estimated considering 5.47 days of hospital stay in the ward (mean length of hospital stay for surgical patients according to the SUS). We used the following formula proposed by Harewood et al.[18] for the total cost of each procedure:

$$[(\text{CP without complications}) \times (1 - \text{CR})] + [(\text{CP with complications}) \times (\text{CR})]$$

where CP is the cost of the procedure and CR is the complication rate.

Considering complication costs in the cost analysis provides a more precise estimation of costs involved. Tables 1 and 2 summarize cost parameters.

Other input parameters

Other input parameters applied to the decision tree analysis are described in Table 3. The sensitivities of EBUS-TBNA and mediastinoscopy for detecting mediastinal lymph node metastasis (MLNM) and complication rates of both procedures were based on two systematic reviews and meta-analyses that compared the use of both techniques in the mediastinal staging of NSCLC.[11,12] The prevalence of MLNM was calculated on the basis of the *Fundação Oncocentro de São Paulo* database, which maintains a hospital cancer registry from the state of São Paulo, Brazil. The data provided by the database covers the period between 2017 and 2019, and patients classified as stage II and III were included to estimate prevalence.

Sensitivity analysis

One-way and two-way deterministic sensitivity analyses were performed for the parameters with the greatest influence on the decision tree model, such as prevalence of MLNM, sensitivity of EBUS-TBNA, sensitivity of mediastinoscopy, and costs of hospital supplies for EBUS. We chose to adopt a wide range (0.25-0.98) for sensitivity of EBUS-TBNA and of mediastinoscopy to account for different scenarios. To account for parameter uncertainty, we also performed a probabilistic sensitivity analysis, in which uncertainties in all values are considered simultaneously. For the probabilistic analysis, the Monte Carlo method was used, with 100,000 event simulations. The uncertainty in clinical probabilities and accuracies and in costs was assumed to have a beta distribution and a gamma distribution, respectively.

Ethics statement

Because the present study did not involve human participants, study approval by a research ethics committee and written consent were waived.

RESULTS

Base-case analysis

For the base-case analysis, initial evaluation with EBUS-TBNA without surgical confirmation of negative results was found to be the least costly strategy ($1,254/I$2,961) in comparison with mediastinoscopy (R$3,255/I$7,688) and EBUS-TBNA with surgical confirmation of negative results (R$3,688/I$8,711).

Sensitivity analysis

One-way sensitivity analysis showed that the EBUS-TBNA strategy without surgical confirmation of negative

Table 1. Parameter values used for costs.

Cost item	Value (R$/I$)	Reference
Post-operative location per day		
Hospital ward	242.41/572.57	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
ICU	741.90/1752.36	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower per hour (average)		
Physician	107.29/253.41	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Nurse	53.64/126.69	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Nursing technician	31.39/74.14	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies and medication (average)		
EBUS	830.22/1,960.97	https://paineldeprecos.planejamento.gov.br/analise-materiais
Mediastinoscopy	805.97/1,903.70	https://paineldeprecos.planejamento.gov.br/analise-materiais
Complication costs[a]		
EBUS or mediastinoscopy	1,325.98/3,131.96	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Total costs for baseline costs[b]		
EBUS	1,155.52/2,729.33	All of the above and Harewood et al.[18]
Mediastinoscopy	3,149.04/7,438.03	All of the above and Harewood et al.[18]

R$: Real (Brazilian currency); and I$: International Dollars. [a]Mean number of days in the hospital ward = 5.47. Complication costs = 5.47 × cost of hospital ward per day (RS242.41/I$498.96). [b]Total costs = (costs without complication costs × 1 − complication rate) + (complication costs × complication rate).

Table 2. Baseline costs and range used for sensitivity analysis.

Cost item	Baseline costs (R$/I$)	Range used for sensitivity analysis (R$ vs. I$)	Reference
EBUS			
Total costs[a]	1,155.52/2,729.33	577.76-1,733.28 vs. 1,364.66-4,094.00	All below and Harewood et al.[18]
Hospitalization	0/0	0-242.41 vs. 0-572.57	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower	320/755.84	160-480 vs. 377.92-1,133.76	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies	830.22/1,960.97	415.11-1,245.33 vs. 980.48-2,941.46	https://paineldeprecos.planejamento.gov.br/analise-materiais
Mediastinoscopy			
Total costs[a]	3,149.04/7,438.03	1,574.52-4,723.56 vs. 3,719.01-11,157.04	all below and Harewood et al.[18]
Hospitalization	1,226.72/2,897.51	613.36-1,840.08 vs. 1,448.75-4,342.58	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/
Manpower	1,091.16/2,577.31	545.58-1,636.74 vs. 1,288.65-3,865.97	http://dados.gov.br/dataset/tabela-de-remuneracao-executivo-federal
Hospital supplies	805.97/1,903.70	402.98-1,208.95 vs. 951.83-2,855.53	https://paineldeprecos.planejamento.gov.br/analise-materiais
Surgery (lobectomy)			
Total costs[a]	3,302.08/7,799.51	1,651.04-4,953.12 vs. 3,899.75-11,699.26	ftp.datasus.gov.br/dissemin/publicos/SIHSUS/200801_/

R$: Real (Brazilian currency); and I$: International Dollars. [a]Total costs = (costs without complication costs × 1 − complication rate) + (complication costs × complication rate).

results was less costly regardless of EBUS-TBNA sensitivity values between 0.25-0.98 and prevalence of MLNM between 0.05-0.88. Mediastinoscopy would become the least costly strategy if the costs for hospital supplies for EBUS-TBNA increased by more than 300% (i.e. R$2,800–I$6,613). Comparing the EBUS-TBNA strategy with surgical confirmation of negative results and the mediastinoscopy strategy, the endosonographic procedure becomes less costly with a prevalence of MLNM of 38% (Figure 2). In the two-way sensitivity analysis, we compared the EBUS-TBNA strategy with surgical confirmation of negative results and the mediastinoscopy strategy, varying the prevalence of MLNM and the sensitivity of

Table 3. Input parameters applied to the decision tree analysis.

Procedure	Baseline sensitivity for detection of MLNM	Range used for sensitivity analysis	Reference
EBUS-TBNA	0.87	0.25-0.98	Ge et al.[12]
Mediastinoscopy	0.86	0.25-0.98	Ge et al.[12]
Procedure	**Baseline complication rate**	**Range used for sensitivity analysis**	**Reference**
EBUS-TBNA	0.004	0.002-0.009	Ge et al.[12] & Sehgal et al.[11]
Mediastinoscopy	0.019	0.0095-0.078	Ge et al.[12] & Sehgal et al.[11]
Patient	**Baseline prevalence of MLNM**	**Range used for sensitivity analysis**	**Reference**
Stage II-III NSCLC	0.23	0.05-0.88	FOSP / O'Connell et al.[20]

MLNM: mediastinal lymph node metastasis; NSCLC: non-small cell lung cancer; and FOSP: *Fundação Oncocentro de São Paulo*.

EBUS-TBNA. In this scenario, considering a prevalence of MLNM of 63%, EBUS-TBNA becomes the preferred strategy if sensitivity is 54% or higher (Figure 3). The probabilistic sensitivity analysis also showed that EBUS-TBNA without surgical confirmation of negative results was the least costly strategy, with a median of R$1,253/I$2,959 (95% uncertainty range [UR]: R$840/I$1,984—R$1,756/I$4,147), followed by mediastinoscopy, with a median of R$3,254/I$7,685 (95% UR: R$2,411/I$5,694—R$4,219/I$9,965), and EBUS-TBNA with surgical confirmation of negative results, with a median of R$3,686/I$8,706 (95% UR: R$2,882/I$6,807—R$4,594/I$10,851).

DISCUSSION

The aim of the present study was to verify whether the use of EBUS-TBNA for the mediastinal staging of NSCLC would be able to reduce costs in comparison with that of mediastinoscopy in the SUS. Our cost-minimization study based on a micro-costing analysis showed that invasive mediastinal staging by EBUS-TBNA without surgical confirmation of negative results is the least costly strategy for mediastinal evaluation in this setting, followed by mediastinoscopy and EBUS-TBNA with surgical confirmation of negative results. Our findings are in agreement with the results of a systematic review of economic evaluation studies comparing both techniques for the mediastinal staging of lung cancer,[13] as well as with the findings of two previous cost-minimization studies.[18,19]

In this model we have considered a prevalence of MLNM of 23% and a sensitivity of EBUS-TBNA and mediastinoscopy of 87% and 86%, respectively. One-way sensitivity analysis showed that, assuming a prevalence of MLNM ≥ 38%, the EBUS-TBNA strategy with surgical confirmation of negative results surgically confirmed becomes less costly than does mediastinoscopy. O'Connell et al.[20] developed a model to predict the probability of MLNM in patients with NSCLC based on findings from chest CT, PET-CT, tumor histopathology, and tumor location. Taking into account this prediction model, a prevalence of MLNM ≥ 38% would be associated with positive findings on chest CT and/or PET-CT, which allows us to infer that a radiological suspicion of MLNM would already indicate the use of EBUS-TBNA, even if a surgical confirmation of negative results is necessary, as a more economical strategy when compared with mediastinoscopy. Two-way sensitivity analysis has demonstrated that, even when we consider a sensitivity of EBUS-TBNA as low as 54%, which is quite unlikely according to results in the literature,[11,12] the EBUS-TBNA strategy would still be the least costly option if the prevalence of MLNM was ≥ 63%. Additionally, according to the prediction model developed by O'Connell et al.,[20] such a scenario would represent a patient with a histopathological diagnosis of adenocarcinoma with enlarged mediastinal lymph nodes on chest CT and/or with hypermetabolic lymph nodes on PET-CT.[20] Considering only the costs of both strategies, the use of mediastinoscopy would become less costly than that of EBUS-TBNA only if we raised the costs of hospital supplies for EBUS-TBNA by 300%. This seems to be a reasonable margin, but it must be highlighted that EBUS costs can significantly increase if the procedure is performed in the operating room with a large number of staff and if hospitalization is necessary.

Our study has some limitations. Initially, since there are no cost estimates related to EBUS-TBNA in the SUS, it was necessary to develop a micro-costing analysis of both strategies to get closer to the costs involved. Although we were careful to collect data from four different hospitals and information from bronchoscopists and thoracic surgeons, it is still uncertain whether this is an accurate reflection of health care system costs in all regions in Brazil. The EBUS procedures were performed under sedation in two hospitals (*Hospital Universitário Clementino Fraga Filho* and *Hospital Universitário Pedro Ernesto*) and under general anesthesia in another (*Instituto Nacional do Câncer*), which makes the evaluation somewhat heterogeneous. We chose to use the average of the costs between the three hospitals in the calculation of the total costs of EBUS-TBNA. Approximately 20-30% of health care services in Brazil are provided by the private network. We adopted the perspective of the public health care system in this model, and the results in the private health care network would not necessarily be the same. Finally, we did not take into account the costs for the acquisition of EBUS equipment

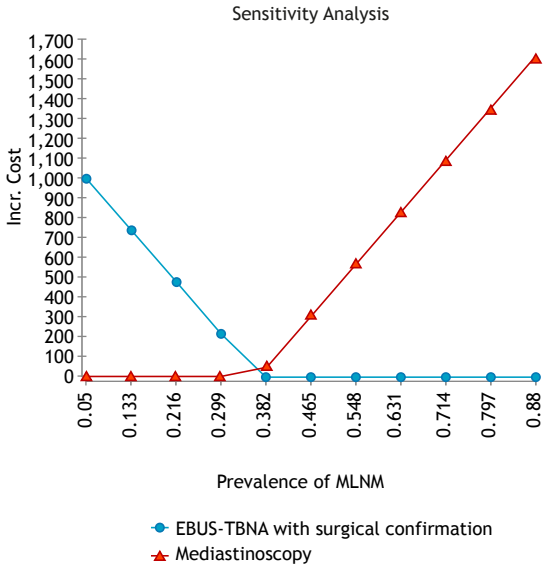


Figure 2. One-way sensitivity analysis: EBUS-TBNA with surgical confirmation of negative results vs. mediastinoscopy. Incr. Cost: incremental cost in Brazilian currency (R$); and MLNM: mediastinal lymph node metastasis.

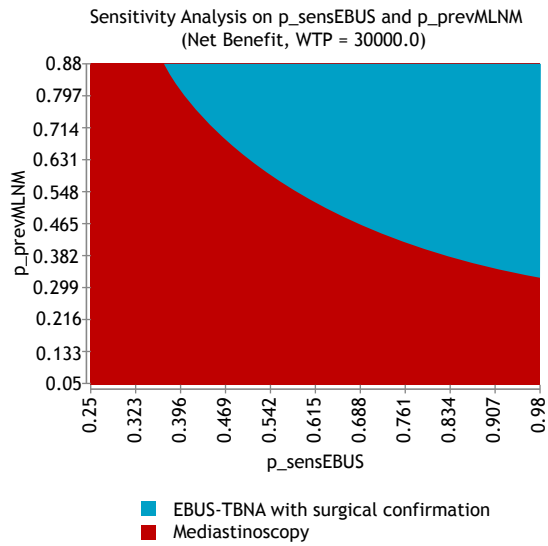


Figure 3. Two-way sensitivity analysis: EBUS-TBNA with surgical confirmation of negative results vs. mediastinoscopy. MLNM: mediastinal lymph node metastasis; p_prevMLNM: prevalence of MLNM; p_sensEBUS: sensitivity of EBUS-TBNA; and WTP: willing to pay (in Brazilian currency).

(dedicated ultrasound processor and endobronchial tube) or mediastinoscopy equipment. It is evident that the costs for purchasing an EBUS system are higher than those for a mediastinoscopy system, even if we consider video-assisted mediastinoscopy. Previous studies published by Sharples et al.[21] and Callister et al.[22] took into account capital (equipment acquisition) and maintenance costs in the cost-effectiveness calculation and, even so, they showed a reduction in costs related to the use of EBUS-TBNA. Using the equipment in referral centers with a high number of procedures can more quickly pay for capital costs.

In conclusion, our economic evaluation study with cost-minimization analyses has demonstrated that the use of EBUS-TBNA is the least costly strategy for the invasive mediastinal assessment of NSCLC in the SUS. Depending on the expected prevalence of MLNM, even the use of EBUS-TBNA with surgical confirmation of negative results is less costly than is the strategy based only on mediastinoscopy. Given the equivalence of EBUS-TBNA and mediastinoscopy in diagnostic performance, and the fact that the endosonographic method is safer, our results regarding the cost advantages of EBUS-TBNA for the diagnosis of mediastinal metastases in patients with NSCLC provide additional evidence for its clinical use and implementation in the SUS.

ACKNOWLEDGMENTS

The following pulmonologists, thoracic surgeons, and anesthesiologists provided information for the micro-costing analysis for the present study: Carlos Henrique Boasquevisque and Viviana Ugento (*Hospital Universitário Clementino Fraga Filho*); Luis Felipe Júdice and Omar Mourad (*Hospital Universitário Antonio Pedro*); Carlos Eduardo Lima, Thiago Mafort, and Denis Muniz Ferraz (*Hospital Universitário Pedro Ernesto*); and Mauro Musa Zamboni (*Instituto Nacional do Cancer*).

AUTHOR CONTRIBUTIONS

JPSM: study design and writing the manuscript. JRLS: study planning and project supervision. AS: interpretation of results and project supervision. RES: model and computational framework design and data analysis. All authors read and approved the final version of the manuscript.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209-249. https://doi.org/10.3322/caac.21660
2. Carretta A. Cost-effectiveness of endoscopic mediastinal staging. Mediastinum. 2020;4:18. https://doi.org/10.21037/med-20-27
3. Silvestri GA, Gonzalez AV, Jantz MA, Margolis ML, Gould MK, Tanoue LT, et al. Methods for staging non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e211S-e250S. https://doi.org/10.1378/chest.12-2355
4. De Leyn P, Dooms C, Kuzdzal J, Lardinois D, Passlick B, Rami-Porta R, et al. Revised ESTS guidelines for preoperative mediastinal lymph node staging for non-small-cell lung cancer. Eur J Cardiothorac Surg. 2014;45(5):787-798. https://doi.org/10.1093/ejcts/ezu028
5. Krasnik M, Vilmann P, Larsen SS, Jacobsen GK. Preliminary experience with a new method of endoscopic transbronchial real time ultrasound guided biopsy for diagnosis of mediastinal and hilar lesions. Thorax. 2003;58(12):1083-1086. https://doi.org/10.1136/thorax.58.12.1083

6. Gu P, Zhao YZ, Jiang LY, Zhang W, Xin Y, Han BH. Endobronchial ultrasound-guided transbronchial needle aspiration for staging of lung cancer: a systematic review and meta-analysis. Eur J Cancer. 2009;45(8):1389-1396. https://doi.org/10.1016/j.ejca.2008.11.043
7. Adams K, Shah PL, Edmonds L, Lim E. Test performance of endobronchial ultrasound and transbronchial needle aspiration biopsy for mediastinal staging in patients with lung cancer: systematic review and meta-analysis. Thorax. 2009;64(9):757-762. https://doi.org/10.1136/thx.2008.109868
8. Varela-Lema L, Fernández-Villar A, Ruano-Ravina A. Effectiveness and safety of endobronchial ultrasound-transbronchial needle aspiration: a systematic review. Eur Respir J. 2009;33(5):1156-1164. https://doi.org/10.1183/09031936.00097908
9. Gompelmann D, Herth FJ. Role of endobronchial and endoscopic ultrasound in pulmonary medicine. Respiration. 2014;87(1):3-8. https://doi.org/10.1159/000356921
10. Kinsey CM, Arenberg DA. Endobronchial ultrasound-guided transbronchial needle aspiration for non-small cell lung cancer staging. Am J Respir Crit Care Med. 2014;189(6):640-649. https://doi.org/10.1164/rccm.201311-2007CI
11. Sehgal IS, Dhooria S, Aggarwal AN, Behera D, Agarwal R. Endosonography Versus Mediastinoscopy in Mediastinal Staging of Lung Cancer: Systematic Review and Meta-Analysis. Ann Thorac Surg. 2016;102(5):1747-1755. https://doi.org/10.1016/j.athoracsur.2016.05.110
12. Ge X, Guan W, Han F, Guo X, Jin Z. Comparison of Endobronchial Ultrasound-Guided Fine Needle Aspiration and Video-Assisted Mediastinoscopy for Mediastinal Staging of Lung Cancer. Lung. 2015;193(5):757-766. https://doi.org/10.1007/s00408-015-9761-3
13. Steinhauser Motta JP, Steffen RE, Samary Lobato C, Souza Mendonça V, Lapa E Silva JR. Endobronchial ultrasound-guided transbronchial needle aspiration versus mediastinoscopy for mediastinal staging of lung cancer: A systematic review of economic evaluation studies. PLoS One. 2020;15(6):e0235479. https://doi.org/10.1371/journal.pone.0235479
14. Czarnecka-Kujawa K, Rochau U, Siebert U, Atenafu E, Darling G, Waddell TK, et al. Cost-effectiveness of mediastinal lymph node staging in non-small cell lung cancer. J Thorac Cardiovasc Surg. 2017;153(6):1567-1578. https://doi.org/10.1016/j.jtcvs.2016.12.048
15. Søgaard R, Fischer BM, Mortensen J, Rasmussen TR, Lassen U. The optimality of different strategies for supplemental staging of non-small-cell lung cancer: a health economic decision analysis. Value Health. 2013;16(1):57-65. https://doi.org/10.1016/j.jval.2012.09.007
16. Navani N, Molyneaux PL, Breen RA, Connell DW, Jepson A, Nankivell M, et al. Utility of endobronchial ultrasound-guided transbronchial needle aspiration in patients with tuberculous intrathoracic lymphadenopathy: a multicentre study. Thorax. 2011;66(10):889-893. https://doi.org/10.1136/thoraxjnl-2011-200063
17. Araujo LH, Baldotto C, Castro G Jr, Katz A, Ferreira CG, Mathias C, et al. Lung cancer in Brazil. J Bras Pneumol. 2018;44(1):55-64. https://doi.org/10.1590/s1806-37562017000000135
18. Harewood GC, Pascual J, Raimondo M, Woodward T, Johnson M, McComb B, et al. Economic analysis of combined endoscopic and endobronchial ultrasound in the evaluation of patients with suspected non-small cell lung cancer. Lung Cancer. 2010;67(3):366-371. https://doi.org/10.1016/j.lungcan.2009.04.019
19. Steinfort DP, Liew D, Conron M, Hutchinson AF, Irving LB. Cost-benefit of minimally invasive staging of non-small cell lung cancer: a decision tree sensitivity analysis. J Thorac Oncol. 2010;5(10):1564-1570. https://doi.org/10.1097/JTO.0b013e3181e8b2e6
20. O'Connell OJ, Almeida FA, Simoff MJ, Yarmus L, Lazarus R, Young B, et al. A Prediction Model to Help with the Assessment of Adenopathy in Lung Cancer: HAL. Am J Respir Crit Care Med. 2017;195(12):1651-1660. https://doi.org/10.1164/rccm.201607-1397OC
21. Sharples LD, Jackson C, Wheaton E, Griffith G, Annema JT, Dooms C, et al. Clinical effectiveness and cost-effectiveness of endobronchial and endoscopic ultrasound relative to surgical staging in potentially resectable lung cancer: results from the ASTER randomised controlled trial. Health Technol Assess. 2012;16(18):1-iv. https://doi.org/10.3310/hta16180
22. Callister ME, Gill A, Allott W, Plant PK. Endobronchial ultrasound guided transbronchial needle aspiration of mediastinal lymph nodes for lung cancer staging: a projected cost analysis. Thorax. 2008;63(4):384. https://doi.org/10.1136/thx.2007.090308

J Bras Pneumol. 2022;48(4):e20210464
https://dx.doi.org/10.36416/1806-3756/e20210464

ORIGINAL ARTICLE

A Brazilian randomized study: Robotic-Assisted vs. Video-assisted lung lobectomy Outcomes (BRAVO trial)

Ricardo Mingarini Terra[1], Pedro Henrique Xavier Nabuco de Araujo[1], Leticia Leone Lauricella[1], Jose Ribas Milanese de Campos[1], Juliana Rocha Mol Trindade[1], Paulo Manuel Pêgo-Fernandes[1]

1. Divisão de Cirurgia Torácica, Departamento de Cardiopneumologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Submitted: 10 November 2021.
Accepted: 26 February 2022.

Study carried out in the Divisão de Cirurgia Torácica, Departamento de Cardiopneumologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To compare 90-day morbidity in patients undergoing lung lobectomy performed by either robotic-assisted thoracic surgery (RATS) or video-assisted thoracic surgery (VATS). Intraoperative complications, drainage time, length of hospital stay, postoperative pain, postoperative quality of life, and readmissions within 90 days were also compared. Methods: This was a two-arm randomized clinical trial including patients with lung lesions (primary lung cancer or lung metastasis) who were candidates for lung lobectomy. Patients with comorbidities that precluded surgical treatment were excluded. All patients followed the same postoperative protocol. Results: The overall sample comprised 76 patients (39 in the VATS group and 37 in the RATS group). The two groups were similar regarding gender, age, BMI, FEV_1 in % of predicted, and comorbidities. Postoperative complications within 90 days tended to be more common in the VATS group than in the RATS group, but the difference was not significant ($p = 0.12$). However, when only major complications were analyzed, this tendency disappeared ($p = 0.58$). Regarding postoperative outcomes, the VATS group had a significantly higher number of readmissions within 90 days than did the RATS group ($p = 0.029$). No significant differences were found regarding intraoperative complications, drainage time, length of hospital stay, postoperative pain, and postoperative quality of life. Conclusions: RATS and VATS lobectomy had similar 90-day outcomes. However, RATS lobectomy was associated with a significant reduction in the 90-day hospital readmission rate. Larger studies are necessary to confirm such a finding.

(ClinicalTrials.gov identifier: NCT02292914 [http://www.clinicaltrials.gov/])

Keywords: Robotic surgical procedures; Thoracic surgery, video-assisted; Lung neoplasms.

INTRODUCTION

Pulmonary lobectomy is the standard treatment for initial lung cancer, and it is also used in selected patients with pulmonary metastases whose characteristics make sublobar resections inadequate.[1] Several studies have compared video-assisted thoracic surgery (VATS) lobectomy with open thoracotomy and demonstrated reduced morbidity and length of hospital stay in favor of the minimally invasive technique without compromising oncologic outcomes.[2-5] In spite of the clear advantages of VATS and the fact that it is strongly recommended by guidelines,[1-6] thoracotomy has remained the most common approach for lobectomies.[3-7] Two-dimensional view and the use of long and inflexible instruments may promote an imprecise dissection and a long and arduous learning curve. These shortcomings might be responsible for the slow implementation of VATS lobectomy worldwide.

Robotic-assisted thoracic surgery (RATS) solves some of the disadvantages of VATS. It offers three-dimensional high-definition view and allows the surgeon to control the camera. Moreover, the robotic platform has endowrist instruments and tremor filtration, allowing a very accurate and safe dissection. Nevertheless, RATS has higher costs that are mainly associated to a large capital investment to acquire the platform. Several studies have confirmed that oncologic outcomes of RATS and VATS lobectomy are equivalent.[8,9] With regard to intra- and post-operative outcomes, one study based on a large database showed that RATS was associated to a lower surgical conversion rate, a lower overall postoperative complication rate, and a shorter length of hospital stay[7]; however, other studies did not find any difference between RATS and VATS.[10-12] In spite of the lack of randomized evidence supporting the benefits of RATS, technical improvements that make minimally

Correspondence to:
Ricardo Mingarini Terra. Divisão de Cirurgia Torácica, Avenida Dr. Enéas de Carvalho Aguiar, 44, CEP 05403-000, São Paulo, SP, Brasil.
Tel.: 55 11 2661-5059. Fax: 55 11 2661-5248. E-mail: rmterra@uol.com.br
Financial support: The Brazilian Ministry of Health funded the acquisition of the DaVinci Si robotic system, surgical instruments, and disposable materials specific to robotic surgery (2012NE800206).

ISSN 1806-3756

invasive surgery easier for the surgeon to perform and potential postoperative benefits have resulted in an increase in RATS procedures from 1% to 11% of all lobectomies performed at non-academic hospitals in the United States from 2009 to 2013.[13]

In this scenario of uncertainties and high costs, a randomized clinical trial would greatly contribute to this subject by providing important and more accurate information on the outcomes of RATS and VATS lobectomy. Therefore, the primary objective of this trial was to compare the 90-day morbidity rate in patients undergoing either RATS or VATS lobectomy. Secondary outcomes included intraoperative complications, drainage time, length of hospital stay, postoperative pain, postoperative quality of life, and readmissions within 90 days.

METHODS

This was a two-arm randomized clinical trial carried out from April of 2015 to June of 2017 at a university teaching hospital in the city of São Paulo, Brazil. All potential candidates with lung cancer underwent clinical staging by chest CT and PET-CT. Patients with neurological symptoms or pulmonary tumors larger than 3 cm underwent brain MRI. Invasive mediastinal staging was performed by mediastinoscopy or EBUS if suspicious hilar/mediastinal lymph nodes, tumors with central location, or tumors larger than 3 cm were found. After surgical indication was confirmed, all patients were evaluated and approved for surgery by the pulmonology team; only then patients were referred to the research team for trial enrollment evaluation.

The trial inclusion criteria were as follows: eligibility for the treatment of lung cancer or lung metastasis by pulmonary lobectomy; presence of tumor of less than 5 cm in diameter; absence of tumor invasion into the chest wall, diaphragm, mediastinum, or another lung lobe; and clinical and anesthetic evaluation results showing that the patient was able to undergo the proposed procedure. Exclusion criteria were as follows: having previously undergone a thoracic surgical procedure in the hemithorax to be operated on; and being unable to remain on single-lung ventilation during the procedure. All patients signed the written informed consent approved by our institutional research ethics committee (CAAE 21934413.2.0000.0065). This study was also registered at ClinicalTrials.gov (NCT02292914).

The Brazilian Ministry of Health funded the acquisition of the DaVinci Si (Intuitive Surgical Inc., Sunnyvale, CA, USA) robotic system and a limited amount of surgical instruments and disposable materials specific to robotic surgery. Therefore, the sample size was defined by convenience. Surgeons recruited outpatients according to inclusion and exclusion criteria. The clinical research nursing team was responsible for providing and collecting the written informed consent forms, and the research center defined the allocation of the patients using a website software (www.randomization.org, Arlington, VA, USA). We used block randomization to allow an adequate distribution of patients between the two groups. Patients were randomized only after having their surgery scheduled, ensuring allocation concealment. However, the randomization status was not blinded, so both patient and medical staff were aware of the randomization assignment.

For RATS lobectomies, we used the DaVinci Si robotic system (Innovative Surgical) and the three-arm technique initially described by Ninan & Dylewski.[14] All VATS lobectomies were performed in accordance with the triportal technique. Figure 1 shows photographs of the two surgical approaches. One 28-Fr chest tube was placed in the patients of both groups. All surgical procedures were performed under selective intubation. Radical hilar and mediastinal lymphadenectomy was performed only in patients with primary pulmonary cancer. The same group of surgeons performed both VATS and RATS procedures. The patients were usually transferred to the hospital ward in the postoperative period; only elderly patients with multiple comorbidities or patients with intraoperative complications were sent to the ICU at the end of the procedure. Postoperative analgesia included patient-controlled epidural anesthesia (local anesthetics and opioids), which was discontinued immediately after chest tube removal.

In the present study the primary outcome was complication rate within 90 days. Postoperative complications were recorded and classified as proposed by Seely et al.[15] As secondary outcomes, we analyzed intraoperative complications, drainage time, length of hospital stay, postoperative pain, postoperative quality of life, and readmissions within 90 days. Drainage time was defined as the interval between surgery and the removal of the chest tube and was measured in days. Length of hospital stay was measured in days after surgery. Postoperative pain was evaluated by a visual analog pain scale[16] on the first, second, and third postoperative days and at the 30-day outpatient visit. We also assessed the need for opioid use at the 30-day outpatient visit. Any hospitalization within the 90-day postoperative period was considered as readmission.

In addition to the variables described above, we collected other pieces of information: demographic characteristics (age, gender, and BMI), FEV_1 (in L and % of predicted), smoking status, presence of systemic arterial hypertension, presence of diabetes mellitus, presence of cardiac, hepatic, or renal diseases, and tumor size. We also collected procedure-related information: operative time, conversion to open surgery, need for extended resection, and resected lobe. During the postoperative period, we collected information on length of ICU stay and need for reoperation. When primary cancer was pulmonary, we collected data on the histological type and the pathological stage as per the 8th edition of the TNM staging classification for lung cancer.[17]

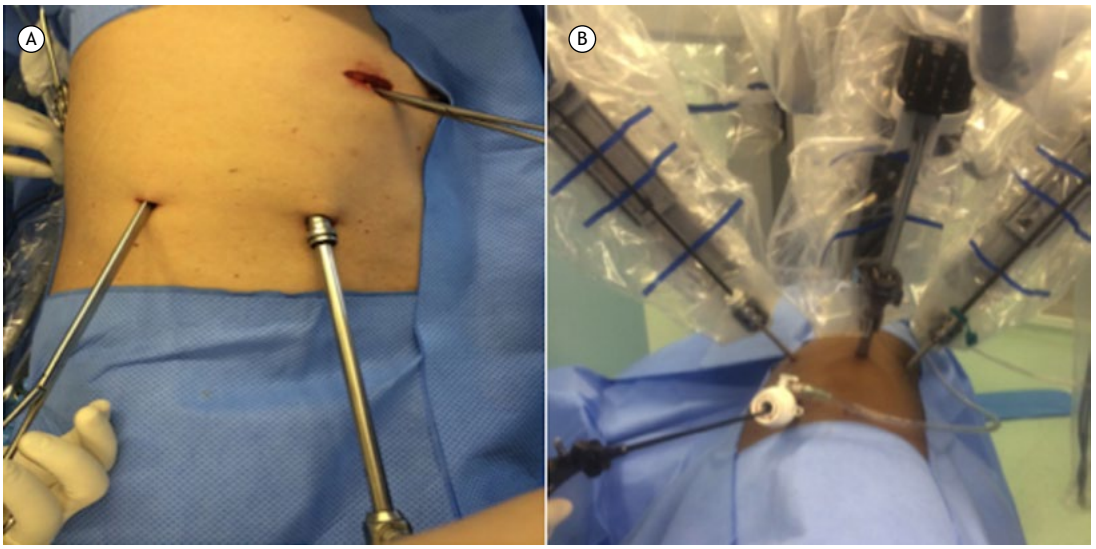


Figure 1. Photographs of the two surgical approaches: in A, video-assisted thoracic surgery; in B, robotic-assisted thoracic surgery

We used descriptive statistical analyses to summarize the characteristics of the studied patients. We compared categorical variables using the Fisher's exact test. We tested numerical variables for their distribution using the Shapiro-Wilk and kurtosis tests. We used the t-test and ANOVA to compare continuous variables with normal distribution and the Mann-Whitney and Wilcoxon tests to compare continuous variables with asymmetrical distribution. All analyses were carried out with a level of significance of $p < 0.05$. The analyzes were performed using the Predictive Analytics Software package, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

From June of 2015 to May of 2017, 107 patients were evaluated for trial enrollment. Of these, 80 met the inclusion criteria and were randomized. Four patients were excluded after randomization (3 in the RATS group and 1 in the VATS group): 2 patients had undiagnosed advanced disease at randomization—malignant pleural effusion, in 1; and brain metastasis after reevaluation of brain MRI results, in 1—1 patient had a severe episode of arrhythmia just before the surgery, and we opted for canceling the procedure and referring the patient to stereotaxic radiotherapy, and 1 patient withdrew consent after randomization. Therefore, the overall sample comprised 76 patients (37 and 39 patients in the RATS and VATS groups, respectively). We used intention-to-treat analysis; however, there was no crossover, and all exclusions occurred after randomization, but before the intervention. The flow chart of the patient selection process is depicted in Figure 2, and the characteristics of the patients included in the study are shown in Table 1.

The overall operative time tended to be longer in the RATS group than in the VATS group, although the difference had no statistical significance—241.7 (218.3-265.1) min vs. 214.4 (200.3-228.5) min ($p = 0.06$). Neither were any intraoperative complications observed, nor was it necessary any surgical conversion in the RATS group. In the VATS group, there were three cases of intraoperative vascular lacerations (arterial and venous lacerations in 2 and 1, respectively), and two of the procedures were converted to open surgery. No patient required blood transfusion. Table 2 shows the results related to the surgeries performed.

With regard to postoperative outcomes (Table 3), the only significant difference observed was in the number of readmissions within 90 days, which were less common in the RATS group (1 patient vs. 8 patients; $p = 0.029$). In the RATS group, hospital was due to bronchospasm/decompensated COPD, whereas, in VATS group, the causes were empyema (in 2 patients, 1 of whom presenting with prolonged air leak), pneumonia (in 2), prolonged air leak that persisted for two months after lobectomy (n 1)—the patient was readmitted for another video-assisted thoracoscopy (in 1)—pleural effusion (in 1), surgical wound infection (in 1), and severe pain (in 1). Three patients required reoperation due to prolonged air leak (in 2; 1 in the VATS group, and 1 in the RATS group during the same hospitalization period) and empyema (1 in the VATS group). Postoperative complications within 90 days tended to be less common in the RATS group than in the VATS group—7 (18.9%) cases vs. 14 (35.9%) cases—with no statistically significant difference ($p = 0.12$). Nevertheless, when we considered only major complications (grade ≥ 3, as per the Common Terminology Criteria for Adverse Events, version 4), this tendency disappeared—7 (18.9%) cases vs. 10 (25.6%) cases ($p = 0.58$). Two patients died (1 in each group), both due to pneumonia

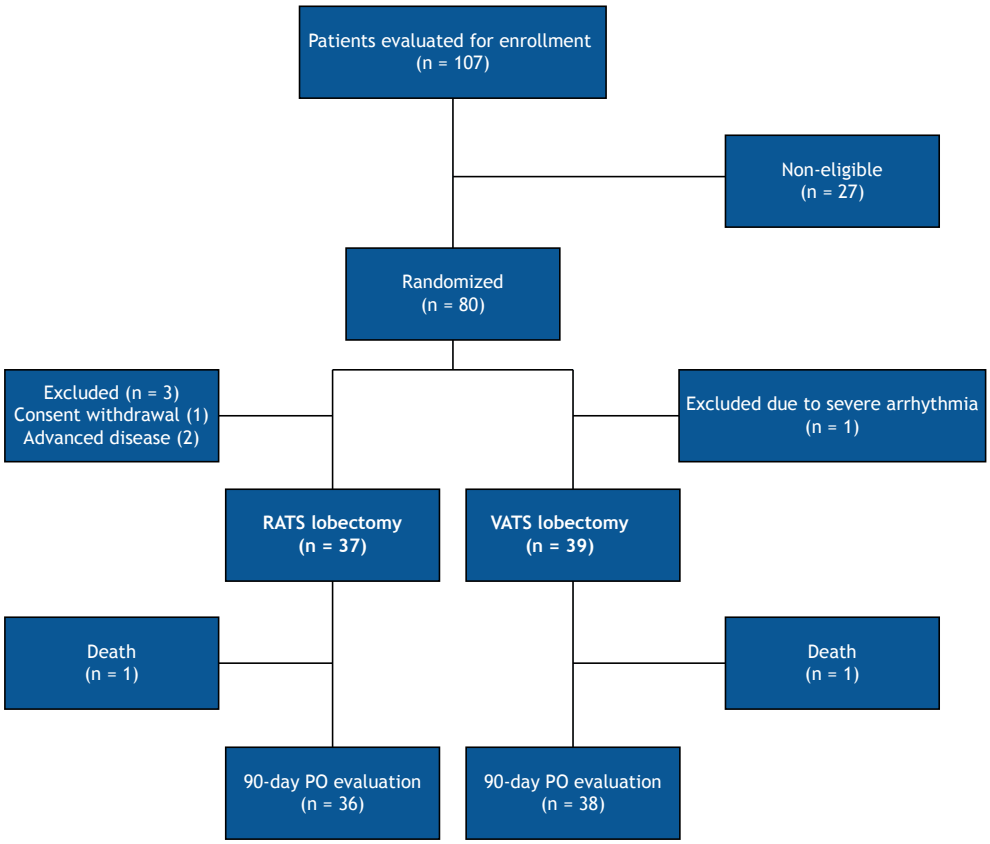


Figure 2. Flow chart of the patient selection process. RATS: robotic-assisted thoracic surgery; VATS: video-assisted thoracic surgery; and PO: postoperative.

and sepsis. All of the postoperative complications are described in Table 4.

No significant differences were found between the groups regarding histological types (p = 0.60) or pathological staging (p = 0.36). Among the 34 patients with primary lung cancer in the RATS group, there was N descriptor upstaging in 3: from cN0 to pN1, in 2; and from cN0 to pN2, in 1. Likewise, among the 35 patients with primary lung cancer in the VATS group, N upstaging occurred in 5: from cN0 to pN1, in 2; and from cN0 to pN2, in 3. However, the difference was not statistically significant (p = 0.71). Table S1 details such findings.

There were no significant differences regarding the perception of postoperative pain (defined as a score > 2 in the visual analog scale)[16] between the groups either during the first 3 postoperative days or 30 days after surgery. We also evaluated the need for any type of opioid medication 30 days after lobectomy. Once again, no significant difference was found between the groups (p = 0.61). Table S2 shows the results regarding postoperative pain.

DISCUSSION

The present study showed a significantly lower 90-day hospital readmission rate in the RATS group when compared with the VATS group (2.7% vs. 20.5%; p = 0.029). Moreover, postoperative complications within 90 days tended to be less common in patients undergoing RATS than in those undergoing VATS, although with no statistical significance (18.9% vs. 35.9%; p = 0.12). This tendency did not occur for major complications (18.9% vs. 25.6%; p = 0.58). The RATS group also showed fewer intraoperative complications and surgical conversions to open thoracotomy than did the VATS group, but again with no statistical significance (respectively, 0 vs. 3; p = 0.24; and 0 vs. 2; p = 0.49). On the other hand, the RATS group tended to have a longer overall operative time: 241.7 (218.3-265.1) min vs. 214.4 (200.3-228.5) min (p = 0.06).

Initially, a few small retrospective studies were published on robotic lobectomy.[8,9] Some presented the technique and the experience of a single institution; others compared RATS with either open surgery or VATS.[8,9] After a greater dissemination of robotic surgery and a consequent increase in the number of patients operated on by this technique, retrospective studies using large multi-institutional databases have been published and showed similar postoperative outcomes between VATS and RATS.[10,11,13]

More recently, Oh et al.[7] published a study showing some benefits of RATS lobectomy. Compared with

Table 1. Demographic and baseline characteristics of the patients per group (N = 76).[a]

Characteristic	Group		p
	RATS (n = 37)	VATS (n = 39)	
Age, years	68.4 (65.2-71.5)	65.7 (61.8-69.5)	0.31
Female	20 (54.0%)	22 (56.4%)	1.00
BMI, kg/m^2	27.5 (26.2-28.8)	26.5 (24.9-28.1)	0.24
FEV_1, L	2.2 (2.0-2.4)	2.1 (1.9-2.3)	0.33
FEV_1, % of predicted	87.3 (81.8-92.8)	81.5 (77.5-85.5)	0.19
Never smoker	12	11	0.78
COPD	12	18	0.28
Morbid obesity (BMI >34.9 kg/m^2)	3	3	1.00
Hypertension	24	21	0.35
Diabetes mellitus	7	11	0.42
Cardiac disease	5	3	0.47
Liver disease	2	5	0.43
Kidney disease	2	1	0.61
NSCLC	34[b]	35[c]	1.00
Tumor size, cm	2.32 (1.90-2.74)	2.45 (2.11-2.79)	0.65

RATS: robotic-assisted thoracic surgery; VATS: video-assisted thoracic surgery; and NSCLC: non-small cell lung cancer. [a]Values expressed as n or median (95% CI), except where otherwise indicated. [b]Metastatic breast cancer, in 1; inflammatory myofibroblastic tumor, in 1; and atypical adenomatous hyperplasia, in 1. [c]Metastatic melanoma, in 1; metastatic renal cell carcinoma, in 2; and small cell lung cancer, in 1.

Table 2. Surgical characteristics and intraoperative complications of the patients per group (N = 76).[a]

Variable	Group		p
	RATS (n = 37)	VATS (n = 39)	
Operative time, min	241.7 (218.3-265.1)	214.4 (200.3-228.5)	0.06
Intraoperative complications	0	3[b]	0.24
Conversion to open surgery	0	2	0.49
Extended resection	1[c]	2[d]	0.59
Resected lobe			0.68
RUL	14	13	
RML	3	0	
RLL	8	8	
LUL	7	9	
LLL	5	9	

RATS: robotic-assisted thoracic surgery; VATS: video-assisted thoracic surgery; RUL: right upper lobe; RML: right middle lobe; RLL: right lower lobe; LUL: left upper lobe; and LLL: left lower lobe. [a]Values expressed as n or median (95% CI). [b]Arterial lacerations, in 2; and venous injury, in 1. [c]Wedge resection. [d]Wedge resection and pericardial resection.

the VATS group, the RATS group had a lower surgical conversion rate (6.3% vs. 13.1%; p < 0.0001), a lower overall postoperative complication rate (34.1% vs. 37.6%; p = 0.0061), and a shorter median of length of hospital stay (5 days vs. 6 days; p = 0.006). However, postoperative and 30-day mortality rates were similar: 0.9% vs. 1.2% (p = 0.44) and 1.2% vs. 1.4%; (p = 0.642), respectively. Thus, for the first time, a multi-institutional study with large numbers of patients demonstrated that RATS lobectomy could be associated with improvements in perioperative outcomes when compared with VATS lobectomy.[7] These findings resemble those found in our study, which suggests that RATS lobectomy may be associated with fewer complications.

Our results for postoperative complications within 90 days in the VATS and RATS groups (35.9% vs. 18.9%) were similar to those in the literature.[7,10,11] Interestingly, patients undergoing VATS had a larger number of isolated minor complications. These cases did not require further interventions or extended hospitalization. We could not identify a specific reason for these findings. The RATS technique might have a more meticulous approach and cause fewer fissures in and less damage to the lungs.

Our results for readmission within 90 days were also similar to those in the literature (18.0%, 16.9%, and 19.8%).[18-20] However, patients undergoing RATS had a significantly lower readmission rate than did

Table 3. Postoperative course, postoperative complications, readmissions, and mortality of the patients per group (N = 76).[a]

Variable	Group		p
	RATS (n = 37)	VATS (n = 39)	
ICU time, days	0 [0-1]	0 [0-2]	0.99
Length of hospital stay, days	3 [2-4]	4 [2-5]	0.55
Chest tube time, days	2 [1-2]	2 [1-4]	0.27
Reoperation	1 (2.7%)[b]	2 (5.1%)[c]	0.59
Complications within 90 days	7 (18.9%)	14 (35.9%)	0.12
≥ 3 complications within 90 days	7 (18.9%)	10 (25.6%)	0.58
Readmissions within 90 days	1 (2.7%)	8 (20.5%)	0.029
90-day mortality	1 (2.7%)	1 (2.5%)	1.0

RATS: robotic-assisted thoracic surgery; and VATS: video-assisted thoracic surgery. [a]Values expressed as median [IQR] or n (%). [b]Prolonged air leak. [c]Prolonged air leak, in 1; and empyema, in 1.

Table 4. Comparison of 90-day postoperative complications in accordance with the Common Terminology Criteria for Adverse Events (version 4) between the groups.[a]

90-day complications	Any grade			Grade ≥ 3		
	RATS (n = 37)	VATS (n = 39)	p	RATS (n = 37)	VATS (n = 39)	p
Any	7 (18.9)	14 (35.9)	0.12	7 (18.9)	10 (25.6)	0.58
Death				1 (2.7)	1 (2.5)	1.00
Prolonged air leak	4 (10.8)	5 (12.8)	1.00	4 (10.8)	5 (12.8)	1.00
Empyema	0	2 (5.1)	0.49	0	2 (5.1)	0.49
Pleural effusion	0	1 (2.5)	1.00	0	1 (2.5)	1.00
Surgical site infection	0	1 (2.5)	1.00	0	1 (2.5)	1.00
Subcutaneous emphysema	0	1 (2.5)	1.00	0	0	1.00
Acute kidney failure	1 (2.7)	2 (5.1)	1.00	1 (2.7)	2 (5.1)	1.00
Pyrexia	0	1 (2.5)	1.00	0	0	1.00
Pneumonia	1 (2.7)	1 (2.5)	1.00	1 (2.7)	1 (2.5)	1.00
Sepsis	2 (5.4)	1 (2.5)	0.61	2 (5.4)	1 (2.5)	0.61
Severe pain	0	1 (2.5)	1.00		1 (2.5)	1.00
Pulmonary embolism	1 (2.7)	0	0.48	1 (2.7)	0	0.48
Arrhythmia	1 (2.7)	0	1.00	1 (2.7)	0	1.00
Bronchospasm	1 (2.7)	2 (5.1)	1.00	1 (2.7)	0	1.00
Atelectasis	0	1 (2.5)	1.00	0	0	1.00

RATS: robotic-assisted thoracic surgery; and VATS: video-assisted thoracic surgery. [a]Values expressed as n (%).

patients undergoing VATS (2.7% vs. 20.5%; p = 0.029), suggesting a potential benefit that has not been previously described. Both groups had similar preoperative characteristics and were exposed to the same postoperative conditions. The tendency that we observed (fewer complications in the RATS group) seems to have been reflected in the 90-day readmission rate.

In general, our intraoperative outcomes are similar to those of most retrospective studies.[7,13,21-23] We observed operative times similar to those in the literature; moreover, we found a tendency toward a longer operative time for RATS when compared with VATS (241.7 ± 72.6 min vs. 214.4 ± 45.1 min; p = 0.06).[7,13,21] We believe that we would achieve a significant difference with a larger number of patients. We had neither intraoperative complications nor need for surgical conversion in the RATS group. Similarly to what has previously been published, we identified the need for more surgical conversions with VATS, although this difference was not statistically significant.[7,22,23]

The medians [IQR] in drainage time were not different between the RATS and VATS groups (2 [1-2] days vs. 2 [1-4] days; p = 0.27). The same occurred regarding the length of hospital stay (3 [2-4] days vs. 4 [2-5]; p = 0.55). These findings are compatible with those of most of the previous studies.[7,10,11,21] However, our trial has no statistical power to evaluate such outcomes. Differences could possibly appear with a larger number of patients, as shown in other studies.[7,23]

This study is a randomized clinical trial. By design, we are eliminating the selection bias inherent to

previous retrospective studies, and this was confirmed by the well balanced groups analyzed in our study. However, this study has some limitations. First, the randomization was not blinded; therefore, we could not guarantee the absence of performance and detection biases. We tried to minimize this problem by sticking to rigid guidelines for postoperative management. Sample size was also an important issue. The study budget had a limited amount of resources for robotic surgeries, which allowed the inclusion of up to 40 patients in the RATS group, which might have impacted on statistical power.

In the present study we found that RATS and VATS lobectomy had similar 90-day outcomes. However, RATS lobectomy was associated with a significant reduction in 90-day hospital readmission rate. This gain in safety may help us understand the growth of RATS lobectomy in recent years.[7] Nonetheless, larger studies are necessary to confirm our findings and better explore differences in postoperative complications.

ACKNOWLEDGMENTS

We would like to thank Dr. Ricardo Abdalla for his expertise, commitment, and dedication to tutoring us in the initial cases. In addition, we would like to thank Professors Ivan Ceconello and Ulysses Ribeiro Junior for their unconditional support and for making it possible to implement a robotic surgery program at the *Instituto do Câncer do Estado de São Paulo* (ICESP). Finally, we would like to thank Evelise Zaidan and the ICESP.

AUTHOR CONTRIBUTIONS

All authors participated in the conception and planning of the study, as well as in the interpretation of evidence, writing and/or reviewing the preliminary and final versions, and approving the final version.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. National Comprehensive Cancer Network (NCCN) [homepage on the Internet]. Plymouth Meeting, PA: NCCN; c2021 [updated 2020 Feb 11; cited 2021 Nov 11]. NCCN Clinical Practice Guidelines in Oncology: Non-Small Cell Lung Cancer. Version 2.2020. [Adobe Acrobat document, 240p.]. Available from: https://www2.tri-kobe.org/nccn/guideline/lung/english/non_small.pdf
2. Paul S, Altorki NK, Sheng S, Lee PC, Harpole DH, Onaitis MW, et al. Thoracoscopic lobectomy is associated with lower morbidity than open lobectomy: a propensity-matched analysis from the STS database. J Thorac Cardiovasc Surg. 2010;139(2):366-378. https://doi.org/10.1016/j.jtcvs.2009.08.026
3. Tsukazan MTR, Terra RM, Vigo Á, Fortunato GA, Camargo SM, de Oliveira HA, et al. Video-assisted thoracoscopic surgery yields better outcomes than thoracotomy for anatomical lung resection in Brazil: a propensity score-matching analysis using the Brazilian Society of Thoracic Surgery database. Eur J Cardiothorac Surg. 2018;53(5):993-998. https://doi.org/10.1093/ejcts/ezx442
4. Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hürtgen M, Petersen RH, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg. 2016;49(2):602-609. https://doi.org/10.1093/ejcts/ezv154
5. Bendixen M, Jørgensen OD, Kronborg C, Andersen C, Licht PB. Postoperative pain and quality of life after lobectomy via video-assisted thoracoscopic surgery or anterolateral thoracotomy for early stage lung cancer: a randomised controlled trial. Lancet Oncol. 2016;17(6):836-844. https://doi.org/10.1016/S1470-2045(16)00173-X
6. Howington JA, Blum MG, Chang AC, Balekian AA, Murthy SC. Treatment of stage I and II non-small cell lung cancer: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2013;143(5 Suppl):e278S-e313S. https://doi.org/10.1378/chest.12-2359
7. Oh DS, Reddy RM, Gorrepati ML, Mehendale S, Reed MF. Robotic-Assisted, Video-Assisted Thoracoscopic and Open Lobectomy: Propensity-Matched Analysis of Recent Premier Data. Ann Thorac Surg. 2017;104(5):1733-1740. https://doi.org/10.1016/j.athoracsur.2017.06.020
8. Veronesi G, Galetta D, Maisonneuve P, Melfi F, Schmid RA, Borri A, et al. Four-arm robotic lobectomy for the treatment of early-stage lung cancer. J Thorac Cardiovasc Surg. 2010;140(1):19-25. https://doi.org/10.1016/j.jtcvs.2009.10.025
9. Park BJ, Melfi F, Mussi A, Maisonneuve P, Spaggiari L, Da Silva RK, et al. Robotic lobectomy for non-small cell lung cancer (NSCLC): long-term oncologic results. J Thorac Cardiovasc Surg. 2012;143(2):383-389. https://doi.org/10.1016/j.jtcvs.2011.10.055
10. Kent M, Wang T, Whyte R, Curran T, Flores R, Gangadharan S. Open, video-assisted thoracic surgery, and robotic lobectomy: review of a national database. Ann Thorac Surg. 2014;97(1):236-244. https://doi.org/10.1016/j.athoracsur.2013.07.117
11. Swanson SJ, Miller DL, McKenna RJ Jr, Howington J, Marshall MB, Yoo AC, et al. Comparing robot-assisted thoracic surgical lobectomy with conventional video-assisted thoracic surgical lobectomy and wedge resection: results from a multihospital database (Premier). J Thorac Cardiovasc Surg. 2014;147(3):929-937. https://doi.org/10.1016/j.jtcvs.2013.09.046
12. Emmert A, Straube C, Buentzel J, Roever C. Robotic versus thoracoscopic lung resection: A systematic review and meta-analysis. Medicine (Baltimore). 2017;96(35):e7633. https://doi.org/10.1097/MD.0000000000007633
13. Louie BE, Wilson JL, Kim S, Cerfolio RJ, Park BJ, Farivar AS, et al. Comparison of Video-Assisted Thoracoscopic Surgery and Robotic Approaches for Clinical Stage I and Stage II Non-Small Cell Lung Cancer Using The Society of Thoracic Surgeons Database. Ann Thorac Surg. 2016;102(3):917-924. https://doi.org/10.1016/j.athoracsur.2016.03.032
14. Ninan M, Dylewski MR. Total port-access robot-assisted pulmonary lobectomy without utility thoracotomy. Eur J Cardiothorac Surg. 2010;38(2):231-232. https://doi.org/10.1016/j.ejcts.2010.01.047
15. Seely AJ, Ivanovic J, Threader J, Al-Hussaini A, Al-Shehab D, Ramsay T, et al. Systematic classification of morbidity and mortality after thoracic surgery. Ann Thorac Surg. 2010;90(3):936-942. https://doi.org/10.1016/j.athoracsur.2010.05.014
16. Schestatsky P, Félix-Torres V, Chaves ML, Câmara-Ehlers B, Mucenic T, Caumo W, et al. Brazilian Portuguese validation of the Leeds Assessment of Neuropathic Symptoms and Signs for patients with chronic pain. Pain Med. 2011;12(10):1544-1550. https://doi.org/10.1111/j.1526-4637.2011.01221.x
17. Amin MB, Edge SB, Greene FL, Byrd DR, Brookland RK, Washington MK, et al, editors. AJCC Cancer Staging Manual. 8th ed. New York: Springer; 2017.
18. Jean RA, Chiu AS, Boffa DJ, Detterbeck FC, Blasberg JD, Kim AW. When good operations go bad: The additive effect of comorbidity and postoperative complications on readmission after pulmonary lobectomy. Surgery. 2018;164(2):294-299. https://doi.org/10.1016/j.surg.2018.03.019
19. Jean RA, Chiu AS, Hoag JR, Blasberg JD, Boffa DJ, Detterbeck FC, et al. Identifying Drivers of Multiple Readmissions After Pulmonary Lobectomy. Ann Thorac Surg. 2019;107(3):947-953. https://doi.

org/10.1016/j.athoracsur.2018.08.070

20. Stiles BM, Poon A, Giambrone GP, Gaber-Baylis LK, Wu X, Lee PC, et al. Incidence and Factors Associated With Hospital Readmission After Pulmonary Lobectomy. Ann Thorac Surg. 2016;101(2):434-443. https://doi.org/10.1016/j.athoracsur.2015.10.001
21. Adams RD, Bolton WD, Stephenson JE, Henry G, Robbins ET, Sommers E. Initial multicenter community robotic lobectomy experience: comparisons to a national database. Ann Thorac Surg. 2014;97(6):1893-1900. https://doi.org/10.1016/j.athoracsur.2014.02.043
22. Oh DS, Cho I, Karamian B, DeMeester SR, Hagen JA. Early adoption of robotic pulmonary lobectomy: feasibility and initial outcomes. Am Surg. 2013;79(10):1075-1080. https://doi.org/10.1177/000313481307901024
23. Reddy RM, Gorrepati ML, Oh DS, Mehendale S, Reed MF. Robotic-Assisted Versus Thoracoscopic Lobectomy Outcomes From High-Volume Thoracic Surgeons. Ann Thorac Surg. 2018;106(3):902-908. https://doi.org/10.1016/j.athoracsur.2018.03.048

J Bras Pneumol. 2022;48(4):e20220121
https://dx.doi.org/10.36416/1806-3756/e20220121

ORIGINAL ARTICLE

Physiotherapy practice for hospitalized patients with COVID-19

Letícia Marcelino Sotelo Dias[1], Fernando Silva Guimaraes[2], Camila Ferreira Leite[3], Flavia Marini Paro[4], Raquel Annoni[5], Ana Carolina Otoni Oliveira[6], Marilita Falangola Accioly[5,6], Marcia Souza Volpe[1,7]

1. Programa de Pós-Graduação Interdisciplinar em Ciências da Saúde, Universidade Federal de São Paulo – UNIFESP – Campus Baixada Santista. Santos (SP) Brasil.
2. Departamento de Fisioterapia Cardiorrespiratória e Musculoesquelética, Faculdade de Fisioterapia, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
3. Programa de Pós-Graduação em Fisioterapia e Funcionalidade, Universidade Federal do Ceará – UFC – Fortaleza (CE) Brasil.
4. Departamento de Educação Integrada em Saúde, Universidade Federal do Espírito Santo – UFES – Vitória (ES) Brasil.
5. Laboratório de Investigação Funcional dos Sistemas Cardiopulmonar e Metabólico, Departamento de Fisioterapia Aplicada, Universidade Federal do Triângulo Mineiro – UFTM – Uberaba (MG) Brasil.
6. Programa de Pós-Graduação em Fisioterapia, Universidade Federal do Triângulo Mineiro, – UFTM – Uberaba (MG) Brasil.
7. Departamento de Ciências do Movimento Humano, Universidade Federal de São Paulo – UNIFESP – Campus Baixada Santista. Santos (SP) Brasil.

Submitted: 7 April 2022.
Accepted: 7 June 2022.

Study carried out at the Universidade Federal de São Paulo – UNIFESP – Campus Baixada Santista, Santos (SP) Brasil; the Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil; the Universidade Federal do Ceará – UFC – Fortaleza (CE) Brasil; the Universidade Federal do Espírito Santo – UFES – Vitória (ES) Brasil; and the Universidade Federal do Triângulo Mineiro – UFTM – Uberaba (MG) Brasil.

ABSTRACT

Objective: To identify the indications for physiotherapy and to evaluate physiotherapy practices in patients with COVID-19 admitted to the ICU (on mechanical ventilation) or to the ward (spontaneously breathing). **Methods:** An online, 50-item survey was completed by physiotherapists who had been treating hospitalized patients with COVID-19 in Brazil. **Results:** Of the 644 physiotherapists who initiated the survey, 488 (76%) completed it. The main reasons for indications for physiotherapy in both settings reported as "very frequently" and "frequently" both in the ICU and the ward by most respondents were oxygenation improvement (> 95%) and prevention of general complications (> 83%). Physical deconditioning was considered an infrequent indication. When compared with mobilization strategies, the use of respiratory interventions showed great variability in both work settings, and techniques considered effective were underutilized. The most frequently used respiratory techniques in the ICU were positioning (86%), alveolar recruitment (73%), and hard/brief expiratory rib cage compression (46%), whereas those in the ward were active prone positioning (90%), breathing exercises (88%), and directed/assisted cough (75%). The mobilization interventions reported by more than 75% of the respondents were sitting on the edge of the bed, active and resistive range of motion exercises, standing, ambulation, and stepping in place. **Conclusions:** The least common reason for indications for physiotherapy was avoidance of deconditioning, whereas oxygenation improvement was the most frequent one. Great variability in respiratory interventions was observed when compared with mobilization therapies, and there is a clear need to standardize respiratory physiotherapy treatment for hospitalized patients with COVID-19.

Keywords: COVID-19; Physical therapy modalities; Hospitalization; Critical illness; Surveys and questionnaires.

INTRODUCTION

Since the COVID-19 outbreak in December of 2019, SARS-CoV-2 has infected more than 450 million people and been responsible for more than 6 million global deaths. Brazil is among the ten most affected countries in terms of mortality, together with the United States of America and the United Kingdom.[1]

Before vaccination, approximately 20% of infected patients required hospitalization, and 5% developed critical illness requiring intensive care support.[2] Physiotherapists have a fundamental role in treating hospitalized patients by using respiratory support and early mobilization, decreasing the length of hospital stay, improving functional capacity, and decreasing the number of readmissions and deaths during the first year after hospital discharge.[3,4] In Brazil, before COVID-19, physiotherapists were already considered essential members of the intensive care team, and the pandemic has strengthened their role.

As in Australia, Canada, Italy, and the United Kingdom, physiotherapists in Brazil are responsible for both respiratory and mobilization therapies.[5-8] They are also accountable for mechanical ventilation management along with the medical team.[9] The main goals of respiratory therapy include promoting adequate gas exchange, clearance of airway secretions, reduction of work of breathing, and prevention of respiratory complications.[10] Respiratory physiotherapy interventions are usually

Correspondence to:
Marcia Souza Volpe. Departamento de Ciências do Movimento Humano, Universidade Federal de São Paulo – UNIFESP – Campus Baixada Santista, Rua Silva Jardim, 136, CEP 11015-020, Santos, SP, Brasil.
Tel.: 55 13 3512-2700. E-mail: marcia.volpe@unifesp.br
Financial support: None.

ISSN 1806-3756

divided into two classes: assistance with airway clearance and promotion of lung expansion. However, some interventions work for both, such as techniques that increase inspiratory volumes, transpulmonary pressures, and collateral ventilation. Mobilization, a key component of inpatient rehabilitation, comprises physical activity sufficient to produce acute physiological effects that increase ventilation, circulation, muscle metabolism, and alertness to avoid physical deconditioning and other effects of prolonged immobility.[10]

Although the role of physiotherapy is well established in many countries, there is no consensus on the effectiveness of many physiotherapy interventions.[11-13] In 2020, some documents with detailed recommendations for physiotherapy treatment of hospitalized patients with COVID-19 were published to guide physiotherapists at the frontline.[6,7,14-16] However, due to the urgent need for support and the lack of scientific information on physiotherapy in COVID-19, owing to the disease's novelty, these guidelines were mainly based on specialists' consensus.

This survey was conducted to identify the indications for physiotherapy and to evaluate physiotherapy practices in patients with COVID-19 admitted to the ICU (on mechanical ventilation) or to the ward (spontaneously breathing).

METHODS

This was a cross-sectional online questionnaire survey. The study was approved by the Research Ethics Committee of Federal University of São Paulo (Protocol n. 44771021.2.0000.5505) and was reported following the Consensus-Based Checklist for Reporting of Survey Studies.[17] The survey was carried out between June and October of 2021.

Physiotherapists who treated hospitalized patients with COVID-19 in Brazil for at least two months were eligible to complete the survey. In Brazil, there is no sampling frame of physiotherapists who worked at referral hospitals for treating patients with COVID-19. According to the Brazilian federal government, we had a mean number of 40,000 ICU beds during the first 15 months of the COVID-19 pandemic. The number of physiotherapists working with patients with COVID-19 could have been estimated on the basis of the number of ICU beds but would probably have been inaccurate. Physiotherapy services differ tremendously among hospitals and regions in Brazil regarding duration of shifts, number of physiotherapists per ICU bed, and others. Therefore, it was not possible to conduct a sample size calculation. Instead, a recruitment strategy based on the snowball effect and the support of professional network groups to spread the survey were employed.

Invitations to participate in the survey were sent to potential participants by social media and e-mails, and these potential participants were encouraged to forward the link of the survey to other colleagues. The *Associação Brasileira de Fisioterapia Cardiorrespiratória e Fisioterapia em Terapia Intensiva* (ASSOBRAFIR, Brazilian Association of Cardiorespiratory Physiotherapy and Intensive Care Physiotherapy) and the *Conselhos Regionais de Fisioterapia e Terapia Ocupacional* (CREFITO, Regional Councils of Physiotherapy and Occupational Therapy) in four states and in one region of Brazil (São Paulo, Minas Gerais, Pernambuco, Rondônia, and northern region) supported the study by sending the survey to their associates.

A committee of experts developed the survey after several meetings. The group consisted of 6 experienced physiotherapists who are professors at federal universities from five different Brazilian states. The survey was designed within a secure, web-based software platform—REDCap[18]—hosted at the *Universidade Federal do Ceará*. The first version of the instrument was previously tested for content validity, clarity, relevance, and completeness by 15 physiotherapists with different experience levels and from different regions of Brazil. Thereafter, the committee discussed their suggestions, and minor modifications were made to the final version of the instrument.

The survey consisted of 50 questions regarding professional information, characteristics of the respondent's hospital of employment, reasons for indications for physiotherapy, and respiratory/mobilization interventions. When answering questions regarding the application of the techniques, participants were requested to consider that the patients had favorable clinical conditions for their use. More information regarding the survey is presented in the supplementary material.

The questions regarding indications for physiotherapy and the interventions used were closed-ended and scored on a five-point Likert scale; response options were "very frequently", "frequently", "occasionally", "rarely", or "never." Questions that inquired about using a specific instrument, such as mechanical in-exsufflation (MI-E), also had a "not available" option. Responses marked as "rarely" or "never" opened another question asking why that specific instrument or technique was "rarely" or "never" used.

The estimated time to complete the survey varied between 10-12 min for physiotherapists working in ICUs or wards and 20-25 min for those who worked at both settings. Respondents who worked in both settings and completed the survey in less than 10 minutes were excluded from the analysis. A copy of the survey is available in the supplementary material.

Data were summarized using descriptive statistics reported as median (IQR) or absolute and relative frequencies for categorical data.

RESULTS

After removing 60 duplicates, the number of physiotherapists who consented to participate and initiated the questionnaire was 643, of whom 488

completed the survey, yielding a completion rate of 76%. However, 3 respondents were excluded because they completed the survey in less than 10 min.

Characteristics of the respondents (N = 485) and the primary hospital of employment are shown in Table 1. The median age of the physiotherapists was 33 years, and the median length of professional experience was 9 years. The most common characteristics of the participants were having a specialization degree (80%), working at hospitals for > 5 years (52%), and working at both wards and ICUs (47%). Most worked at a public hospital (66%) that was not connected to a university (61%) and had some training on COVID-19 (88%). Their median experience treating patients with COVID-19 was 15 months, and the median number of patients seen per shift of 6 h in the ICU was 10.

Table 1. Characteristics of the respondents (N = 485).[a]

Variable	Result
Age, years	33 [28-40]
Male gender	126 (26)
Brazilian regions	
Southeast	298 (61)
Northeast	102 (21)
South	54 (11)
Central-West	21 (4)
North	10 (2)
Years since graduation	9 [4-15]
Qualifications	
Specialization degree[b]	390 (80)
Stricto sensu graduate degree	96 (20)
Certified specialist	61 (13)
Hospitalist experience, months	
< 3	7 (1)
3-11	56 (12)
12-60	169 (35)
> 61	253 (52)
Work setting	
Ward	47 (10)
ICU	213 (44)
Both	225 (47)
Type of hospital	
Public	320 (66)
Private	124 (26)
Other	41 (9)
University hospital	
Yes	188 (39)
Patients seen in the ICU per a six-hour shift	10 [7-10]
Hospitalist experience with COVID-19, months	15 [12-16]
Training in COVID-19	
Yes	425 (88)
Type of training in COVID-19	
Virtual	380 (78)
Virtual (10 h at least)	224 (46)
Reading articles	391 (81)

[a]Values expressed as n (%) or median [IQR]. [b]Specialization degrees must have a minimum workload of 360 h.

Perceived reasons for indications for physiotherapy in the ICU and the ward

The frequency of perceived reasons for indications for physiotherapy is shown in Figure 1. Mechanical ventilation management, oxygenation improvement, mechanical ventilation weaning, airway clearance, lung expansion, and prevention of pulmonary and general complications were reported a frequent indication for physiotherapy by the majority (> 80%) of the respondents working in the ICU. Avoidance of physical deconditioning, which included recovering or preserving aerobic capacity and muscle strength, was reported as a frequent indication for physiotherapy by less than 65% of the physiotherapists.

Oxygenation improvement, reduction of work of breathing, and prevention of pulmonary and general complications were considered frequent indications for physiotherapy by more than 80% of the respondents working in the ward. However, avoidance of physical deconditioning was considered a frequent indication by less than 58% of the respondents, whereas airway clearance was reported as "rarely' or "never" by 46% of the respondents.

Physiotherapy practice in the ICU

Figure 2 illustrates the frequencies of reported respiratory and mobilization interventions for patients with COVID-19 on mechanical ventilation. The most frequently reported airway clearance technique was positioning (82%), followed by hard/brief expiratory rib cage compression (46%). The least frequently reported techniques were chest percussion (1%), PEEP-zero end-expiratory pressure (PEEP-ZEEP) maneuver (13%), and manual hyperinflation (18%). For lung expansion, the most frequently cited interventions were positioning (89%) and alveolar recruitment maneuver (73%), whereas manual hyperinflation was the least cited one (15%).

Regarding mobilization, active and resistive range of motion exercises, sitting on the edge of the bed, standing, ambulation, and stepping in place were reported as "very frequently" and "frequently" by more than 70% of the respondents. The least frequently cited ones were neuromuscular electrical stimulation (NMES), squats, and climbing steps. However, among the 54% of the respondents who "never" cited NMES, 39% reported that the device was unavailable at their institutions, the same occurring with cycle ergometers, in 20% and 14%, respectively (Figure 2).

Figure 3 shows the reasons for selecting "never" or "rarely" regarding the use the survey's least frequently reported respiratory interventions. Clearly, the main reason for not using manual hyperinflation for neither airway clearance nor lung expansion was biosecurity due to the risk of aerosol production. Almost 70%, 35%, and 34% of the physiotherapists, respectively, did not know how to apply expiratory

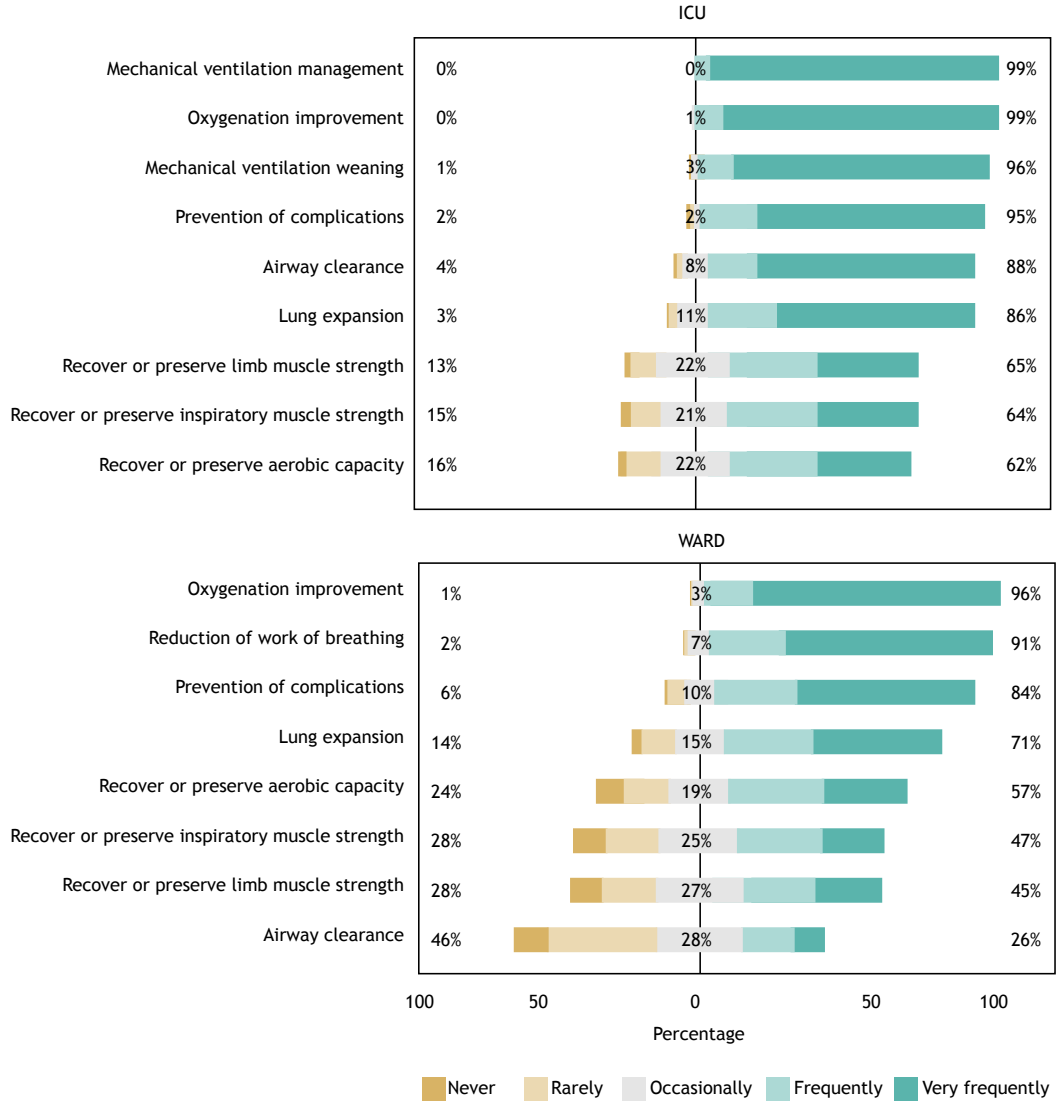


Figure 1. Frequencies of perceived reasons for indications for physiotherapy for patients with COVID-19 admitted to the ICU and the ward.

flow bias, ventilator hyperinflation, and the PEEP-ZEEP maneuver. Chest percussion, vibration, and manual chest compression-decompression (MCCD) maneuver were reported as "never" or "rarely" used mainly due to the belief that these techniques have no scientific evidence supporting their efficacy and that there are others that are more effective. Detailed reasons for selecting "never" or "rarely" regarding the use of each of the surveyed respiratory interventions are shown in Tables S1 and S2.

Ninety percent of the respondents who reported "never" or "rarely" using passive range of motion exercises believed that other techniques were more effective. The most common reasons for not using squats or climbing steps were the poor functional status of most patients with COVID-19 and the critical clinical condition of most patients (Table S3).

Physiotherapy practice in the ward

Figure 4 illustrates the frequencies of respiratory and mobilization interventions for patients with COVID-19 breathing spontaneously. The most frequently cited airway clearance techniques were positioning, in 78%; directed/assisted cough, in 75%; active cycle of breathing technique (ACBT), in 64%; and forced expiratory technique (FET), in 59%. The least frequently reported ones were percussion (1%), autogenic drainage (20%), and vibration (35%). For lung expansion, the most frequently cited interventions were active prone positioning (90%) and deep breathing exercises (88%). Only squat, climbing steps, and NMES were less commonly reported for avoidance of deconditioning. NMES and cycle ergometer were "never" used by 41% of 68% of the respondents and

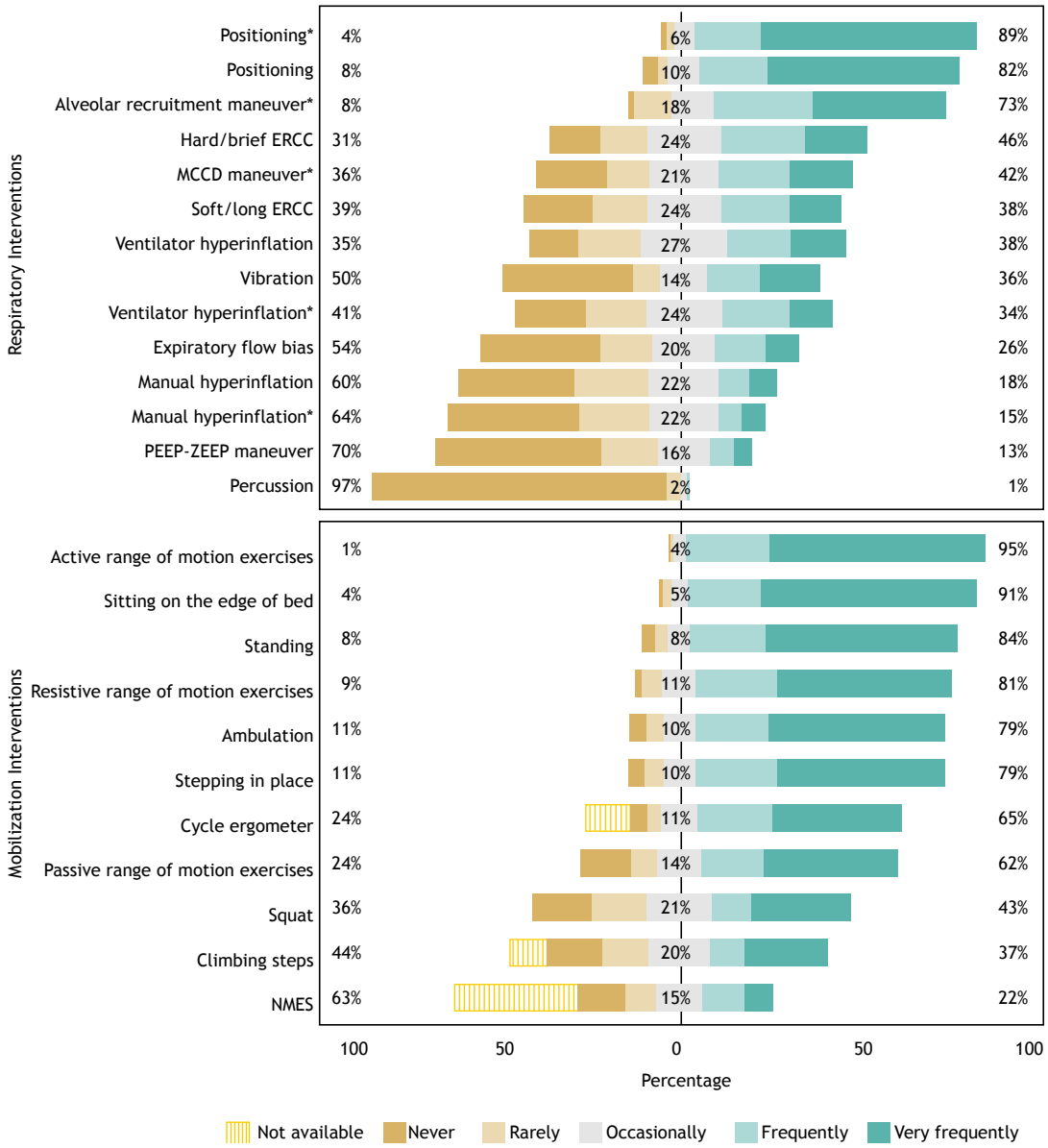


Figure 2. Frequencies of reported respiratory and mobilization interventions for mechanically ventilated patients. Respiratory interventions include techniques for lung expansion and airway clearance. ERCC: expiratory rib cage compression; MCCD: manual chest compression-decompression; ZEEP: zero end-expiratory pressure; and NMES: neuromuscular electrical stimulation. *Techniques used for lung expansion.

by 15% of 24%, respectively, because the devices were unavailable at their institutions.

The instrumental interventions less commonly used were MI-E (86%), incentive spirometry (77%), and oscillatory positive expiratory pressure (PEP) devices (70%; Figure S1). However, a significant proportion of physiotherapists informed that MI-E (48%) and oscillatory PEP devices (31%) were unavailable at their institutions.

Figure 5 shows the reasons for selecting "never" or "rarely" regarding the use of the survey's least frequently cited respiratory interventions. The most frequently declared reason for not using percussion and incentive spirometry was that the techniques have no scientific support; with regard to vibration, autogenic drainage, oscillatory PEP, intermittent positive pressure breathing, and MCCD, the main reason was that there are other more effective techniques; and PEP masks were never/rarely used because they were not part of their institution's protocol. Oscillatory PEP and intermittent positive pressure breathing were also less frequently applied because of biosecurity reasons. A common reason for not using MI-E was that the technique was not part of their institution's

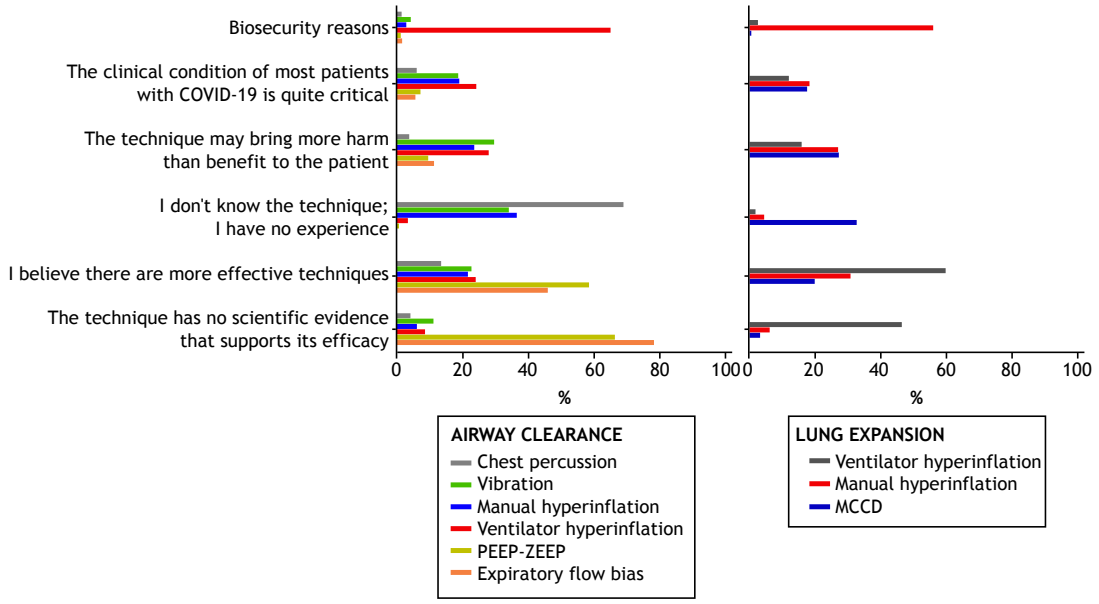


Figure 3. Reported reasons for selecting "never" or "rarely" regarding the use of the survey's least frequently cited respiratory chest physiotherapy techniques for mechanically ventilated patients. Interventions to assist airway clearance are displayed on the left and those to promote lung expansion are displayed on the right. ZEEP: zero end-expiratory pressure, and MCCD: manual chest compression-decompression.

protocol, but also the fact that they did not know how to use it.

The most frequently reported reason for not using squats or climbing steps was the poor functional status of most patients with COVID-19. Detailed reasons for selecting "never" or "rarely" regarding the use of each of the surveyed respiratory and mobilization interventions are shown in Tables S4 to S6.

DISCUSSION

This is the first study to describe self-reported answers about indications for physiotherapy and physiotherapy practice in hospitalized patients with COVID-19. The least frequent reason for indications for physiotherapy in patients on mechanical ventilation was avoidance of physical deconditioning, which included recovering or preserving aerobic capacity and muscle strength. In spontaneously breathing patients, avoidance of deconditioning was also less frequently reported along with airway clearance. Moreover, the present study revealed great variability in respiratory interventions compared with mobilization practices for both mechanically ventilated and spontaneously breathing patients, and there was an underutilization of techniques that are considered effective.

The low number of referrals for mobilization therapy might have at least two explanations: the critical condition of patients with COVID-19 and the high demand for respiratory treatment combined with limited staff. Due to the increased number of hospitalizations during the pandemic, patients with COVID-19 referred to physiotherapy usually had severe or critical illness, limiting mobilization interventions. An observational study conducted in the United Kingdom reported that the mean time to first mobilize ICU patients with COVID-19 was 14 days owing to the severity of illness,[5] whereas the time to first mobilize ICU patients without COVID-19 was 8 days in a previous study by the same group.[19] The high demand for respiratory treatment combined with limited staff is supported by the finding that the respondents treated a median of 10 patients in a 6-h shift. This means that considering that it takes at least 1 h to solve bureaucratic assignments, such as registering physiotherapy sessions in the patients' records, they had 30 min per patient, which is quite tricky to deliver complete treatment and use personal protective equipment (PPE) appropriately, as recommended. This is in accordance with the study by Li et al.,[20] who reported that physiotherapy sessions, including respiratory management and mobility exercises, for patients with COVID-19 lasted 30-40 min, without including PPE donning and doffing time. In addition, to reinforce this point of view, it has been shown that more than one person is needed to mobilize a critically ill patient on mechanical ventilation safely.[21]

Although airway clearance was considered a frequent indication for physiotherapy in mechanically ventilated, only 26% of the respondents reported it as a frequent indication for physiotherapy in patients breathing spontaneously in the ward. This result agrees with studies that have reported that retained airway secretions was expected to occur in only 28-33% of patients with severe COVID-19 admitted to the ward.[22,23]

The indications for physiotherapy most frequently reported by the respondents working in the

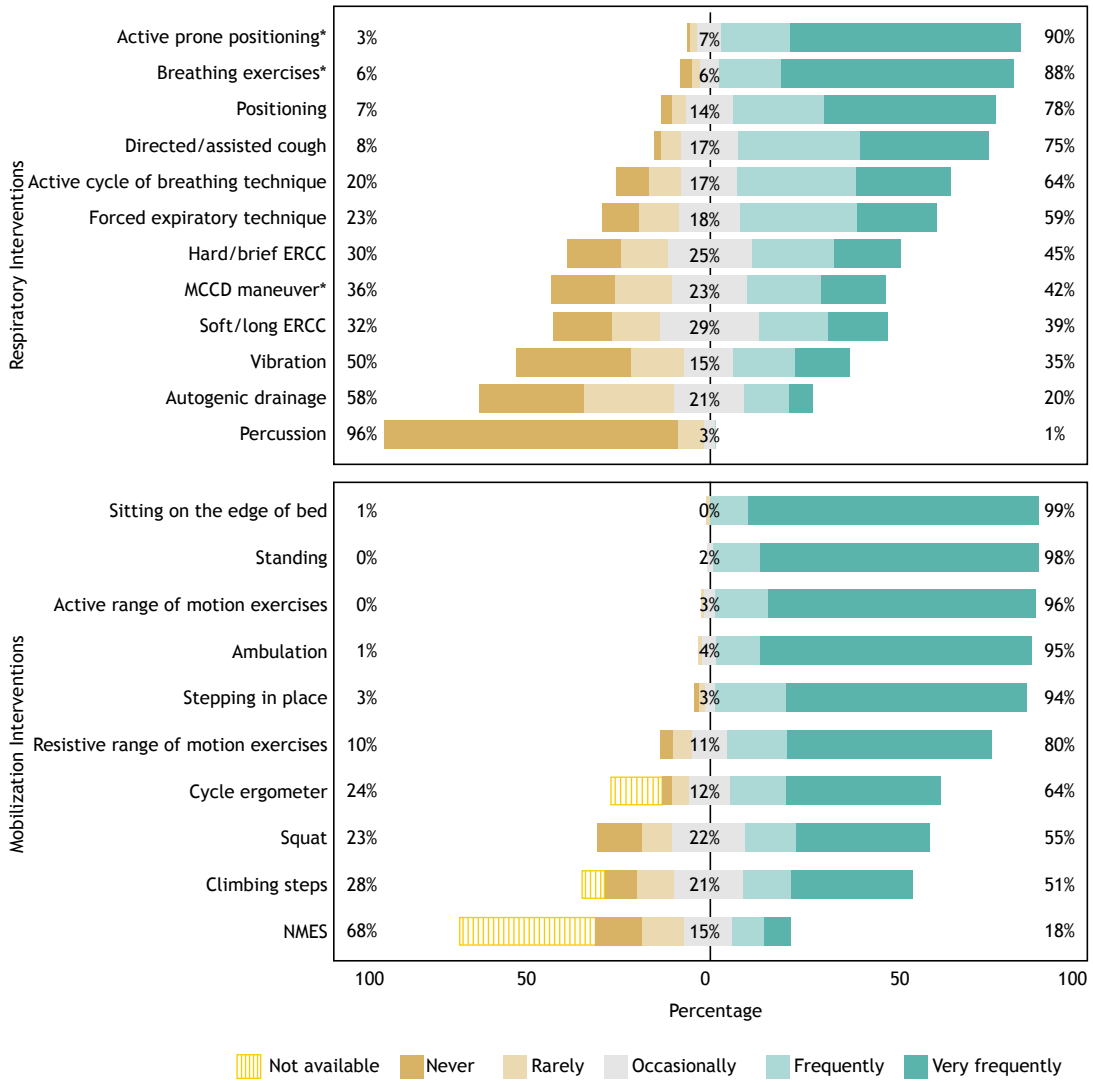


Figure 4. Frequencies of reported respiratory and mobilization interventions for spontaneously breathing patients in the ward. Respiratory interventions include techniques for lung expansion and airway clearance. ERCC: expiratory rib cage compression; MCCD: manual chest compression-decompression; ZEEP: zero end-expiratory pressure; and NMES: neuromuscular electric stimulation. *Techniques used for lung expansion.

ICU—mechanical ventilation management and oxygenation improvement—and by those working in the ward—also oxygenation improvement and reduction of work of breathing—reinforce the severity of respiratory illness of hospitalized patients with COVID-19.

Noticeably, the reported use of respiratory interventions was more erratic than that of mobilization interventions both in the ICU and the ward. This might be explained by the lack of consensus worldwide about the most effective respiratory interventions for mechanically ventilated and spontaneously breathing patients.[11-13] In addition, COVID-19, as a new disease, might have brought more uncertainty to physiotherapists during their practice.

In our study, manual techniques were less frequently applied for both mechanically ventilated and spontaneously breathing patients. Indeed, percussion and vibration were rejected by 96% and 50% of the respondents, respectively, mainly because they believed that there was no scientific evidence supporting their efficacy. Hard/brief expiratory rib cage compression and MCCD were the most commonly manual techniques applied, but only by 45% and 42% of the respondents, respectively. Because physiotherapists were instructed always to consider the benefits of hands-on treatment versus the risks of virus transmission and PPE was scarce,[14] the decision not to use manual interventions might have been strengthened.

In the case of mechanically ventilated patients, manual hyperinflation, a procedure that is widely contraindicated in the guidelines because of aerosol production, was applied by only 15-18% of the

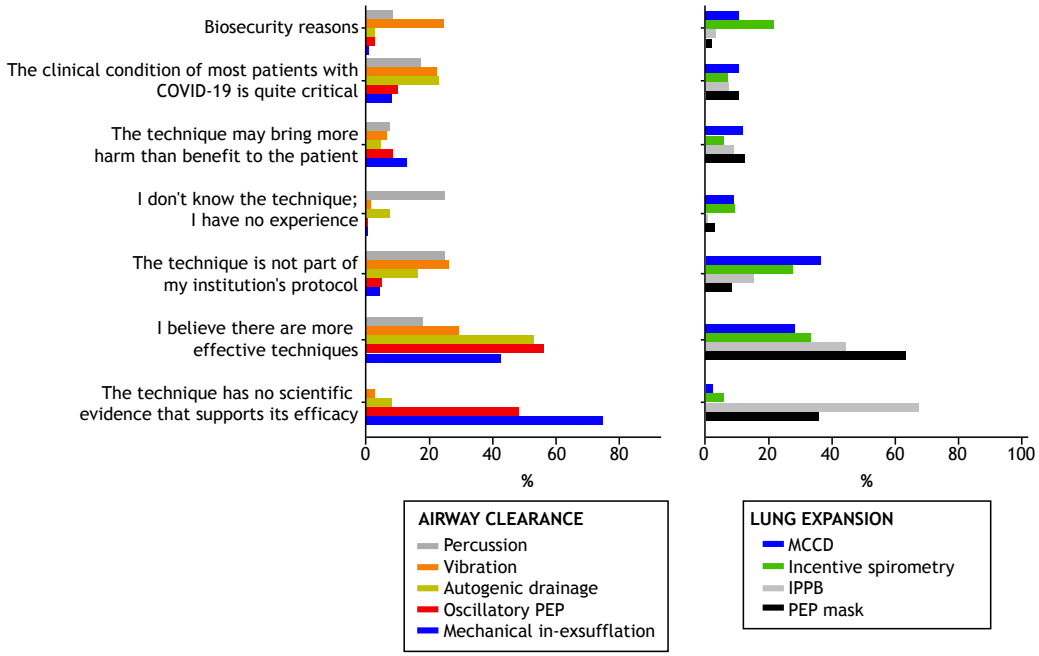


Figure 5. Reported reasons for selecting "never" or "rarely" regarding the use of the survey's least frequently cited chest physiotherapy techniques for spontaneously breathing patients. Interventions to assist airway clearance are displayed on the left and those to promote lung expansion are displayed on the right. PEP: positive expiratory pressure; MCCD: manual chest compression-decompression; and IPPB: intermittent positive pressure breathing.

respondents.[7] PEEP-ZEEP maneuver, ventilator hyperinflation, and especially expiratory flow bias were infrequently applied, because the respondents did not know or have experience applying these techniques. Since the use of expiratory flow bias has a clear rationale[24,25] and ventilator hyperinflation is as effective as manual hyperinflation—with advantages and no risk of aerosol dispersion[7,26]—these results portray the delay between the production of knowledge and its incorporation into clinical practice. The second main reason for not applying PEEP-ZEEP and ventilator hyperinflation was that the respondents believed that these techniques could bring more harm than benefits to the patient. Some professionals were likely to be wary of applying high distension pressures and ZEEP in the context of COVID-19 due to the risk of augmenting lung injury.[27,28] Indeed, it is worth mentioning that the PEEP-ZEEP maneuver and the use of expiratory flow bias require more studies to support their application.[29,30]

Techniques that use airflow modulation to assist secretion removal are considered effective for patients with mucus hypersecretion and are usually preferred by them.[31,32] Of those techniques, ACBT was recommended by most guidelines for hospitalized patients with COVID-19.[7,14,16,33] According to our survey, ACBT, FET, and autogenic drainage were used by 64%, 59%, and 28% of the respondents, respectively. The main reason for not using ACBT, FET, and especially autogenic drainage was that the respondents believed that there were other more effective techniques. These results suggested that the respondents might not be well instructed in those techniques. A more plausible reason for not using airflow modulation techniques would be the critical condition of patients with COVID-19. All techniques actively performed by the patient may increase the work of breathing, which is not recommended to patients with moderate/severe illness, especially those with low respiratory reserve.[6]

Indeed, the poor functional status of patients with COVID-19 was the most frequently reported reason for not using squats and climbing steps during mobilization therapy. These exercises are highly energy demanding for most patients with COVID-19, and the guidelines recommend that exercise intensity be set from light to moderate depending on the patient's clinical condition. For instance, Righetti et al.[9] recommended using a score < 3 on the modified Borg rating of perceived exertion scale for patients with mild COVID-19 in the acute phase, whereas Zhao et al.[34] suggested a score ≤ 3 for mild disease and < 3 for moderate disease.

Concerning instrumental interventions, incentive spirometry and oscillatory PEP were extremely underutilized at the institutions where they were available. Incentive spirometry, which is not recommended by two guidelines,[6,7] was rejected by almost 70% of the respondents, because they believe that no scientific evidence supported its use. Oscillatory PEP was included in the list of potentially aerosol-generating procedures, which probably explains the poor adherence to this technique.[7]

Surprisingly, most respondents had a specialization degree in physiotherapy related to hospital practice, but this did not prevent the underutilization of effective techniques. In order to have such a degree, participants must have a minimum of 360 h of training. However, no further information was collected to determine the quality of the programs; for example, whether a specialization program was accredited by the Brazilian Ministry of Education.

This study has some limitations. First, a convenience sample was used, which may not accurately represent physiotherapists in Brazil. However, the sample in this study included respondents from all Brazilian regions, although in different proportions. Second, because the respondents were instructed to answer the questions considering that the patients' safety criteria for use of the techniques were met, the percentages of reported interventions might differ from physiotherapy practice in the actual scenario. Therefore, the results of this study reflect preferences, perceptions of, and limitations to practice of the physiotherapists involved in treating patients with COVID-19.

This survey of self-reported physiotherapy practice revealed that the least common reason for the indication for physiotherapy was avoidance of deconditioning, whereas oxygenation improvement was the most frequent one for both mechanically ventilated and spontaneously breathing patients with COVID-19. It also revealed great variability in respiratory interventions in comparison with mobilization therapies. Moreover, it brought to light some gaps regarding physiotherapists' understanding of respiratory interventions, as well as the clear need to standardize the respiratory physiotherapy treatment for this population of patients.

Future research should first establish which physiotherapy interventions and outcomes should be investigated. Thereafter, these interventions should be evaluated through high-quality studies to clarify the best evidence-based physiotherapy treatment for critically ill patients with COVID-19.

ACKNOWLEDGMENTS

We sincerely thank all of the physiotherapists who completed the survey, as well as the ASSOBRAFIR, CREFITO-1, CREFITO-3, CREFITO-4, CREFITO-12, and CREFITO-18 for sharing the questionnaire.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

LMSD, FSG, CLF, and MSV: study design and drafting of the manuscript. LMSD and ACOO: data collection. CLF, FMP, RA, MA, and MSV: guarantors of data integrity. LMSD, FSG, CLF, and MSV: data analysis. All authors reviewed and approved the final manuscript.

REFERENCES

1. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2022 [cited 2022 Apr 3]. Coronavirus Disease (COVID-19) Dashboard. Available from: https://covid19.who.int
2. Wu Z, McGoogan JM. Characteristics of and Important Lessons From the Coronavirus Disease 2019 (COVID-19) Outbreak in China: Summary of a Report of 72 314 Cases From the Chinese Center for Disease Control and Prevention. JAMA. 2020;323(13):1239-1242. https://doi.org/10.1001/jama.2020.2648
3. Needham DM, Korupolu R, Zanni JM, Pradhan P, Colantuoni E, Palmer JB, et al. Early physical medicine and rehabilitation for patients with acute respiratory failure: a quality improvement project. Arch Phys Med Rehabil. 2010;91(4):536-542. https://doi.org/10.1016/j.apmr.2010.01.002
4. Morris PE, Griffin L, Berry M, Thompson C, Hite RD, Winkelman C, et al. Receiving early mobility during an intensive care unit admission is a predictor of improved outcomes in acute respiratory failure. Am J Med Sci. 2011;341(5):373-377. https://doi.org/10.1097/MAJ.0b013e31820ab4f6
5. McWilliams D, Weblin J, Hodson J, Veenith T, Whitehouse T, Snelson C. Rehabilitation Levels in Patients with COVID-19 Admitted to Intensive Care Requiring Invasive Ventilation. An Observational Study. Ann Am Thorac Soc. 2021;18(1):122-129. https://doi.org/10.1513/AnnalsATS.202005-560OC
6. Lazzeri M, Lanza A, Bellini R, Bellofiore A, Cecchetto S, Colombo A, et al. Respiratory physiotherapy in patients with COVID-19 infection in acute setting: a Position Paper of the Italian Association of Respiratory Physiotherapists (ARIR). Monaldi Arch Chest Dis. 2020;90(1):10.4081/monaldi.2020.1285. https://doi.org/10.4081/monaldi.2020.1285
7. Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. J Physiother. 2020;66(2):73-82. https://doi.org/10.1016/j.jphys.2020.03.011
8. Newman ANL, Kho ME, Harris JE, Fox-Robichaud A, Solomon P. Survey of Physiotherapy Practice in Ontario Cardiac Surgery Intensive Care Units. Physiother Can. 2022;74(1):25-32. https://doi.org/10.3138/ptc-2020-0069
9. Righetti RF, Onoue MA, Politi FVA, Teixeira DT, Souza PN, Kondo CS, et al. Physiotherapy Care of Patients with Coronavirus Disease 2019 (COVID-19) - A Brazilian Experience. Clinics (Sao Paulo). 2020;75:e2017. https://doi.org/10.6061/clinics/2020/e2017
10. Gosselink R, Bott J, Johnson M, Dean E, Nava S, Norrenberg M, et al. Physiotherapy for adult patients with critical illness: recommendations of the European Respiratory Society and European Society of Intensive Care Medicine Task Force on Physiotherapy for Critically Ill Patients. Intensive Care Med. 2008;34(7):1188-1199. https://doi.org/10.1007/s00134-008-1026-7
11. Stiller K. Physiotherapy in intensive care: an updated systematic review. Chest. 2013;144(3):825-847. https://doi.org/10.1378/chest.12-2930
12. van der Lee L, Hill AM, Patman S. A survey of clinicians regarding respiratory physiotherapy intervention for intubated and mechanically ventilated patients with community-acquired pneumonia. What is current practice in Australian ICUs?. J Eval Clin Pract. 2017;23(4):812-820. https://doi.org/10.1111/jep.12722
13. van der Lee L, Hill AM, Jacques A, Patman S. Efficacy of Respiratory Physiotherapy Interventions for Intubated and Mechanically Ventilated Adults with Pneumonia: A Systematic Review and Meta-Analysis. Physiother Can. 2021;73(1):6-18. https://doi.org/10.3138/ptc-2019-0025
14. Felten-Barentsz KM, van Oorsouw R, Klooster E, Koenders N, Driehuis F, Hulzebos EHJ, et al. Recommendations for Hospital-Based Physical Therapists Managing Patients With COVID-19. Phys Ther. 2020;100(9):1444-1457. https://doi.org/10.1093/ptj/pzaa114
15. Vitacca M, Carone M, Clini EM, Paneroni M, Lazzeri M, Lanza A,

et al. Joint Statement on the Role of Respiratory Rehabilitation in the COVID-19 Crisis: The Italian Position Paper. Respiration. 2020;99(6):493-499. https://doi.org/10.1159/000508399

16. Jiandani MP, Agarwal B, Baxi G, Kale S, Pol T, Bhise A, et al. Evidence-based National Consensus: Recommendations for Physiotherapy Management in COVID-19 in Acute Care Indian Setup. Indian J Crit Care Med. 2020;24(10):905-913. https://doi.org/10.5005/jp-journals-10071-23564
17. Sharma A, Minh Duc NT, Luu Lam Thang T, Nam NH, Ng SJ, Abbas KS, et al. A Consensus-Based Checklist for Reporting of Survey Studies (CROSS). J Gen Intern Med. 2021;36(10):3179-3187. https://doi.org/10.1007/s11606-021-06737-1
18. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)–a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform. 2009;42(2):377-381. https://doi.org/10.1016/j.jbi.2008.08.010
19. McWilliams D, Jones C, Atkins G, Hodson J, Whitehouse T, Veenith T, et al. Earlier and enhanced rehabilitation of mechanically ventilated patients in critical care: A feasibility randomised controlled trial. J Crit Care. 2018;44:407-412. https://doi.org/10.1016/j.jcrc.2018.01.001
20. Li L, Yu P, Yang M, Xie W, Huang L, He C, et al. Physical Therapist Management of COVID-19 in the Intensive Care Unit: The West China Hospital Experience. Phys Ther. 2021;101(1):pzaa198. https://doi.org/10.1093/ptj/pzaa198
21. Pawlik AJ, Kress JP. Issues affecting the delivery of physical therapy services for individuals with critical illness. Phys Ther. 2013;93(2):256-265. https://doi.org/10.2522/ptj.20110445
22. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. N Engl J Med. 2020;382(18):1708-1720. https://doi.org/10.1056/NEJMoa2002032
23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China [published correction appears in Lancet. 2020 Jan 30;:]. Lancet. 2020;395(10223):497-506. https://doi.org/10.1016/S0140-6736(20)30183-5
24. Volpe MS, Adams AB, Amato MB, Marini JJ. Ventilation patterns influence airway secretion movement. Respir Care. 2008;53(10):1287-1294.
25. Li Bassi G, Saucedo L, Marti JD, Rigol M, Esperatti M, Luque N, et al. Effects of duty cycle and positive end-expiratory pressure on mucus clearance during mechanical ventilation*. Crit Care Med. 2012;40(3):895-902. https://doi.org/10.1097/CCM.0b013e318236efb5
26. Paulus F, Binnekade JM, Vroom MB, Schultz MJ. Benefits and risks of manual hyperinflation in intubated and mechanically ventilated intensive care unit patients: a systematic review. Crit Care. 2012;16(4):R145. https://doi.org/10.1186/cc11457
27. Slutsky AS. Lung injury caused by mechanical ventilation. Chest. 1999;116(1 Suppl):9S-15S. https://doi.org/10.1378/chest.116.suppl_1.9S-a
28. Matthay MA, Aldrich JM, Gotts JE. Treatment for severe acute respiratory distress syndrome from COVID-19. Lancet Respir Med. 2020;8(5):433-434. https://doi.org/10.1016/S2213-2600(20)30127-2
29. Amaral BLR, de Figueiredo AB, Lorena DM, Oliveira ACO, Carvalho NC, Volpe MS. Effects of ventilation mode and manual chest compression on flow bias during the positive end- and zero end-expiratory pressure manoeuvre in mechanically ventilated patients: a randomised crossover trial. Physiotherapy. 2020;106:145-153. https://doi.org/10.1016/j.physio.2018.12.007
30. Volpe MS, Guimarães FS, Morais CC. Airway Clearance Techniques for Mechanically Ventilated Patients: Insights for Optimization. Respir Care. 2020;65(8):1174-1188. https://doi.org/10.4187/respcare.07904
31. McIlwaine M, Bradley J, Elborn JS, Moran F. Personalising airway clearance in chronic lung disease. Eur Respir Rev. 2017;26(143):160086. https://doi.org/10.1183/16000617.0086-2016
32. Fink JB. Forced expiratory technique, directed cough, and autogenic drainage. Respir Care. 2007;52(9):1210-1223.
33. Battaglini D, Robba C, Caiffa S, Ball L, Brunetti I, Loconte M, et al. Chest physiotherapy: An important adjuvant in critically ill mechanically ventilated patients with COVID-19. Respir Physiol Neurobiol. 2020;282:103529. https://doi.org/10.1016/j.resp.2020.103529
34. Zhao HM, Xie YX, Wang C; Chinese Association of Rehabilitation Medicine; Respiratory Rehabilitation Committee of Chinese Association of Rehabilitation Medicine; Cardiopulmonary Rehabilitation Group of Chinese Society of Physical Medicine and Rehabilitation. Recommendations for respiratory rehabilitation in adults with coronavirus disease 2019. Chin Med J (Engl). 2020;133(13):1595-1602. https://doi.org/10.1097/CM9.0000000000000848

J Bras Pneumol. 2022;48(4):e20210329
https://dx.doi.org/10.36416/1806-3756/e20210329

PET/CT and inflammatory mediators in systemic sclerosis-associated interstitial lung disease

Andréa L Bastos[1], Gilda A Ferreira[2], Marcelo Mamede[1], Eliane V Mancuzo[3], Mauro M Teixeira[4], Flávia P S T Santos[5], Cid S Ferreira[6], Ricardo A Correa[3]

1. Departamento de Anatomia e Imagem, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
2. Departamento do Aparelho Locomotor, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
3. Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
4. Departamento de Bioquímica e Imunologia, Instituto de Ciências Biológicas, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
5. Serviço de Reumatologia, Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
6. Departamento de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.

Submitted: 7 October 2021.
Accepted: 3 March 2022.

Study carried out under the auspices of the Programa de Pós-Graduação em Ciências Aplicadas à Saúde do Adulto, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To investigate the correlation of HRCT findings with pulmonary metabolic activity in the corresponding regions using ^{18}F-FDG PET/CT and inflammatory markers in patients with systemic sclerosis (SSc)-associated interstitial lung disease (ILD). **Methods:** This was a cross-sectional study involving 23 adult patients with SSc-associated ILD without other connective tissue diseases. The study also involved ^{18}F-FDG PET/CT, HRCT, determination of serum chemokine levels, clinical data, and pulmonary function testing. **Results:** In this cohort of patients with long-term disease (disease duration, 11.8 ± 8.7 years), a nonspecific interstitial pneumonia pattern was found in 19 (82.6%). Honeycombing areas had higher median standardized uptake values (1.95; p = 0.85). Serum levels of soluble tumor necrosis factor receptor 1, soluble tumor necrosis factor receptor 2, C-C motif chemokine ligand 2 (CCL2), and C-X-C motif chemokine ligand 10 were higher in SSc patients than in controls. Serum levels of CCL2—a marker of fibroblast activity—were correlated with pure ground-glass opacity (GGO) areas on HRCT scans (p = 0.007). ^{18}F-FDG PET/CT showed significant metabolic activity for all HRCT patterns. The correlation between serum CCL2 levels and GGO on HRCT scans suggests a central role of fibroblasts in these areas, adding new information towards the understanding of the mechanisms surrounding cellular and molecular elements and their expression on HRCT scans in patients with SSc-associated ILD. **Conclusions:** ^{18}F-FDG PET/CT appears to be unable to differentiate the intensity of metabolic activity across HRCT patterns in chronic SSc patients. The association between CCL2 and GGO might be related to fibroblast activity in these areas; however, upregulated CCL2 expression in the lung tissue of SSc patients should be investigated in order to gain a better understanding of this association.

Keywords: Tomography; Lung diseases, interstitial; Scleroderma, systemic; Cytokines.

INTRODUCTION

In patients with systemic sclerosis (SSc), interstitial lung disease (ILD) and pulmonary hypertension are the main causes of impaired quality of life and mortality. SSc-associated ILD involves autoantibody activity, inflammation, obstruction of small vessels, and tissue collagen deposition that further develops into fibrosis.[1] It often occurs in diffuse cutaneous form and may take on varied expressions throughout its progression.[2] A histological pattern of nonspecific interstitial pneumonia (NSIP) predominates, and usual interstitial pneumonia (UIP) and organizing pneumonia (OP) are seldom found.[1,3] A newly described pattern of interstitial lung involvement is centrilobular fibrosis, which has been associated with chronic pulmonary aspiration through gastroesophageal reflux.[4] Lung pathology is the gold standard method for an accurate classification of ILD. Open lung biopsy is an invasive procedure and is indicated in only a few cases because of its potential risks. Because of a strong correlation between a reticular pattern and fibrosis, HRCT has gained a central role in determining the nature of interstitial lung involvement, as well as in establishing referral criteria for biopsies and other procedures in selected cases.[5] However, HRCT is less accurate in cases of ground-glass opacity (GGO) because this pattern may be related to both inflammation and interstitial fibrosis.[6,7]

The literature reports on the usefulness of ^{18}F-FDG PET/CT in the evaluation of non-neoplastic and connective tissue diseases,[8] as well as pulmonary inflammatory conditions[9,10] and pulmonary fibrotic conditions.[11-13] For the evaluation of pulmonary metabolism, ^{18}F-FDG PET/CT has the advantage of being a noninvasive technique and allowing quantitative assessment of the entire lung during image acquisition. However, radiation exposure

Correspondence to:
Andréa Lima Bastos. Departamento de Anatomia e Imagem, Faculdade de Medicina, Universidade Federal de Minas Gerais, Avenida Prof. Alfredo Balena, 190, Sala 179, CEP 30130-100, Belo Horizonte, MG, Brasil.
Tel.: 55 31 3409-9770. E-mail: andblima@yahoo.com.br
Financial support: None.

ISSN 1806-3756

should be taken into consideration. Although PET radiation exposure is mainly due to the incorporation of radiopharmaceuticals, the combined use of PET and HRCT may increase this exposure. However, in most cases the benefits (i.e., the information provided) outweigh the risks and justify the use of the method both in clinical practice and in research. In addition, radiation exposure should be optimized to a dose as low as reasonably achievable.

In SSc, the activation of macrophages and T cells in the bloodstream and tissues is responsible for the characteristic damage that occurs at the expense of the production of mediators that regulate inflammation and fibrosis. These mediators have been investigated as potential surrogates of inflammatory and fibrotic activity.[14] Inflammatory mediators that originate from various sources, such as the alveolar epithelium, macrophages, activated T lymphocytes, and the endothelium, are related to interstitial damage.[14,15] Soluble tumor necrosis factor receptor 1 (sTNFR1), soluble tumor necrosis factor receptor 2 (sTNFR2), C-X-C motif chemokine ligand 8 (CXCL8), macrophage migration inhibitory factor (MIF), C-C motif chemokine ligand 2 (CCL2), C-X-C motif chemokine ligand 9 (CXCL9), and C-X-C motif chemokine ligand 10 (CXCL10) have been investigated.[15]

The objective of this study was to investigate the correlation of HRCT findings with pulmonary metabolic activity in the corresponding regions using ^{18}F-FDG PET/CT and inflammatory markers in patients with SSc-associated ILD.

METHODS

This was a cross-sectional study conducted in the Pulmonology and Rheumatology Departments of the Federal University of Minas Gerais *Hospital das Clínicas*, located in the city of Belo Horizonte, Brazil. Adult SSc patients (> 18 years of age) with interstitial lung involvement on HRCT scans were recruited. The diagnosis of SSc-associated ILD was made in accordance with the 2013 American College of Rheumatology criteria.[16] The study was approved by the local research ethics committee, and all participants gave written informed consent. The exclusion criteria were as follows: overlapping of SSc with other connective tissue diseases, current or prior smoking, a diagnosis of occupational lung disease, acute or chronic infectious pulmonary disease, known exposure to toxic environmental antigens or toxic drugs, previous use of antineoplastic chemotherapy, pulse therapy with cyclophosphamide and/or methylprednisolone within six months of inclusion in the study, and HRCT signs suggestive of pulmonary aspiration. Serum levels of inflammatory mediators, clinical data, and lung function data were collected concurrently with the imaging examinations.

^{18}F-FDG PET-CT and HRCT were performed with a PET/CT scanner (Discovery 690; GE Healthcare, Milwaukee, WI, USA) coupled to a 64-channel CT scanner (LightSpeed VCT; GE Healthcare). The study participants fasted for at least 6 h and were checked for blood glucose levels prior to intravenous administration of 3.7 MBq/kg (0.1 mCi/kg) of the radiopharmaceutical ^{18}F-FDG.[11,12]

Approximately 50 min after ^{18}F-FDG administration, HRCT was performed from the lung apex to the base in the supine position and for the duration of a maximal inspiratory apnea, the following parameters being used: slice thickness, 0.6 mm; voltage, 120 kV; and current, 200 mA. The data were reconstructed with specific algorithms for a lung and mediastinum study and evaluated with a window level of −700 HU and a window width of 1,200 HU for the lung, and a window level of 40 HU and a window width of 400 HU for the mediastinum.[8]

^{18}F-FDG PET/CT images were acquired with a helical CT scanner from the skull to the thigh and with the use of a low-dose radiation protocol (voltage, 90 kV; and modulated current) to create an attenuation map and locate the anatomical regions of interest. This procedure was followed by the acquisition of molecular images in the corresponding regions; the images were acquired with the use of a 2-min acquisition time per bed position and were reconstructed in accordance with the manufacturer's iterative protocol, with 24 subgroups and 4 iterations.[8,12]

Radiopharmaceutical uptake was defined as abnormal when it was higher than the mediastinal uptake.[8,12] This procedure was performed and interpreted by a senior nuclear medicine physician who was blinded to patient clinical status and the radiological patterns, and who used the maximum standardized uptake value corrected for lean body mass (SULmax) in the axial plane. The maximum values for each lung segment were recorded.

The baseline metabolic activity of the lung parenchyma was also estimated in normal regions on HRCT scans, being used in order to determine the background lung uptake and calculate the target-to-background ratio (TBR) as described by Groves et al.[16] To quantify the mean metabolic activity in each lung lobe, the volume of interest was visually assessed on the CT images by a thoracic radiologist, the mean standardized uptake value corrected for lean body mass (SULmean) being calculated using the PMOD software, version 3.609 (Bruker Corporation, Billerica, MA, USA).

The HRCT images were analyzed by two senior radiologists who have more than 20 years of experience in chest radiology and ILD diagnosis, and who were blinded to the results of ^{18}F-FDG PET/CT. All images were read on dedicated workstations. Differences in opinion were decided by consensus among radiologists. The HRCT patterns of chronic interstitial pneumonia evaluated in the present study were NSIP, UIP, and OP. In addition, the presence of pure GGO (i.e., without concurrent interstitial lung abnormalities), honeycombing, GGO with fibrosis (a reticular pattern, bronchiectasis, or honeycombing),

and consolidation, as defined elsewhere,[17] was also analyzed. Segments without lesions were classified as normal. The reticular patterns were considered together with the other variables suggesting fibrosing disease because the participants had advanced-stage lung disease. The SULmax and SULmean for each lung lobe were compared to the HRCT patterns identified.

Pulmonary function tests were performed by a senior pulmonologist. The six-minute walk test was performed in accordance with international standards.[18] Lung volumes and DL_{CO} were obtained with the use of a Collins system (Ferraris Respiratory, Louisville, CO, USA), and the results were reported as absolute numbers and percentages in relation to the predicted values for the Brazilian population.[19]

To determine the serum levels of inflammatory mediators, blood samples were collected from sex- and age-matched SSc patients and controls before performing PET/CT because reference values have yet to be established. Chemokines were quantified by sandwich ELISA in accordance with the manufacturer instructions (R&D Systems, Minneapolis, MN, USA). Serum levels of sTNFR1, sTNFR2, and MIF were also measured.[14] The inclusion criteria for controls were as follows: being over 18 years of age, having no chronic inflammatory disease, having no malignancy, having used no immunomodulators in the six weeks preceding blood sample collection, having undergone no surgery in the previous month, having suffered no extensive trauma in the previous month, having no history of kidney or liver failure, and reporting no current pregnancy.

The normality of data distribution was verified by the Kolmogorov-Smirnov test with Lilliefors correction, the Shapiro-Wilk test, and graphical analysis. The variables were presented as median (minimum and maximum). Associations between categorical variables were evaluated by the chi-square test or Fisher's exact test, as appropriate. Univariate comparison of means and medians was performed by the Mann-Whitney U test. Correlations between continuous variables were evaluated by Pearson's or Spearman's correlation coefficient, and the Kruskal-Wallis test was used for comparison of medians in more than two groups with nonparametric distribution. Interobserver agreement was measured by Cohen's kappa statistic. All tests were performed at a significance level (α) of 0.05, with the Predictive Analytics Software package, version 18.0 for Windows (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 27 patients screened between November of 2013 and November of 2014, 2 were excluded because of an exclusive small airway pattern on HRCT scans, 1 was excluded because of the development of neoplastic disease, and 1 was excluded because of the withdrawal of his consent. Therefore, 23 patients were enrolled. Of those, 78% were female, and the mean age was 47 years. The main clinical and lung function data are presented in Table 1. At enrollment, 6 patients were receiving prednisone therapy (mean dose, 8.7 ± 4.0 mg; range, 5.0-15.0 mg), another 6 were receiving treatment with azathioprine, and 5 were receiving treatment with methotrexate. The pulmonary function test results showed that 7 patients (30.4%) had normal TLC and 15 (65.1%) had abnormal lung function. Of those, 9 (39.1%) had restrictive lung disease, 5 (21.7%) had mixed restrictive and obstructive lung disease, and 1 (4.3%) had obstructive lung disease. One patient was unable to perform the maneuvers required to measure lung volumes.

HRCT analysis

HRCT scans revealed a greater involvement of the lower lobes, with a predominance of GGO with bronchiectasis (90.0%), followed by pure GGO (65.4%). In addition, NSIP, UIP, and OP patterns were found in 19 (82.7%), 3 (13.0%), and 1 (4.3%) of the patients, respectively. Interobserver agreement was 0.82.

^{18}F-FDG PET/CT analysis

Metabolic activity was analyzed by determining the SULmax and SULmean in lung lobes, the background lung uptake in normal areas, and the TBR. A total of 414 lung segments were analyzed, 140 (33.8%) of which had sufficient metabolic activity to allow SULmax measurements (Figure 1).

Median SULmean, SULmax, and TBR were 0.81 (0.44-1.69), 2.7 (1.50-5.30), and 4.91 (3.71-11.52),

Table 1. Clinical and demographic characteristics of patients with systemic sclerosis (n = 23), as well as pulmonary function test results.[a]

Characteristic	Value
Female sex	18 (78.0)
Age, years	47.6 ± 12.5
Duration of disease, years	11.8 ± 8.7
Limited form	09 (39.1)
Diffuse form	14 (60.9)
Raynaud's phenomenon[b]	21 (91.0)
Digital ulcers[b]	06 (28.0)
Digital pitting scar[b]	05 (24.0)
Arthralgia/arthritis[b]	14 (64.0)
Pyrosis, dysphagia, diarrhea[b]	11 (48.0)
Telangiectasia[b]	04 (16.0)
Cough and dyspnea[b]	15 (65.0)
TLC, L	4.2 ± 0.7
TLC, % predicted	87.4 ± 14.5
FVC, % predicted	69.8 ± 17.6
FEV_1, L	2.0 ± 0.5
FEV_1, % predicted	69.5 ± 17.5
FEV_1/FVC	81.2 ± 5.4
DL_{CO}, %	64.7 ± 14.4
6MWD, meters	470.3 ± 72.5
SpO_2, %	88.7 ± 13.2

6MWD: six-minute walk distance. [a]Values expressed as n (%) or mean ± SD. [b]Clinical variables accumulated during disease progression.

respectively. The mean background lung uptake was 0.51 (0.083). Although ^{18}F-FDG uptake values were highest for honeycombing, there were no significant differences in ^{18}F-FDG uptake values between honeycombing and GGO. The correlations between HRCT patterns and ^{18}F-FDG uptake values are shown in Table 2.

Of 13 lung lobes showing normal HRCT findings, 12 (92.3%) had no significant metabolic activity for the uptake measurement. In addition, the median SULmean (0.63) was similar to the baseline SULmax (0.51). There was no correlation between ^{18}F-FDG uptake values and clinical and functional variables or concurrent therapy (data not shown). Furthermore, there was no difference between SULmean and SULmax values in patients with or without dyspnea (data not shown). There were no correlations between clinical or functional variables and ^{18}F-FDG PET/CT findings, HRCT findings, or biomarker parameters.

Inflammatory mediators

Figure 2 shows a comparison of inflammatory mediators between the SSc-associated ILD group and the control group. Median serum concentrations of sTNFR1, sTNFR2, CCL2, and CXCL10 were significantly higher in the SSc-associated ILD group than in the control group. On the other hand, there were significant differences across HRCT patterns regarding serum levels of sTNFR2 ($p = 0.017$), CCL2 ($p = 0.001$), CXCL10 ($p = 0.049$), CXCL9 ($p = 0.011$), and MIF ($p = 0.023$; Figure 3).

In the multiple comparisons of these inflammatory mediators, the Mann-Whitney U test with Bonferroni correction was applied to the level of significance, which was set at 0.01. As can be seen in Figure 4, serum levels of CCL2 were significantly higher for GGO than for honeycombing ($p = 0.007$). Inflammatory markers and ^{18}F-FDG uptake values were not significantly correlated. Disease duration had a moderate negative correlation with inflammatory mediators ($p < 0.05$).

DISCUSSION

The number of studies employing ^{18}F-FDG PET/CT in the evaluation of ILD has recently increased.[10,11,13] The present study involved patients with SSc-associated ILD and the use of ^{18}F-FDG PET/CT. The results showed significant metabolic activity for all HRCT patterns. However, there was remarkable metabolic activity for honeycombing (an HRCT pattern that is frequently associated with fibrotic disease) and GGO.[7] Furthermore, a correlation was found between GGO and serum CCL2 levels.

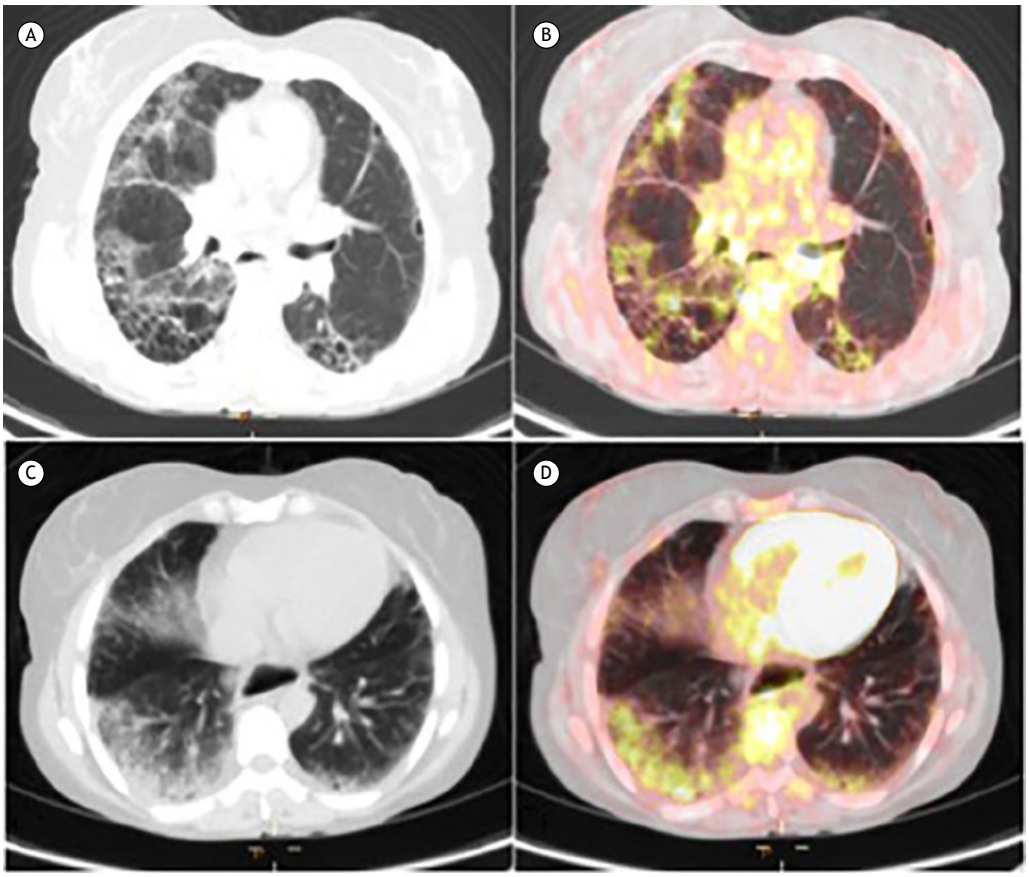


Figure 1. Low-dose CT and PET/CT scans of the chest showing honeycombing (in A), with scattered distribution of abnormal ^{18}F-FDG uptake (in B), as well as ground-glass opacity (in C), with uniform distribution of abnormal ^{18}F-FDG uptake (in D).

Table 2. Comparison of median maximum standardized uptake value corrected for lean body mass, mean standardized uptake value corrected for lean body mass, and target-to-background ratio values with HRCT patterns in lung lobes.[a]

	HRCT PATTERNS					
	Honeycombing (n = 16)	GGO (n = 28)	p	GGOF (n = 53)	GGO (n = 28)	p*
SULmax	1.95 [0.0-3.8]	1.75 [0.0-3.8]	0.589	1.79 [0.0-5.3]	1.75 [0.0-3.8]	0.850
SULmean	0.92 [0.57 -2.06]	3.4 [0.44-1.48]	0.179	0.77 [0.35-1.67]	0.79 [0.44-1.48]	0.980
TBR	4.0 [0.0-7.17]	0.0 [0.0-7.04]	0.880	3.6 [0.0-11.52]	0.0 [0.0-7.04]	0.195
	Normal (n = 13)	GGO (n = 28)		Normal (n = 13)	Honeycombing (n = 16)	
SULmax	0.0 [0.0-1.21]	1.75 [0.0-3.8]	0.001	0.0 [0.0-1.21]	1.95 [0.0-3.8]	0.002
SULmean	0.63 [0.46-0.76]	0.79 [0.44-1.48]	0.001	0.63 [0.46-0.76]	0.92 [0.57-2.06]	< 0.001
TBR	0.0 [0.0-2.57]	0.0 [0.0-7.04]	0.001	0.0 [0.0-2.57]	4.0 [0.0-7.17]	0.002

GGO: pure ground-glass opacity; GGOF: ground-glass opacity with fibrosis (a reticular pattern, bronchiectasis, or honeycombing); SULmax: maximum standardized uptake value corrected for lean body mass; SULmean: mean standardized uptake value corrected for lean body mass; and TBR: target-to-background ratio. [a]Values expressed as median (min-max). *Mann-Whitney U test. Note: SULmax and TBR values equal to zero are related to regions without any qualitatively outstanding metabolic activity for measurement.

The GGO pattern is known as a marker of active or early-stage disease[7]; however, the association between GGO and fibrotic disease in SSc was previously suggested by Shah et al.,[20] in a cohort of 41 patients undergoing serial HRCT examinations over a five year-period. The authors found that fibrosis progression was more common than lesion regression after treatment with D-penicillamine, cyclophosphamide, a combination of cyclophosphamide and D-penicillamine, or prednisone in patients with GGO on HRCT scans.[20]

Chen et al.[12] demonstrated the sensitivity of ^{18}F-FDG PET/CT in the assessment of acute pulmonary parenchymal inflammation.[12] The authors evaluated the neutrophilic response induced by direct instillation of endotoxin into a lung segment in healthy individuals and showed that ^{18}F-FDG PET/CT allowed quantification of the inflammatory response.[12] Groves et al.[11] studied pulmonary parenchymal metabolic activity in 36 patients with fibrosis, including idiopathic fibrosis with typical HRCT findings (18 patients) and fibrosis related to other diffuse pulmonary diseases. They found a mean SULmax of 2.8 and a predominance of activity in areas of honeycombing.

In the present study, PET was not useful for monitoring ILD in SSc patients because it failed to demonstrate significant differences between inflammatory activity and fibrotic areas, as suggested by findings of similar uptake for GGO and honeycombing images. However, if we take into consideration that SSc is a disease characterized by diffuse parenchymal involvement, the absence of significant ^{18}F-FDG uptake in lung segments showing parenchymal lesions suggests that ^{18}F-FDG PET/CT is useful in demonstrating the stability of the disease. Recently, three retrospective studies evaluated PET/CT scans of SSc patients under investigation for neoplastic disease, reporting that patients with progressing SSc-associated ILD had significantly higher pulmonary ^{18}F-FDG uptake at baseline than did those with stable SSc-associated ILD.[21-23] As demonstrated by Peelen at al., ^{18}F-FDG PET/CT scanning might distinguish SSc-associated ILD patients from SSc patients without ILD because in their study SSc-associated ILD had significantly higher pulmonary ^{18}F-FDG uptake than did SSc without ILD.[21]

The quantification of ^{18}F-FDG-uptake in the lung parenchyma is challenging and highly dependent on breathing movements and signal from blood and water compartments. The ideal method for quantifying ^{18}F-FDG lung uptake should exclusively reflect the metabolic activity in the lung cells to determine its pathogenic role. Although some methods have been tested, none was able to provide this information. Thus, comparison with clinical data is required in order to interpret PET quantification parameters correctly.[24]

Not many studies have assessed the role of air and blood fraction correction vs. noncorrected images in ^{18}F-FDG PET/CT examinations. Although we did not make these corrections, they have been reported to be important,[12,25] and the fact that we did not make them could explain why we did not find a clear relationship between ^{18}F-FDG-PET signal and other measures.

Visual identification of small variations in ^{18}F-FDG uptake in the lung parenchyma is often difficult, especially when there are highly heterogeneous parenchymal lesions.[20,26,27] The TBR is a measure of the variation in ^{18}F-FDG lung uptake. When next to 1, the TBR can indicate uniform ^{18}F-FDG uptake, and a high TBR has recently been related to poor survival in idiopathic pulmonary fibrosis.[28] In the present study, we found high TBRs in fibrosis and GGO patterns, especially

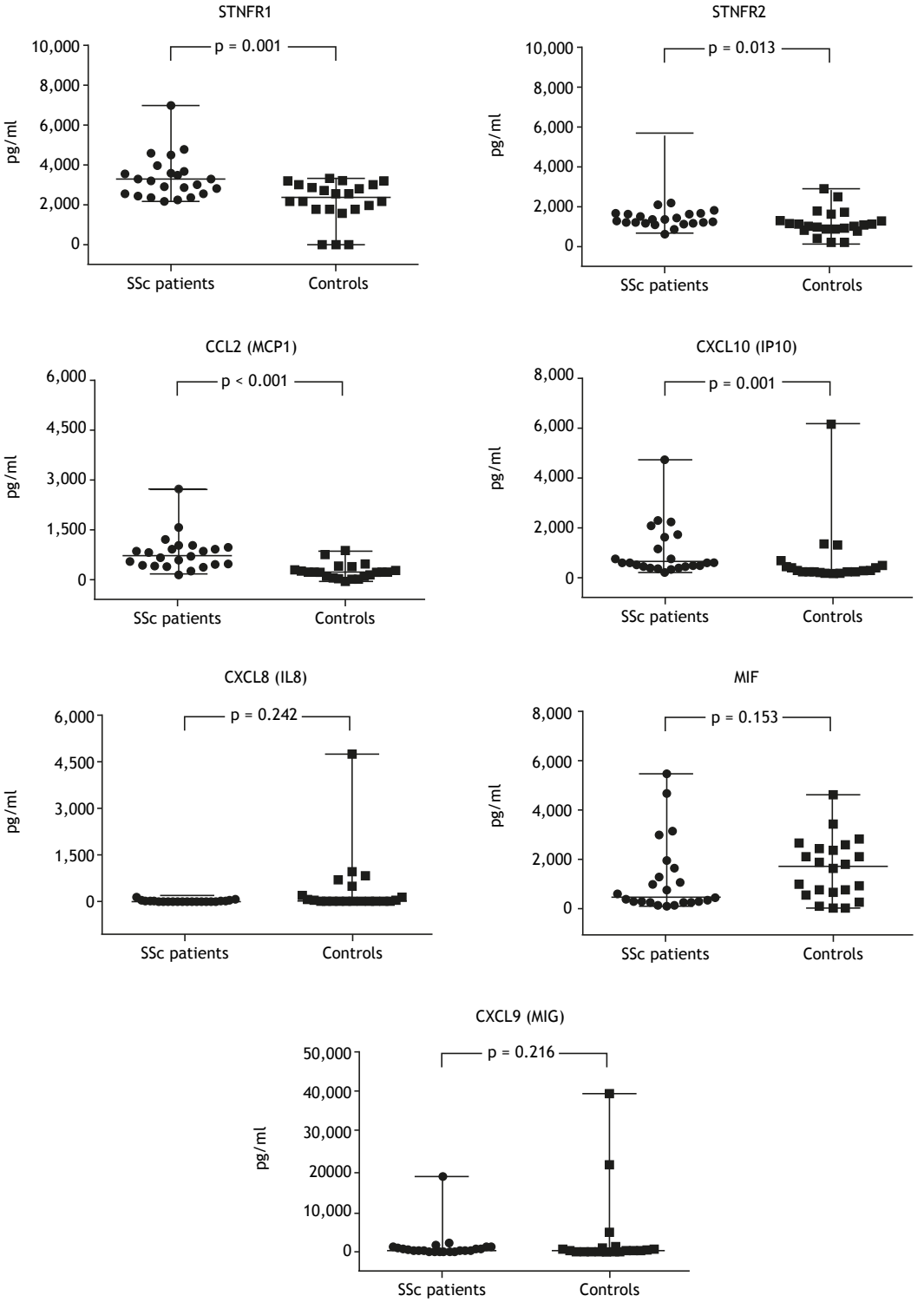


Figure 2. Comparative analysis of serum levels of inflammatory mediators in systemic sclerosis (SSc) patients (n = 23) and controls (n = 22). Mann-Whitney U test for determination of p values. sTNFR1: soluble tumor necrosis factor receptor 1; sTNFR2: soluble tumor necrosis factor receptor 2; CXCL8: C-X-C motif chemokine ligand 8; MIF: macrophage migration inhibitory factor; CCL2: C-C motif chemokine ligand 2; CXCL10: C-X-C motif chemokine ligand 10; and CXCL9: C-X-C motif chemokine ligand 9.

in areas of honeycombing (TBR, 4.02). Therefore, we considered it appropriate to add the ^{18}F-FDG uptake value to that of the whole lung by determining the SULmean by volumetric segmentation of the lung lobes,

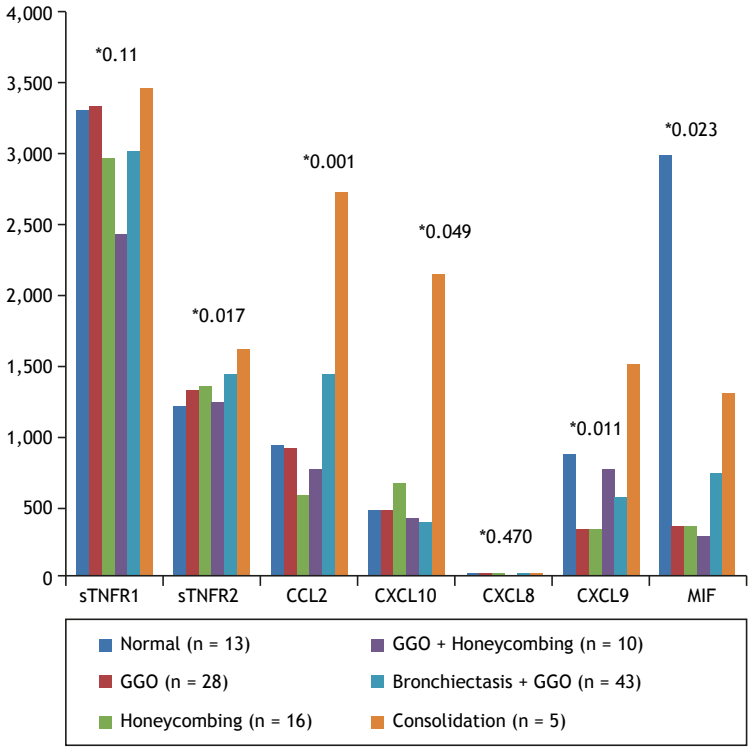


Figure 3. Comparative analysis of median serum levels of inflammatory mediators and HRCT patterns. *Kruskal-Wallis test for determination of p values. sTNFR1: soluble tumor necrosis factor receptor 1; sTNFR2: soluble tumor necrosis factor receptor 2; CCL2: C-C motif chemokine ligand 2; CXCL10: C-X-C motif chemokine ligand 10; CXCL8: C-X-C motif chemokine ligand 8; CXCL9: C-X-C motif chemokine ligand 9; MIF: macrophage migration inhibitory factor; and GGO: ground-glass opacity.

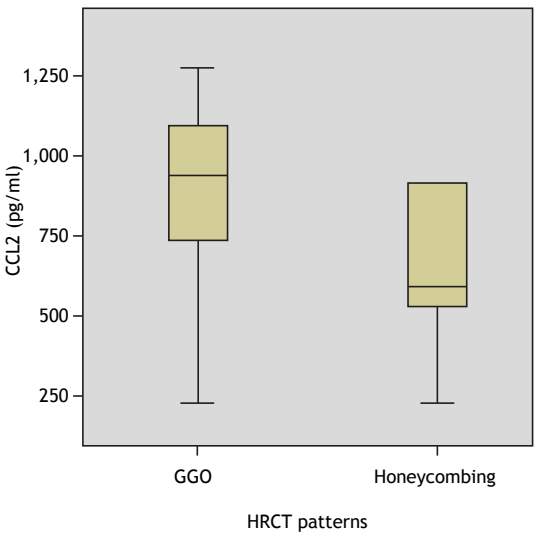


Figure 4. Differences between HRCT findings of ground-glass opacity (GGO) and honeycombing in terms of median serum levels of CCL2. p = 0.007 (Mann-Whitney U test). CCL2: C-C motif chemokine ligand 2; and GGO: ground-glass opacity.

in addition to measuring the SULmax qualitatively in the areas of interest.[13] The SULmax values are included in this volumetric analysis (SULmean), which results in much lower values.

The role of biomarkers in connective tissue disease-associated ILD was reviewed by Bonnela et al.[15] Although the authors reported several correlations between increased levels of lung-derived proteins and chemokines and the presence or severity of ILD in these patients, they stated that they individually lack predictive value, and that disease prediction may depend mostly on combinatorial analysis of many of these mediators.[15]

The inflammatory mediators whose serum levels were higher in the SSc-associated ILD patients than in the controls in the present study, i.e., sTNFR1, sTNFR2, CCL2, and CXCL10, are directly involved in the etiopathogenesis of SSc. Indeed, Hasegawa et al. reported that the levels of CXCL10, CXCL9, and CCL2 were higher in SSc patients than in controls, and that the variations in CCL2 over the three-year study period indicate skin and lung disease activity in SSc.[29]

Regarding the association between cytokines and HRCT patterns, higher levels of CCL2 were observed when GGO predominated (p = 0.007). This chemokine is known to stimulate inflammation and collagen production through fibroblast activation and inhibition of the production of prostaglandin E2 by alveolar epithelial cells, which in turn results in greater fibroblast proliferation, thus corroborating its important role in the genesis of fibrosis.[30-32] Thus, the correlation between CCL2 and GGO may indicate a predominance of fibrotic activity

in these areas due to the presence of active fibroblasts probably present in early pulmonary involvement. The impact of fibroblastic activity on ^{18}F-FDG lung uptake is supported by a preclinical study by Bondue et al., who demonstrated ^{18}F-FDG lung uptake at a late fibrotic stage and an important reduction in labeled leukocyte recruitment in a mouse model of pulmonary fibrosis.[33]

The main limitations of the present study include the small sample size, which is due to the fact that this was a single-center study, and the high cost of ^{18}F-FDG PET scans, making it difficult to perform any further analyses; nevertheless, rigorous selection criteria were adopted to guarantee sample homogeneity. On the other hand, segmental analysis of the lung parenchyma improved the analysis of HRCT patterns and their correspondence to the ^{18}F-FDG PET/CT results. Another point to be considered is that the use of immunomodulators by some patients may have had some influence on cytokine levels and ^{18}F-FDG uptake on PET/CT scans; however, they could not be discontinued because of the potential risks of drug withdrawal. For the same reason, lung pathology was not used as a reference in the comparison of the methods studied. Correlations among HRCT patterns, metabolic activity, inflammatory mediators, and clinical/functional variables could not be demonstrated in this study, probably because of the small sample size.

It is well worth mentioning that cross-sectional studies preclude the establishment of causal relationships. As a corollary, the meaning of these effects cannot be intuited in patients at disease stages earlier than those investigated here. However, sample homogeneity, the simultaneous acquisition of HRCT images, the use of ^{18}F-FDG PET/CT, the contemporary collection of serum inflammatory mediators, and pulmonary function testing made the results suitable for the objectives of the study.

AUTHOR CONTRIBUTIONS

ALB, RAC, and GAP: study concept and design. ALB, RAC, GAP, MM, EVM, MT, FPSTS, and CSF: data analysis and interpretation. ALB, RAC, GAP, EVM, and MM: drafting and review of the manuscript for important intellectual content. All of the authors approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Perelas A, Silver RM, Arrossi AV, Highland KB. Systemic sclerosis-associated interstitial lung disease. Lancet Respir Med. 2020;8(3):304-320. https://doi.org/10.1016/S2213-2600(19)30480-1
2. Wells AU, Steen V, Valentini G. Pulmonary complications: one of the most challenging complications of systemic sclerosis. Rheumatology (Oxford). 2009;48 Suppl 3:iii40-iii44. https://doi.org/10.1093/rheumatology/kep109
3. Taylor JG, Bolster MB. Bronchiolitis obliterans with organizing pneumonia associated with scleroderma and scleroderma spectrum diseases. J Clin Rheumatol. 2003;9(4):239-245. https://doi.org/10.1097/01.rhu.0000083860.27509.f1
4. de Souza RB, Borges CT, Capelozzi VL, Parra ER, Jatene FB, Kavakama J, et al. Centrilobular fibrosis: an underrecognized pattern in systemic sclerosis. Respiration. 2009;77(4):389-397. https://doi.org/10.1159/000156958
5. Mathieson JR, Mayo JR, Staples CA, Müller NL. Chronic diffuse infiltrative lung disease: comparison of diagnostic accuracy of CT and chest radiography. Radiology. 1989 Apr;171(1):111-6. https://doi.org/10.1148/radiology.171.1.2928513
6. Wells AU, Hansell DM, Corrin B, Harrison NK, Goldstraw P, Black CM, et al. High resolution computed tomography as a predictor of lung histology in systemic sclerosis. Thorax. 1992;47(9):738-742. https://doi.org/10.1136/thx.47.9.738
7. Wells AU. High-resolution computed tomography and scleroderma lung disease. Rheumatology (Oxford). 2008;47 Suppl 5:v59-v61. https://doi.org/10.1093/rheumatology/ken271
8. Nishiyama Y, Yamamoto Y, Dobashi H, Kameda T. Clinical value of 18F-fluorodeoxyglucose positron emission tomography in patients with connective tissue disease. Jpn J Radiol. 2010;28(6):405-413. https://doi.org/10.1007/s11604-010-0445-x
9. Capitanio S, Nordin AJ, Noraini AR, Rossetti C. PET/CT in nononcological lung diseases: current applications and future perspectives. Eur Respir Rev. 2016;25(141):247-258. https://doi.org/10.1183/16000617.0051-2016
10. Chen DL, Bedient TJ, Kozlowski J, Rosenbluth DB, Isakow W, Ferkol TW, et al. [18F]fluorodeoxyglucose positron emission tomography for lung antiinflammatory response evaluation. Am J Respir Crit Care Med. 2009;180(6):533-539. https://doi.org/10.1164/rccm.200904-0501OC
11. Groves AM, Win T, Screaton NJ, Berovic M, Endozo R, Booth H, et al. Idiopathic pulmonary fibrosis and diffuse parenchymal lung disease: implications from initial experience with 18F-FDG PET/CT. J Nucl Med. 2009;50(4):538-545. https://doi.org/10.2967/jnumed.108.057901
12. Chen DL, Rosenbluth DB, Mintun MA, Schuster DP. FDG-PET imaging of pulmonary inflammation in healthy volunteers after airway instillation of endotoxin. J Appl Physiol (1985). 2006;100(5):1602-1609. https://doi.org/10.1152/japplphysiol.01429.2005
13. Win T, Lambrou T, Hutton BF, Kayani I, Screaton NJ, Porter JC, et al. 18F-Fluorodeoxyglucose positron emission tomography pulmonary imaging in idiopathic pulmonary fibrosis is reproducible: implications for future clinical trials. Eur J Nucl Med Mol Imaging. 2012;39(3):521-528. https://doi.org/10.1007/s00259-011-1986-7
14. Lota HK, Renzoni EA. Circulating biomarkers of interstitial lung disease in systemic sclerosis. Int J Rheumatol. 2012;2012:121439. https://doi.org/10.1155/2012/121439
15. Bonella F, Costabel U. Biomarkers in connective tissue disease-associated interstitial lung disease. Semin Respir Crit Care Med. 2014;35(2):181-200. https://doi.org/10.1055/s-0034-1371527
16. van den Hoogen F, Khanna D, Fransen J, Johnson SR, Baron M, Tyndall A, et al. 2013 classification criteria for systemic sclerosis: an American College of Rheumatology/European League against Rheumatism collaborative initiative. Arthritis Rheum. 2013;65(11):2737-2747. https://doi.org/10.1002/art.38098
17. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. https://doi.org/10.1148/radiol.2462070712
18. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-968. https://doi.org/10.1183/09031936.05.00035205
19. Souza RB, Pereira CA. Diretrizes para testes de função pulmonar. J Pneumol. 2002;28(3):155-165.
20. Shah RM, Jimenez S, Wechsler R. Significance of ground-glass opacity on HRCT in long-term follow-up of patients with systemic sclerosis. J Thorac Imaging. 2007;22(2):120-124. https://doi.org/10.1097/01.rti.0000213572.16904.40
21. Peelen DM, Zwezerijnen BGJC, Nossent EJ, Meijboom LJ, Hoekstra OS, Van der Laken CJ, et al. The quantitative assessment of interstitial lung disease with positron emission tomography

scanning in systemic sclerosis patients. Rheumatology (Oxford). 2020;59(6):1407-1415. https://doi.org/10.1093/rheumatology/kez483

22. Ledoult E, Morelle M, Soussan M, Mékinian A, Béhal H, Sobanski V, et al. 18F-FDG positron emission tomography scanning in systemic sclerosis-associated interstitial lung disease: a pilot study. Arthritis Res Ther. 2021;23(1):76. https://doi.org/10.1186/s13075-021-02460-8
23. Bellando-Randone S, Tartarelli L, Cavigli E, Tofani L, Bruni C, Lepri G, et al. 18F-fluorodeoxyglucose positron-emission tomography/CT and lung involvement in systemic sclerosis. Ann Rheum Dis. 2019;78(4):577-578. https://doi.org/10.1136/annrheumdis-2018-213376
24. Chen DL, Rosenbluth DB, Mintun MA, Schuster DP. FDG-PET imaging of pulmonary inflammation in healthy volunteers after airway instillation of endotoxin. J Appl Physiol (1985). 2006;100(5):1602-1609. https://doi.org/10.1152/japplphysiol.01429.2005
25. Chen DL, Cheriyan J, Chilvers ER, Choudhury G, Coello C, Connell M, et al. Quantification of Lung PET Images: Challenges and Opportunities. J Nucl Med. 2017;58(2):201-207. https://doi.org/10.2967/jnumed.116.184796
26. Lambrou T, Groves AM, Erlandsson K, Screaton N, Endozo R, Win T, et al. The importance of correction for tissue fraction effects in lung PET: preliminary findings. Eur J Nucl Med Mol Imaging. 2011;38(12):2238-2246. https://doi.org/10.1007/s00259-011-1906-x
27. Schroeder T, Melo MF, Venegas JG. Analysis of 2-[Fluorine-18]-Fluoro-2-deoxy-D-glucose uptake kinetics in PET studies of pulmonary inflammation. Acad Radiol. 2011;18(4):418-423. https://doi.org/10.1016/j.acra.2010.11.019
28. Chen DL, Mintun MA, Schuster DP. Comparison of methods to quantitate 18F-FDG uptake with PET during experimental acute lung injury. J Nucl Med. 2004;45(9):1583-1590.
29. Win T, Screaton NJ, Porter JC, Ganeshan B, Maher TM, Fraioli F, et al. Pulmonary 18F-FDG uptake helps refine current risk stratification in idiopathic pulmonary fibrosis (IPF). Eur J Nucl Med Mol Imaging. 2018;45(5):806-815. https://doi.org/10.1007/s00259-017-3917-8
30. Hasegawa M, Fujimoto M, Matsushita T, Hamaguchi Y, Takehara K, Sato S. Serum chemokine and cytokine levels as indicators of disease activity in patients with systemic sclerosis. Clin Rheumatol. 2011;30(2):231-237. https://doi.org/10.1007/s10067-010-1610-4
31. Bandinelli F, Del Rosso A, Gabrielli A, et al. CCL2, CCL3 and CCL5 chemokines in systemic sclerosis: the correlation with SSc clinical features and the effect of prostaglandin E1 treatment. Clin Exp Rheumatol. 2012;30(2 Suppl 71):S44-S49.
32. Lindahl GE, Stock CJ, Shi-Wen X, Leoni P, Sestini P, Howat SL, et al. Microarray profiling reveals suppressed interferon stimulated gene program in fibroblasts from scleroderma-associated interstitial lung disease. Respir Res. 2013;14(1):80. https://doi.org/10.1186/1465-9921-14-80
33. Bondue B, Sherer F, Van Simaeys G, Doumont G, Egrise D, Yakoub Y, et al. PET/CT with 18F-FDG- and 18F-FBEM-labeled leukocytes for metabolic activity and leukocyte recruitment monitoring in a mouse model of pulmonary fibrosis. J Nucl Med. 2015;56(1):127-132. https://doi.org/10.2967/jnumed.114.147421

J Bras Pneumol. 2022;48(4):e20210412
https://dx.doi.org/10.36416/1806-3756/e20210412

ORIGINAL ARTICLE

Sleep-onset time variability and sleep characteristics on weekday and weekend nights in patients with COPD

Daniele Caroline Dala Pola[1], Raquel Pastrello Hirata[1], Lorena Paltanin Schneider[1], Mariana Pereira Bertoche[1], Karina Couto Furlanetto[1,2], Arthur Eumann Mesas[3,4], Fabio Pitta[1]

1. Laboratório de Pesquisa em Fisioterapia Pulmonar – LFIP – Departamento de Fisioterapia, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
2. Centro de Pesquisa em Ciências da Saúde, Universidade Pitágoras-Universidade Norte do Paraná – UNOPAR – Londrina (PR) Brasil.
3. Programa de Pós-Graduação em Saúde Coletiva, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.
4. Health and Social Research Center, Universidad de Castilla-La Mancha, Cuenca, Spain.

Submitted: 7 October 2011.
Accepted: 29 May 2022.

Study carried out in the Laboratório de Pesquisa em Fisioterapia Pulmonar – LFIP – Departamento de Fisioterapia, Universidade Estadual de Londrina – UEL – Londrina (PR) Brasil.

ABSTRACT

Objective: To evaluate sleep-onset time variability, as well as sleep characteristics on weekday and weekend nights, in individuals with moderate-to-severe COPD. **Methods:** Sleep was objectively assessed by an activity/sleep monitor for seven consecutive nights in individuals with COPD. For analysis, individuals were divided into two groups according to sleep-onset time variability results, characterized by intrasubject standard deviation of sleep-onset time (SOT_V) ≥ 60 min or < 60 min. **Results:** The sample comprised 55 individuals (28 males; mean age = 66 ± 8 years; and median FEV_1 % of predicted = 55 [38-62]). When compared with the SOT_V<60min group (n = 24), the SOT_V≥60min group (n = 31) presented shorter total sleep time (5.1 ± 1.3 h vs. 6.0 ± 1.3 h; p = 0.006), lower sleep efficiency (73 ± 12% vs. 65 ± 13%; p = 0.030), longer wake time after sleep onset (155 ± 66 min vs. 115 ± 52 min; p = 0.023), longer duration of wake bouts (19 [16-28] min vs. 16 [13-22] min; p = 0.025), and higher number of steps at night (143 [104-213] vs. 80 [59-135]; p = 0.002). In general, sleep characteristics were poor regardless of the day of the week, the only significant difference being that the participants woke up about 30 min later on weekends than on weekdays (p = 0.013). **Conclusions:** Sleep-onset time varied over 1 h in a standard week in the majority of individuals with COPD in this sample, and a more irregular sleep onset indicated poor sleep quality both on weekdays and weekends. Sleep hygiene guidance could benefit these individuals if it is integrated with their health care.

Keywords: Pulmonary disease, chronic obstructive; Sleep; Actigraphy.

INTRODUCTION

Sleep constitutes approximately one third of the average lifetime, and good sleep quality is important for both physical and mental health, especially for patients with a chronic disease.[1] Disturbed sleep is common in individuals with COPD,[2,3] and it is one of the most important complaints after dyspnea and fatigue.[4] The most common complaints related to sleep include sleep-onset insomnia, nighttime awakenings and unrefreshing sleep.[5,6] Upon assessment, many individuals with COPD present poor sleep quality, characterized by decreased sleep efficiency, increased sleep-onset latency and fragmentation of the sleep architecture, independently of the severity of airflow limitation.[7] Despite the high frequency of these sleep disturbances and their possible influence on clinical outcomes, there are limited data in the literature about the objectively assessed characterization of sleep in individuals with COPD.

Previous studies have investigated the relationship of sleep regularity with metabolic abnormalities,[8] obesity,[9] and risk of cardiovascular diseases.[10,11] In children, there is evidence of an association of low sleep regularity (or high variability) with altered plasma levels of insulin, low density lipoprotein, and C-reactive protein.[8] In adolescents, a high sleep variability is related to increased consumption of fat and carbohydrates, as well as a higher consumption of snacks after dinner, which is directly related to obesity.[9] Furthermore, in the elderly, high sleep variability was associated with increased risk of cardiovascular diseases[10] and increased prevalence and incidence of metabolic abnormalities.[11] There is also evidence linking sleep irregularity with a higher risk of neurological, respiratory, and gastrointestinal problems, as well as pain and depression.[12]

Sleep irregularity can be measured by sleep-onset time variability (i.e., intrasubject standard deviation of sleep-onset time). Despite the growing interest in this topic in different populations, to the best of our knowledge, there are no studies available describing and exploring the variability of sleep-onset time in individuals

Correspondence to:
Fabio Pitta, Departamento de Fisioterapia – CCS, Hospital Universitário de Londrina, Avenida Robert Koch, 60, Vila Operária, CEP 86038-350, Londrina, PR, Brasil.
Tel.: 55 43 3371-2477. E-mail: fabiopitta@uel.br
Financial support: Karina Couto Furlanetto is the recipient of a grant from the Brazilian *Fundação Nacional de Desenvolvimento do Ensino Superior Particular* (FUNADESP, National Foundation for the Development of Privately-held Institutions of Higher Education; Grant no. 5301164). Fabio Pitta is the recipient of a grant from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grant no. 303131/2017-9).

with COPD. Furthermore, only one study investigated differences in sleep characteristics between weekdays and weekends,[13] a more in-depth approach being required. Therefore, the aims of this study were to analyze the repercussion of sleep-onset time variability on the quantity and quality of sleep in individuals with moderate-to-severe COPD and to describe sleep characteristics on weekday and weekend nights in this population.

METHODS

This was a cross-sectional analysis of retrospective data from a convenience sample of patients evaluated in the Laboratory of Research in Respiratory Physiotherapy at the State University of Londrina, located in the city of Londrina, Brazil. Subjects enrolled in these baseline-only analyses subsequently took part in an unrelated larger longitudinal observational study.[14] The larger study was approved by the local research ethics committee (Protocol no. 123/09), and written informed consent was obtained from all participants.

Inclusion criteria were having a diagnosis of COPD in accordance with the GOLD,[15] no infections or exacerbations in the last three months, and no severe comorbidities interfering with the assessments. The exclusion criterion was not reaching the minimum daily time wearing the activity/sleep monitor, as further described below.

Assessments

Pulmonary function was assessed with a portable spirometer (Spirobank G; MIR, Rome, Italy) in accordance with the American Thoracic Society guidelines[16] and reference values used for the Brazilian population.[17] For characterization, exercise capacity was assessed by the six-minute walk test (6MWT). The test was conducted according to international standardization[18] and reference values for the Brazilian population.[19]

Sleep was objectively assessed by the multisensor activity/sleep monitor SenseWear® Pro2 Armband (BodyMedia, Pittsburgh, PA, USA). Individuals were instructed to wear the monitor 24 h a day for seven consecutive days and nights; however, data from daytime physical activity was not analyzed in this study. This device is a small and light multisensor monitor to be worn around the upper region of the right arm (triceps brachii muscle).[20] A minimum on-body time of 22 h per day was considered as a valid assessment day, and the sleep monitor should be worn for at least four valid assessment days, Saturday and Sunday included.

The following variables were used to evaluate sleep: total time in bed, total sleep time (TST), sleep efficiency, wake time after sleep onset (WASO), number of sleep bouts, duration of sleep bouts, number of wake bouts, duration of wake bouts, bedtime, wake-up time, and steps at night (Chart 1). The seven-day standard deviation of sleep-onset time was calculated to quantify sleep regularity. The actigraphic signals were scored as wake or sleep for each one-minute epoch according to increases or decreases in activity count.

We analyzed sleep characteristics as the mean of all valid assessments for each individual, as well as the comparison of these on weekdays and weekends. In addition, individuals were classified into two groups regarding their sleep-onset time variability: those with a higher night-to-night sleep-onset time variability, characterized by an intrasubject standard deviation of sleep-onset time (SOT_v) equal to or higher than 60 min ($SOT_v \geq 60$ min), and those with a lower night-to-night sleep-onset variability ($SOT_v < 60$ min). This cutoff point has already been used in the literature to evaluate the sleep-onset time variability in adults and in the elderly.[10,11]

Statistical analysis

Analysis of data distribution was performed using the Shapiro-Wilk test. Normally distributed numerical data were described as mean ± standard deviation and compared using the t-test, whereas non-normally distributed data were described as median [IQR] and compared using the Mann-Whitney test. Categorical variables were compared using the chi-square test. Correlations between sleep variability and clinical outcomes were investigated using Pearson's or Spearman's coefficients according to the normality of the data. Statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA) and the GraphPad Prism software, version 6.0 (GraphPad Software, Inc., San Diego, CA). Statistical significance was set at $p < 0.05$.

RESULTS

The original sample comprised 58 individuals, 3 of whom were excluded because the minimum number of valid days for sleep assessment was not reached. Therefore, the final sample consisted of 55 individuals with moderate-to-severe COPD in accordance with the GOLD definition.[15] The mean number of days and the mean time during which the participants wore the monitor were, respectively, 6.78 ± 0.6 days and 23.3 ± 0.4 h/day. The median sleep-onset time variability in the overall sample was 65 [47-96] min. In general, the sample was characterized by elderly individuals with a mean BMI of 26 ± 5 kg/m^2 and a relatively preserved exercise capacity (Table 1).

Sleep characteristics

Table 2 shows that, in general, individuals spent a median of approximately 8 h lying in bed for sleep at night, sleep efficiency and TST being approximately 69% and 5.6 h, respectively. When comparing sleep characteristics, patients woke up approximately half an hour later on weekends than on weekdays. There were no statistically significant differences between weekdays and weekends regarding total time in bed, TST, sleep efficiency, WASO, sleep-onset latency, number

Chart 1. Nighttime sleep measurements derived from actigraphic data.

Variable name	Description
Total time in bed (TIB)	Total time spent lying in bed for sleep during the night
Total sleep time (TST)	Sum of all minutes scored as sleep during TIB
Sleep efficiency	TST/TIB, expressed as %
Wake time after sleep onset	Time spent awake during TIB after the first sleep bout
Number of sleep bouts	Absolute number of nocturnal sleep bouts during TIB
Duration of sleep bouts	Mean duration of nocturnal sleep bouts during TIB
Number of wake bouts	Absolute number of nocturnal wake bouts during TIB
Duration of wake bouts	Mean duration of nocturnal wake bouts during TIB
Bedtime	Hour and minute when the individual lies down in bed to sleep at night
Wake-up time	Hour and minute when the individual gets up from bed to start the day
Steps at night	Absolute number of steps eventually taken between bedtime and wake-up time

Table 1. Demographic and clinical characteristics of the participants (N = 55).[a]

Variable	Result
Male	28 (51)
Age, years	66 ± 8
BMI, kg/m^2	26 ± 5
6MWD, m	474 ± 76
6MWD, % predicted	88 ± 14
Pulmonary function	
FVC, L	2.2 [1.7-3.0]
FVC, % predicted	76 [60-86]
FEV_1, L	1.3 ± 0.5
FEV_1, % predicted	55 [38-62]
FEV_1/ FVC, %	55 [43-63]
GOLD 1/2/3/4, n	1/34/11/9
Comorbidities	
Heart disease, yes/no, %	16/84
Hypertension, yes/no, %	51/49
Diabetes, yes/no, %	22/78

6MWD: six-minute walk distance. [a]Values expressed as n (%), mean ± SD, or median [IQR] according to the normality of data distribution, except where otherwise indicated.

and duration of sleep and wake bouts, bedtime, and steps at night (Table 2).

Sleep-onset time variability

The SOT_V≥60min and the SOT_V<60min groups comprised 31 individuals (56% of the total sample) and 24 individuals (44% of the total sample), respectively. Table 3 shows that there were no significant differences regarding clinical characteristics, lung function parameters, and comorbidities between the groups. Moreover, Table 4 shows that the SOT_V≥60min group presented worse sleep quantity and sleep quality indicators, such as lower TST, lower sleep efficiency, higher WASO, longer duration of wake bouts, and higher number of steps during the night when compared with the SOT_V<60min group. Figure 1 illustrates an example of two representative patients, one from each group. Furthermore, there were no significant correlations between sleep variability and the following outcomes: BMI, history of hospitalization, and presence of hypertension or diabetes mellitus.

DISCUSSION

To the best of our knowledge, this is the first study that objectively evaluated sleep characteristics of individuals with COPD comparing weekdays and weekends and that measured sleep-onset time variability. In general, these subjects maintained their sleep patterns throughout the whole week, the only statistically significant difference being the fact that they woke up half an hour later on weekends. Moreover, it was shown that individuals with a higher sleep-onset time variability (i.e., variation of more than 60 min from night-to-night time that they go to bed) presented considerably worse indicators of sleep quantity and quality.

Various methods are available for the investigation of sleep disorders. Polysomnography is a complete diagnostic method that is considered the gold standard for sleep assessment[21]; however, it may be regarded as expensive in certain settings and does not reflect the natural environment of the individuals. Sleep-wake monitoring with accelerometry is a lower-cost method for assessing sleep that is highly correlated with polysomnography[22] and can provide useful information about sleep characteristics in the natural environment. In addition to estimating sleep, accelerometry can also be used as a screening tool for other sleep-related disorders such as insomnia,[5] restless legs syndrome,[23] and sleep-related hypoxemia.[24] Hypoxemia during sleep is very common in individuals with COPD, being reported in up to 70% of patients with daytime saturations between 90% and 95%.[25] Supplemental oxygen may improve sleep in individuals with COPD and nocturnal hypoxemia,[26] whereas it has been shown that treatment with bronchodilators can also improve sleep quality.[27] Actigraphy does not record oximetry during the night, but nocturnal hypoxemia may be associated with a greater number of nocturnal awakenings and lead to sleep fragmentation, and these are easily identified by the instrument.[24] In addition to objective records, there is a number of self-reported instruments which investigates the clinical complaints of patients related to sleep, such as the Pittsburgh Sleep Quality Index (PSQI).[28] This questionnaire is widely used in clinical practice and has proven to be effective and capable of providing useful information about the quality of sleep. The PSQI has shown worse

Table 2. Sleep characteristics described as the mean per night on weekdays (Monday to Friday; N = 310 nights) and weekends (Saturday and Sunday; N = 113).[a]

Variable	Total	Weekdays	Weekends
Total time in bed, h	8 [7-9]	8 [7-9]	8 [7-10]
Total sleep time, h	5.6 [4.3-6.8]	5.7 [4.4-6.9]	5.5 [4.1-6.5]
Sleep efficiency, %	69 [59-81]	70 [60-81]	68 [55-81]
Wake time after sleep onset, min	128 [70-188]	123 [70-176]	136 [74-218]
Sleep-onset latency, min	11 [2-22]	11 [2-23]	10 [2-22]
Number of sleep bouts	7 [5-10]	7 [5-10]	7 [5-9]
Duration of sleep bouts, min	46 [33-71]	47 [33-72]	45 [30-68]
Number of wake bouts	7 [5-9]	7 [5-10]	6 [4-9]
Duration of wake bouts, min	17 [11-25]	16 [11-24]	18 [11-27]
Bedtime, h:min	23:13 [22:07-00:04]	23:17 [22:06-00:06]	23:10 [22:07-00:00]
Wake-up time, h:min	7:15 [6:28-8:06]	7:11 [6:25-8:00]	7:38 [6:39-8:27]*
Steps at night	125 [67-174]	87 [43-174]	112 [48-205]

[a]Values are presented as median [IQR]. *p < 0.05 vs. weekdays.

Table 3. Demographic and clinical characteristics of individuals with COPD according to the cutoff point of 60 min for sleep-onset time variability.[a]

Variable	Group		p
	SOT_V < 60 min (n = 24)	SOT_V ≥ 60 min (n = 31)	
Male	11 (46)	17 (55)	0.508
Age, years	66 ± 7	68 ± 9	0.206
BMI, kg/m^2	26 ± 5	26 ± 6	0.633
6MWD, m	467 ± 77	479 ± 75	0.542
6MWD, % predicted	88 ± 15	89 ± 12	0.839
Pulmonary function			
FVC, L	2.1 [1.7-3.2]	2.3 [1.8-3.0]	0.993
FVC, % predicted	75 ± 17	71 ± 17	0.472
FEV_1, L	1.2 ± 0.4	1.3 ± 0.6	0.437
FEV_1, % predicted	49 ± 16	51 ± 18	0.670
FEV_1/ FVC, %	51 [41-62]	60 [50-64]	0.159
Comorbidities			
Heart disease, yes/no, %	88/12	81/19	0.754
Hypertension, yes/no, %	50/50	52/48	0.906
Diabetes, yes/no, %	21/79	23/77	0.876

SOT_V: sleep-onset time variability; and 6MWD: six-minute walking distance. [a]Values expressed as n (%), mean ± SD, or median [IQR] according to the normality of data distribution, except where otherwise indicated.

quality of sleep in patients with COPD.[29] A combined assessment using objective and subjective methods could provide a wider view about sleep disturbances in individuals with COPD. Unfortunately, data from the PSQI were unavailable for the present study.

Individuals with COPD present sleep characteristics that are distinct from the general population. Nunes et al.,[30] using accelerometry as a sleep assessment method, showed that individuals with COPD presented worse sleep quality when compared with a control group.[30] The present study provides a more detailed characterization of the sleep patterns of individuals with COPD, identifying that sleep quality is severely impaired in this population. In addition, our data showed that the wake-up time on weekends was 30 min later than that on weekdays. Spina et al.[13] analyzed the sleep of individuals with COPD regarding the severity of the disease, dyspnea, gender, and sleep on weekends. On weekends, participants had more fragmented sleep and spent more time awake after sleep onset than on weekdays; however, the variable wake-up time was not analyzed.[13] Although social jet lag (misalignment between social and biological times) takes into consideration the differences in sleep time between weekdays and weekends, we believe that this phenomenon was not present in this study, since our sample was essentially composed of elderly and retired individuals.

In the present study, it can be observed that patients with higher sleep-onset time variability had worse indicators of sleep quality and a higher number of steps at night. The majority of scientific evidence has focused on associations regarding sleep duration or quality,[31] leaving a gap in the literature regarding other sleep characteristics, such as sleep regularity. A recent systematic review analyzed the associations of

Table 4. Comparison of sleep characteristics of the participants according to the cutoff point of 60 min for sleep-onset time variability.[a]

Variable	Group		p
	SOT_V < 60 min (n = 24)	SOT_V ≥ 60 min (n = 31)	
Total time in bed, h	8.2 ± 1.3	8.0 ± 1.4	0.709
Total sleep time, h	6.0 ± 1.3	5.1 ± 1.3	0.006
Sleep efficiency, %	73 ± 12	65 ± 13	0.030
Wake time after sleep onset, min	115 ± 52	155 ± 66	0.023
Sleep-onset latency, min	16 [10-23]	11 [6-19]	0.127
Number of sleep bouts	6.8 [5.8-8.2]	6.9 [5.9-8.9]	0.905
Duration of sleep bouts, min	56 [44-71]	46 [36-64]	0.131
Number of wake bouts	6.6 [5.7-8.1]	6.7 [5.7-8.5]	0.845
Duration of wake bouts, min	16 [13-22]	19 [16-28]	0.025
Bedtime, h:min	23:23 [22:38-23:46]	23:11 [22:02-23:58]	0.553
Wake-up time, h:min	7:20 [6:37-7:55]	7:18 [6:13-8:13]	0.953
Steps at night	80 [59-135]	143 [104-213]	0.002

SOT_V: sleep-onset time variability. [a]Values expressed as mean ± SD or median [IQR] according to the normality of data distribution, except where otherwise indicated.

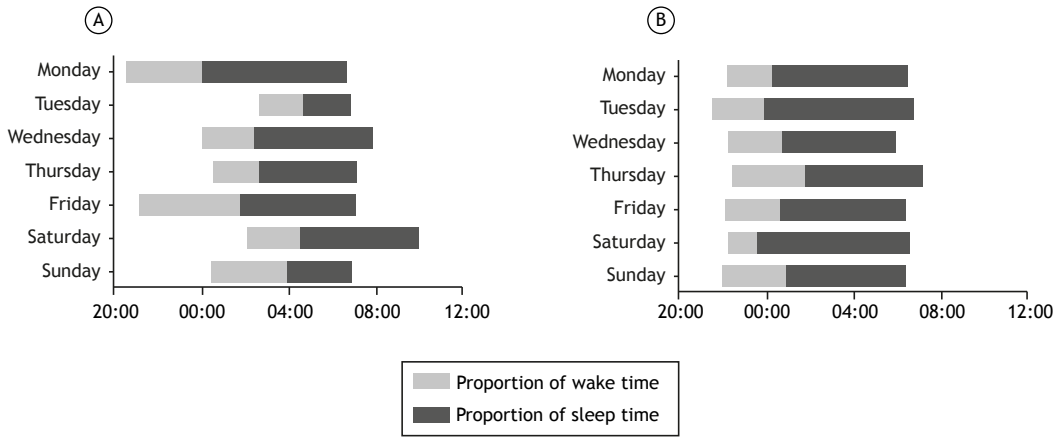


Figure 1. Representation of the sleep patterns over seven days in two individuals with COPD. In A, an individual from the SOT_v≥60min group (male; 76 years of age; FEV_1 = 57% of predicted; and SOT_v = 131 min). In B, an individual from the SOT_v<60min group (male; 75 years of age; FEV_1 = 40% of predicted; and SOT_v = 18 min). Each bar represents the total time in bed for each day of the week; the light gray bar represents the proportion of time spent awake during the total time in bed, and the dark gray bar represents the proportion of time spent sleeping during the total time in bed. Note that in A there is a substantial variation in the sleep-onset time throughout the week, whereas, in B, a regular sleep schedule is maintained. Moreover, the proportion of sleep seems to be lower in A than in B. SOT_V: sleep-onset time variability.

sleep time and sleep regularity with health outcomes, showing that a higher sleep variability was associated with negative health outcomes.[32] Another recent study in the Latin population showed that the regularity of sleep-wake time was as important as sleep duration, since sleep irregularity was associated with a higher prevalence of hypertension and increased systolic blood pressure in adults and in the elderly.[33] Huang & Redline[11] showed that for each one-hour increase in sleep-onset time variability, there was an increased odds ratio of 1.23 of prevalent metabolic syndrome when compared with sleep-onset time variability ≤ 30 min (95% CI: 1.96-1.42; p = 0.005) in adults participating in a multi-ethnic study of atherosclerosis. The same group investigated sleep variability in the context of cardiovascular disease and concluded that irregularities in sleep-onset time and sleep duration may be considered risk factors for cardiovascular disease, regardless of the traditional risk factors and the quantity and/or quality of sleep.[10] There is evidence showing that older people with greater bedtime variability, wake time, and duration of time in bed have higher levels of IL-6 and TNF-α.[34] Individuals with COPD also have even higher levels of inflammatory markers than do healthy elderly people.[35] It might be that, in individuals with COPD and greater sleep-onset time variability, the inflammatory scenario may be even worse, generating negative consequences on the level of physical activities in daily life,[36] sensation of fatigue, and symptoms of depression.[37] However, further research is needed to support the hypothesis of a possible relationship between sleep variability and

inflammatory markers in individuals with COPD. It is also known that the association of COPD with other respiratory disorders, such as obstructive sleep apnea, may increase complaints of worsened sleep quality in these patients.[3] There seems to be a gap in the scientific literature regarding the possible mechanisms that are involved in or that contribute to the occurrence of sleep variability, whether in COPD alone or in combination with obstructive sleep apnea. This is a broad field of research that can still be explored in the future. The present study, with a cross-sectional and retrospective design, did not aim to establish any causal relationship, but only to characterize sleep variability in individuals with COPD.

Sleep disturbances in individuals with COPD may also be due to non-optimal pharmacological control of the primary disease or due to side effects of pharmacotherapy. The first principle of managing sleep-disordered breathing in COPD should be to optimize the underlying condition, as this may have beneficial effects on breathing.[38] Furthermore, despite advances in pharmacological optimization, the role of nonpharmacological therapies remains unquestioned. These include smoking cessation, disease management, use of oxygen therapy, pulmonary rehabilitation, and sleep hygiene measures.[39] Since the individuals with COPD with higher sleep-onset time variability presented with characteristics of poor sleep quantity and quality in the present study, these subjects should be strongly encouraged and educated to adopt healthier sleep habits, especially to maintain a regular sleep-onset schedule. Further prospective research is required to evaluate the influence of such interventions on clinical aspects in individuals with COPD.

The present study has some strengths and limitations. Sleep regularity has been shown to be an important aspect associated with worse clinical outcomes in different studies. To our knowledge, this is the first study that evaluated sleep-onset time variability in individuals with COPD. Another strength of this study is the use of actigraphy, which is a quite useful and accessible method to evaluate sleep-wake characteristics. As for the limitations, patients were not assessed regarding the presence of any sleep disorders, because neither polysomnography nor polygraphy was available for this research project; in addition, the study did not involve a control group. Also, information regarding self-reported clinical complaints related to sleep was unfortunately unavailable. Therefore, these data should be interpreted with caution due to the absence of a control group and subjective complaints about sleep.

In conclusion, the sleep-onset time in the majority of individuals with moderate-to-severe COPD varied in more than one hour in a standard week, and a more irregular sleep onset indicated worse sleep quality. Poor sleep quality in this population occurred both on weekdays and weekends. Sleep hygiene guidance is a simple strategy that could benefit these individuals if it is integrated with their health care.

AUTHOR CONTRIBUTIONS

DCDP: conceptualization, methodology, formal analysis, and drafting of the manuscript. LPS and MPB: methodology, data collection, and data interpretation. KCF: data collection, formal analysis, and critical review of the manuscript. RPH: conceptualization, methodology, formal analysis and interpretation, and drafting of the manuscript. AEM: methodology, formal analysis and critical review of the manuscript. FP: conceptualization, coordination of the project as a whole, formal analysis and interpretation, and drafting and critical review of the manuscript. All authors approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Vanfleteren LE, Beghe B, Andersson A, Hansson D, Fabbri LM, Grote L. Multimorbidity in COPD, does sleep matter?. Eur J Intern Med. 2020;73:7-15. https://doi.org/10.1016/j.ejim.2019.12.032
2. Agusti A, Hedner J, Marin JM, Barbé F, Cazzola M, Rennard S. Night-time symptoms: a forgotten dimension of COPD. Eur Respir Rev. 2011;20(121):183-194. https://doi.org/10.1183/09059180.00004311
3. McNicholas WT, Verbraecken J, Marin JM. Sleep disorders in COPD: the forgotten dimension. Eur Respir Rev. 2013;22(129):365-375. https://doi.org/10.1183/09059180.00003213
4. Kinsman RA, Yaroush RA, Fernandez E, Dirks JF, Schocket M, Fukuhara J. Symptoms and experiences in chronic bronchitis and emphysema. Chest. 1983;83(5):755-761. https://doi.org/10.1378/chest.83.5.755
5. Budhiraja R, Parthasarathy S, Budhiraja P, Habib MP, Wendel C, Quan SF. Insomnia in patients with COPD. Sleep. 2012;35(3):369-375. https://doi.org/10.5665/sleep.1698
6. Price D, Small M, Milligan G, Higgins V, Gil EG, Estruch J. Impact of night-time symptoms in COPD: a real-world study in five European countries. Int J Chron Obstruct Pulmon Dis. 2013;8:595-603. https://doi.org/10.2147/COPD.S48570
7. Mulloy E, McNicholas WT. Ventilation and gas exchange during sleep and exercise in severe COPD. Chest. 1996;109(2):387-394. https://doi.org/10.1378/chest.109.2.387
8. Spruyt K, Molfese DL, Gozal D. Sleep duration, sleep regularity, body weight, and metabolic homeostasis in school-aged children. Pediatrics. 2011;127(2):e345-e352. https://doi.org/10.1542/peds.2010-0497
9. He F, Bixler EO, Berg A, Imamura Kawasawa Y, Vgontzas AN, Fernandez-Mendoza J, et al. Habitual sleep variability, not sleep duration, is associated with caloric intake in adolescents. Sleep Med. 2015;16(7):856-861. https://doi.org/10.1016/j.sleep.2015.03.004
10. Huang T, Mariani S, Redline S. Sleep Irregularity and Risk of Cardiovascular Events: The Multi-Ethnic Study of Atherosclerosis. J Am Coll Cardiol. 2020;75(9):991-999. https://doi.org/10.1016/j.jacc.2019.12.054
11. Huang T, Redline S. Cross-sectional and Prospective Associations of Actigraphy-Assessed Sleep Regularity With Metabolic Abnormalities: The Multi-Ethnic Study of Atherosclerosis. Diabetes Care. 2019;42(8):1422-1429. https://doi.org/10.2337/dc19-0596
12. Slavish DC, Taylor DJ, Lichstein KL. Intraindividual variability in sleep and comorbid medical and mental health conditions. Sleep. 2019;42(6):zsz052. https://doi.org/10.1093/sleep/zsz052
13. Spina G, Spruit MA, Alison J, Benzo RP, Calverley PMA, Clarenbach CF, et al. Analysis of nocturnal actigraphic sleep measures in patients

with COPD and their association with daytime physical activity. Thorax. 2017;72(8):694-701. https://doi.org/10.1136/thoraxjnl-2016-208900

14. Rodrigues A, Camillo CA, Furlanetto KC, Paes T, Morita AA, Sposito T, et al. Cluster analysis identifying patients with COPD at high risk of 2-year all-cause mortality. Chron Respir Dis. 2019;16:1479972318809452. https://doi.org/10.1177/1479972318809452
15. Global Initiative for Chronic Obstructive Lung Disease [homepage on the Internet]. Bethesda: GOLD [cited 2021 Oct 1]. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease 2021 report. Available from: https://goldcopd.org
16. Miller MR, Crapo R, Hankinson J, Brusasco V, Burgos F, Casaburi R, et al. General considerations for lung function testing. Eur Respir J. 2005;26(1):153-161. https://doi.org/10.1183/09031936.05.00034505
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. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446. https://doi.org/10.1183/09031936.00150314
19. Britto RR, Probst VS, de Andrade AF, Samora GA, Hernandes NA, Marinho PE, et al. Reference equations for the six-minute walk distance based on a Brazilian multicenter study. Braz J Phys Ther. 2013;17(6):556-563. https://doi.org/10.1590/S1413-35552012005000122
20. Hill K, Dolmage TE, Woon L, Goldstein R, Brooks D. Measurement properties of the SenseWear armband in adults with chronic obstructive pulmonary disease. Thorax. 2010;65(6):486-491. https://doi.org/10.1136/thx.2009.128702
21. Rundo JV, Downey R 3rd. Polysomnography. Handb Clin Neurol. 2019;160:381-392. https://doi.org/10.1016/B978-0-444-64032-1.00025-4
22. Ancoli-Israel S, Cole R, Alessi C, Chambers M, Moorcroft W, Pollak CP. The role of actigraphy in the study of sleep and circadian rhythms. Sleep. 2003;26(3):342-392. https://doi.org/10.1093/sleep/26.3.342
23. Kohnen R, Allen RP, Benes H, Garcia-Borreguero D, Hening WA, Stiasny-Kolster K, et al. Assessment of restless legs syndrome--methodological approaches for use in practice and clinical trials [published correction appears in Mov Disord. 2008 Jun;23(8):1200-2]. Mov Disord. 2007;22 Suppl 18:S485-S494. https://doi.org/10.1002/mds.21588
24. Cormick W, Olson LG, Hensley MJ, Saunders NA. Nocturnal hypoxaemia and quality of sleep in patients with chronic obstructive lung disease. Thorax. 1986;41(11):846-854. https://doi.org/10.1136/thx.41.11.846
25. Lewis CA, Fergusson W, Eaton T, Zeng I, Kolbe J. Isolated nocturnal desaturation in COPD: prevalence and impact on quality of life and sleep. Thorax. 2009;64(2):133-138. https://doi.org/10.1136/thx.2007.088930
26. Calverley PM, Brezinova V, Douglas NJ, Catterall JR, Flenley DC. The effect of oxygenation on sleep quality in chronic bronchitis and emphysema. Am Rev Respir Dis. 1982;126(2):206-210.
27. McNicholas WT, Calverley PM, Lee A, Edwards JC; Tiotropium Sleep Study in COPD Investigators. Long-acting inhaled anticholinergic therapy improves sleeping oxygen saturation in COPD. Eur Respir J. 2004;23(6):825-831. https://doi.org/10.1183/09031936.04.00085804
28. Buysse DJ, Reynolds CF 3rd, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28(2):193-213. https://doi.org/10.1016/0165-1781(89)90047-4
29. Akinci B, Aslan GK, Kiyan E. Sleep quality and quality of life in patients with moderate to very severe chronic obstructive pulmonary disease. Clin Respir J. 2018;12(4):1739-1746. https://doi.org/10.1111/crj.12738
30. Nunes DM, de Bruin VM, Louzada FM, Peixoto CA, Cavalcante AG, Castro-Silva C, et al. Actigraphic assessment of sleep in chronic obstructive pulmonary disease. Sleep Breath. 2013;17(1):125-132. https://doi.org/10.1007/s11325-012-0660-z
31. Hirshkowitz M, Whiton K, Albert SM, Alessi C, Bruni O, DonCarlos L, et al. National Sleep Foundation's updated sleep duration recommendations: final report. Sleep Health. 2015;1(4):233-243. https://doi.org/10.1016/j.sleh.2015.10.004
32. Chaput JP, Dutil C, Featherstone R, Ross R, Giangregorio L, Saunders TJ, et al. Sleep timing, sleep consistency, and health in adults: a systematic review. Appl Physiol Nutr Metab. 2020;45(10 (Suppl. 2)):S232-S247. https://doi.org/10.1139/apnm-2020-0032
33. Abbott SM, Weng J, Reid KJ, Daviglus ML, Gallo LC, Loredo JS, et al. Sleep Timing, Stability, and BP in the Sueño Ancillary Study of the Hispanic Community Health Study/Study of Latinos. Chest. 2019;155(1):60-68. https://doi.org/10.1016/j.chest.2018.09.018
34. Okun ML, Reynolds CF 3rd, Buysse DJ, Monk TH, Mazumdar S, Begley A, et al. Sleep variability, health-related practices, and inflammatory markers in a community dwelling sample of older adults. Psychosom Med. 2011;73(2):142-150. https://doi.org/10.1097/PSY.0b013e3182020d08
35. Eagan TM, Ueland T, Wagner PD, Hardie JA, Mollnes TE, Damås JK, et al. Systemic inflammatory markers in COPD: results from the Bergen COPD Cohort Study. Eur Respir J. 2010;35(3):540-548. https://doi.org/10.1183/09031936.00088209
36. Fitzgibbons CM, Goldstein RL, Gottlieb DJ, Moy ML. Physical Activity in Overlap Syndrome of COPD and Obstructive Sleep Apnea: Relationship With Markers of Systemic Inflammation. J Clin Sleep Med. 2019;15(7):973-978. https://doi.org/10.5664/jcsm.7874
37. Al-shair K, Kolsum U, Dockry R, Morris J, Singh D, Vestbo J. Biomarkers of systemic inflammation and depression and fatigue in moderate clinically stable COPD. Respir Res. 2011;12(1):3. https://doi.org/10.1186/1465-9921-12-3
38. McNicholas WT. Impact of sleep in COPD. Chest. 2000;117(2 Suppl):48S-53S. https://doi.org/10.1378/chest.117.2_suppl.48S
39. Mulhall P, Criner G. Non-pharmacological treatments for COPD. Respirology. 2016;21(5):791-809. https://doi.org/10.1111/resp.12782

J Bras Pneumol. 2022;48(4):e20210511
https://dx.doi.org/10.36416/1806-3756/e20210511

ORIGINAL ARTICLE

Normative values and reference equation for the six-minute step test to evaluate functional exercise capacity: a multicenter study

Vanessa Salles Albuquerque[1], Simone Dal Corso[2], Daniel Pereira do Amaral[2], Túlio Medina Dutra de Oliveira[1], Gerson Fonseca Souza[3], Rachel Naara Silva de Souza[3], Ana Karolyn Menezes Nogueira[3], Pedro Dal Lago[4], Maria Luísa Rocha Dadalt[4], Isadora Faraco Correa[4], Graziella França Bernardelli Cipriano[5], Fabíola Maria Ferreira Silva[5], Raquel Rodrigues Britto[6], Anderson José[1], Carla Malaguti[1]

1. Programa de Pós-Graduação em Ciências de Reabilitação e Desempenho Físico-Funcional, Universidade Federal de Juiz de Fora – UFJF – Juiz de Fora (MG) Brasil.
2. Programa de Pós-Graduação em Ciências de Reabilitação, Universidade Nove de Julho – UNINOVE – São Paulo (SP) Brasil.
3. Departamento de Fisioterapia, Universidade Federal do Rio Grande do Norte – UFRN – Natal (RN) Brasil.
4. Programa de Pós-Graduação em Ciências de Reabilitação, Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA – Porto Alegre (RS) Brasil.
5. Programa de Pós-Graduação em Ciências e Tecnologias em Saúde. Universidade de Brasília – UnB – Brasília (DF) Brasil.
6. Programa de Pós-Graduação em Ciências de Reabilitação, Universidade Federal de Minas Gerais –UFMG – Belo Horizonte (MG) Brasil.

Submitted: 5 January 2022.
Accepted: 22 June 2022.

Study carried out at the Universidade Federal de Juiz de Fora – UFJF – Juiz de Fora (MG) Brasil; the Universidade Nove de Julho – UNINOVE – São Paulo (SP) Brasil; the Universidade Federal do Rio Grande do Norte – UFRN – Natal (RN) Brasil; the Universidade Federal de Ciências da Saúde de Porto Alegre – UFCSPA – Porto Alegre (RS) Brasil; and the Universidade de Brasília – UnB – Brasília (DF) Brasil.

ABSTRACT

Objective: To establish normative values and a reference equation for the number of steps climbed during the six-minute step test (6MST) in healthy adults, and to assess the reliability of the test and of the equation. **Methods:** This was a multicenter cross-sectional study involving 468 healthy volunteers (age range: 18-79 years) recruited from the general community in six research laboratories across different regions of Brazil, which is a country with continental dimensions. The 6MST was performed twice (30-min interval), and clinical, demographic, and functional variables were evaluated. An independent sample of 24 volunteers was evaluated to test the reference equation a posteriori. **Results:** The number of steps had excellent test-retest reliability (intraclass correlation coefficient = 0.96 [95%CI: 0.95-0.97]), and the mean number of steps was 175 ± 45, the number being 14% greater in males than in females. The best performance on the test was correlated with age (r = −0.60), sex (r = 0.28), weight (r = 0.13), height (r = 0.41), BMI (r = −0.22), waist circumference (r = −0.22), thigh circumference (r = 0.15), FVC (r = 0.54), and physical activity level (r = 0.17; $p < 0.05$ for all). In the regression analysis, age, sex, height, and weight explained 42% of the variability of the 6MST. Normative values were established for the 6MST according to age and sex. There was no difference between the 6MST values from the independent sample and its predicted values (157 ± 29 steps vs. 161 ± 25 steps; p = 0.47; 97% of predicted values). **Conclusions:** The normative values and the reference equation for the 6MST in this study seem adequate to accurately predict the physical functional performance in adults in Brazil.

Keywords: Exercise test; Physical functional performance; Patient outcome assessment; Reference values; Regression analysis.

INTRODUCTION

With the advent of the COVID-19 pandemic, rehabilitation programs were forced into remote and home delivery models.[1,2] While studies have progressively emerged showing that it is possible to provide physical training, physical activity (PA) counseling, education, and self-management training in settings that differ from traditional rehabilitation centers,[3,4] most exercise tests for initial assessment are still carried out at those centers. With regard to home-based rehabilitation programs, in order to assess exercise capacity, professionals have to make adaptations to create conditions and opportunities for accessibility in different inpatient and outpatient settings. To solve issues such as the need for space (e.g., long corridors) and difficulties in evaluating patients receiving supplemental oxygen, which are limitations that hinder the use of the six-minute walk test, interest has been increasing in the six-minute step test (6MST), a self-paced test in which an individual must go up and down a single step for six minutes.[5-7] The 6MST has the following advantages: it is an easy-to-perform, inexpensive, space-saving test

Correspondence to:
Carla Malaguti. Programa de Pós-Graduação em Ciências de Reabilitação e Desempenho Físico-Funcional, Universidade Federal de Juiz de Fora, Rua Eugênio do Nascimento, s/n, Dom Bosco, CEP 36038-330, Juiz de Fora, MG, Brasil.
Tel. 55 32 2102-3257. Email: carlamalaguti@gmail.com
Financial support: This study received partial financial support from the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Finance Code 001).

ISSN 1806-3756

that is practical for long-term oxygen therapy users and has been tested and proven to be reliable and valid in different clinical populations.[6,8-12] However, the need for normative values and well-established reference equations makes the interpretability of the test difficult.

One reference equation for the 6MST has been established.[13] However, there were some methodological limitations in that study[13] that may compromise the external validity of that equation. For instance, the study involved a small, single-center sample (N = 91), the method for selecting the participants was not reported, the study included obese volunteers, and there were few individuals in each age group. In addition, it was not possible to establish normative values, and the authors did not perform analyses with an independent sample to verify the reliability of the equation.[13] Thus, such limitations hamper the interpretation of the test and the identification of individuals with low functional capacity. Therefore, normative values and a reference equation based on a large multicenter sample could improve the interpretability of the 6MST. Normative and/or reference values characterize a defined population in a specific time period, evaluate and compare the performance of an individual within a population, establish comparisons between different clinical conditions, and evaluate the effectiveness of interventions.[14] Thus, the main objectives of the present study were to examine the reliability of the 6MST, to establish the normative values and a reference equation using a large multicenter sample comprising healthy adults from a wide range of ages, and validate the new reference equation for use in Brazil.

METHODS

Study design and ethical aspects

This was a multicenter cross-sectional study carried out in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.[15] Data were collected between March of 2018 and May of 2019. This study was approved by the Research Ethics Committee of the *Universidade Federal de Juiz de Fora* (Report n. 3.134.323). All volunteers gave written informed consent.

Procedures

The study prospectively included 476 healthy participants of both sexes (range: 18-79 years of age) who were able to understand and perform all of the procedures proposed. None had any disease that could limit exercise tolerance, such as pulmonary, cardiovascular (except for controlled hypertension without the use of a beta-blocker), and rheumatic diseases. Exclusion criteria were as follows: 18 kg/m^2 < BMI < 30 kg/m^2; alterations in lung function (FVC < 80% of the predicted value; FEV_1 < 80%; and FEV_1/FVC ratio < 0.7); and significant pain and/or discomfort at the time of evaluation.

The participants were recruited from all regions in Brazil: north, northeast, south, southeast, and central-west (see supplementary material).

Measurements

Anthropometric measurements such as weight and height were performed using a stadiometer with a mechanical scale (Welmy, São Paulo, Brazil). A tape measure was used for the determination of abdomen and leg circumference (see supplementary material).

Lung function was assessed before the 6MST in accordance with the Brazilian guidelines for pulmonary function tests.[16] The measurements were then compared with those predicted for the Brazilian population.[17] The PA level (see supplementary material) was determined using the short version of the International Physical Activity Questionnaire.[18,19]

Two 6MSTs were performed with a 30-min rest interval. A wooden step (20 cm high × 40 cm wide × 60 cm long) with no upper limb support was used. The test speed was not controlled and was determined by the participants themselves. The participants were instructed to go up and down the step for 6 min as many times as possible.[5] They received standardized instructions (see supplementary material) before the start of the test,[20] as well as verbal feedback.[21] HR, SpO_2, and blood pressure, as well as dyspnea and leg fatigue according to the modified Borg Scale,[22] were recorded at rest, immediately after the test, and after the first minute of recovery. The test was interrupted in cases of evidence of oxygen desaturation below 85%,[23] complaints of chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, dizziness, pale or ashen appearance, or any other sign that threatened the safety of the participant. The participant could choose to interrupt the test to rest; however, in any case, the timer was not stopped during the interruption. The best result of the two tests was used for the analysis.

After establishing the normative values and the reference equation, an independent sample of healthy participants from a single center, which was composed of individuals selected using the same eligibility criteria as in the initial sample, performed the 6MST to validate the normative values and the reference equation.

Sample size

For the calculation of the sample size, the equation by Tabachnick & Fidell[24] was used, which considers $N > 50 + 8K$, where K represents the number of independent variables. Eight independent variables (sex, weight, height, age, abdominal circumference, thigh circumference, calf circumference, and lower limb length) were used, resulting in at least 114 participants. However, we increased the sample size to include a representative number of subjects from each center due to various correlations and multiple regression analysis.

Statistical analysis

The data were analyzed using the IBM SPSS Statistics software package, version 26.0 (IBM Corp., Armonk, NY, USA). Data distribution was assessed using the Shapiro-Wilk test. Normally distributed data were expressed as means and standard deviations. The 10th percentile was calculated for age range and sex. Sex differences were analyzed with the t-test for independent variables or the Mann-Whitney U test, whereas comparisons among centers were assessed using the one-way ANOVA or the Kruskal-Wallis test, followed by post-hoc tests, when appropriate.

Reliability was analyzed using the intraclass correlation coefficient (ICC) of the two-way randoms effect model with 95% CIs with a single rating, $ICC_{(2,1)}$, and Bland-Altman analysis. The paired t-test was used in order to compare the performance between the first and second 6MST. The standard error of the mean (SEM) was calculated for the standard error of measurement (SEM = SD ´ $\sqrt{}$[1 − ICC]) and for the minimal detectable change (MDC) at 95% CI—absolute MDC = 1.96 × SEM × $\sqrt{}$2; and relative MDC (%) = (MDC/mean of 1st and 2nd tests) × 100.[25,26] The test-retest learning effect was calculated as follows: (learning effect (%) = [2nd test − 1st test]/1st test × 100).

The best of the two test results was considered to establish the normative values. Thus, normative values are presented separately by sex and 10-year age groups (18-28, 29-39, 40-49, 50-59, 60-69, and 70-79 years). The lower limit of normal was obtained from the following equation: mean value − (1.64 × SEE), where SEE is the standard error of the estimate.

Pearson's or Spearman's correlation coefficients were used, when appropriate, to verify the bivariate correlation between independent variables (age, weight, height, sex, BMI, abdominal circumference, thigh circumference, leg circumference, PA level, FVC, FEV_1 [in L and in % of predicted values for both], and FEV_1/FVC) and the dependent variable (number of steps).

To establish the reference equation to estimate the number of steps on the 6MST, the stepwise multiple linear regression analysis was used. Outliers (extremely high or low values) were excluded. Outliers were identified by the box plot: data points > 1.5 times above the upper quartile or below the lower quartile of the IQR. Only statistically significant variables were kept in the final model ($p < 0.05$). The best model was constructed considering the variables with the best independent coefficient of determination (R^2), and the SEE was calculated. Independent variables were checked for multicollinearity. There was no evidence for multicollinearity when tolerance values were > 0.1, the variance inflation factor was < 10, or correlation coefficients were < 0.7.[27] The normality of the residual values was tested using the Kolmogorov-Smirnov test with Lilliefors correction.

To verify the reliability of the proposed reference equations, data from an independent sample of 24 individuals recruited according to the same inclusion/exclusion criteria were used as an additional analysis. The independent sample was recruited from a single center in the southern region. The formula derived from the regression model was applied in this sample, and the predicted values were calculated for the 6MST. In addition, Bland-Altman plots were constructed using this independent sample to visualize the agreement between actual and predicted values for the 6MST. Statistical significance was set at $p < 0.05$ for all analyses.

RESULTS

Of the 570 healthy participants selected, 94 (16%) were excluded due to BMI ≥ 30 kg/m^2 (n = 24), altered spirometry (n = 39), and comorbidities (n = 31). Therefore, 476 were enrolled for initial analysis and, after removing outliers and participants who were unable to perform the second 6MST, 468 participants remained for all analyses (Figure 1). The included participants were divided by age range, in years: 18-28 (n = 135); 29-39 (n = 110); 40-49 (n = 65); 50-59 (n = 65); 60-69 (n = 60); and 70-79 (n = 33).

Multicenter sample characteristics

The overall sample comprised healthy individuals only; 58% were women, 60% were physically active or very active, and the age range was 18-79 years (Table 1). A more detailed view of all results from each center is available in the supplementary material (Table S1).

Performance and reliability of the test

The reliability analysis included 468 participants. Physiological responses and symptoms induced by the first and second 6MST (6MST-1 and 6MST-2) are reported in Table S2. Regarding the number of steps, although there was a statistical difference between 6MST-1 and 6MST-2 (169 ± 38 steps vs. 175 ± 45 steps; $p < 0.001$), this was lower than the absolute and relative MDC (21 steps and 12%, respectively), with excellent agreement (ICC: 0.96; 95% CI: 0.95-0.97), and SEM was 7.79. The learning effect between 6MST-1 and 6MST-2 was 4.2 ± 13.7%. The Bland-Altman analysis showed that the agreement between the number of steps climbed during the two tests had a mean difference of −8 steps, with limits of agreement between −39 and 22 steps (Figure S1).

Normative values

The mean number of steps climbed during the 6MST was 175 ± 45 (95%CI: 171-179). In general, the mean number of steps was 14% lower for women than for men, and elderly individuals had worse performances on the test. Table 2 shows the mean, standard deviation, 95% CI, and lower limit of normal for the 6MST in the total sample and also by age group and sex. In the independent sample, all participants

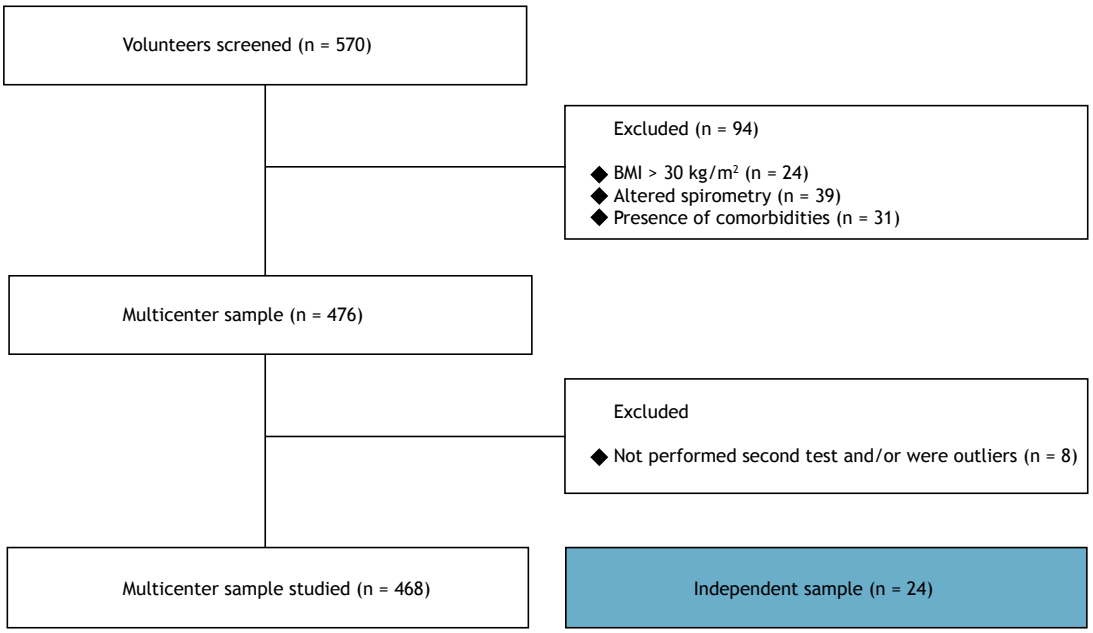


Figure 1. Flow chart of the participant selection process.

reached more than 80% of the normative value for the 6MST (Table 2).

Reference equation

The results of the correlation analysis of anthropometric, demographic, and physiological variables with the best performances on the 6MST are shown in Table 3. The number of steps climbed showed significant positive correlations with, sex, weight, height, thigh circumference, calf circumference, PA level, and FVC (in L and in % of predicted value), whereas it showed significant negative correlations with age, BMI, and waist circumference.

To establish the reference equation, variables that showed a significant correlation with the number of steps were tested in the regression analysis. There was no multicollinearity between the independent variables. The regression analysis showed that age, sex, height, and weight explained 42% of the variability in the 6MST: $F(4,463) = 87.117$; $p < 0.001$; $R^2 = 0.42$. The results revealed the following equation (Table 4):

$$6MST = 106 + (17.02 \times [0:woman; 1:man]) + (-1.24 \times age) + (0.8 \times height) + (-0.39 \times weight)$$

where 6MST is expressed in number of steps; age, in years; height, in cm; and weight, in kg.

Reliability of the reference equation

The independent sample consisted of 24 participants (12 men), with a mean age of 48.0 ± 3.5 years, a mean BMI of 25 ± 3 kg/m^2, and a mean FEV_1 of 96 ± 9% of the predicted value (Table 1). When the reference equation for 6MST was applied to this group, there was no difference between the number of steps climbed during the 6MST and the estimated value from the reference equation (157 ± 29 steps vs. 161 ± 26 steps; $p = 0.47$), with a mean difference of 4 steps and a 95%CI of −10 to 2 steps. Bland-Altman plots for this comparison can be seen in the supplementary material (Figure S1).

DISCUSSION

The present study established normative values for the number of steps climbed during the 6MST in adult participants. Men climbed more steps than did women, and younger participants climbed more steps than older participants, respectively. This study also provided an accurate reference equation for the 6MST. It should be emphasized that this study had three robust methodological features: a large sample for the purpose of establishing 6MST normative values, a multicenter design, and a prospective validation of the normative values.

As expected, elderly individuals had worse performances on the 6MST. Aging is associated with reduced aerobic and anaerobic capacity, resulting from reduced cardiovascular function and from changes in oxidative capacity, and muscle fiber type, as well as in of skeletal muscle structure and function.[28,29] Therefore, this decline seems to be due to both central and peripheral adaptations. Other studies have shown similar results in the relationship between age and exercise capacity using different exercise tests.[13,30]

There was no difference between the normative values in the present study and performance in the independent sample. The 6MST results of all participants were higher than 80% of the predicted value in relation to the normative value. Therefore, we suggest that the normative values in the present

Table 1. Sample characteristics.[a]

Variable	Multicenter sample				Independent sample	
	Total (N = 468)	Male (n = 198)	Female (n = 270)	p*	Total (n = 24)	p**
Age, years	41 ± 17	40 ± 17	42 ± 18	0.15	48 ± 16	0.05
Height, cm	165 ± 10	173 ± 8	160 ± 7	< 0.01	167 ± 8	0.49
Weight, kg	68 ± 13	77 ± 12	62 ± 9	< 0.01	71 ± 13	0.37
BMI, kg/m^2	25 ± 3	25 ± 3	24 ± 3	< 0.01	25 ± 3	0.47
WC, cm	87 ± 10	91 ± 10	84 ± 10	< 0.01	88 ± 11	0.45
LRLL, cm	84 ± 8	87 ± 8	83 ± 8	< 0.01	86 ± 7	0.25
TC, cm	54 ± 6	53 ± 6	54 ± 6	0.09	51 ± 5	0.02
CC, cm	36 ± 3	37 ± 3	35 ± 3	< 0.01	37 ± 3	0.25
Spirometry						
FVC, L	3.7 ± 1.0	4.6 ± 0.8	3.1 ± 0.6	< 0.01	3.8 ± 1.0	0.78
FVC, % predicted	94 ± 10	96 ± 11	93 ± 9	0.01	91 ± 8	0.06
FEV_1, L	3.2 ± 0.8	3.8 ± 0.7	2.7 ± 0.5	0.08	3.2 ± 0.8	0.84
FEV_1, % predicted	98 ± 11	99 ± 12	98 ± 10	0.32	96 ± 9	0.18
FEV_1/FVC	86 ± 6	85 ± 6	87 ± 6	0.01	86 ± 7	0.69
Comorbidities						
Hypertension	47 (10)	19 (10)	28 (10)	0.70	8 (33)	< 0.01
Diabetes	8 (2)	1 (0.5)	7 (2)	0.08	1 (4)	0.36
Smoking	9 (2)	6 (3)	3 (1)	0.08	0 (0)	0.63
BMI classification						
Underweight	11 (2)	4 (2)	7 (2)	< 0.01	2 (8)	0.40
Normal weight	242 (51)	84 (42)	158 (58)		8 (33)	
Overweight	215 (46)	110 (55)	105 (39)		14 (58)	
Age range, years						
18-28	135 (29)	64 (32)	71 (26)	0.10	4 (17)	0.04
29-39	110 (23)	47 (24)	63 (23)		4 (17)	
40-49	65 (14)	26 (13)	39 (14)		4 (17)	
50-59	65 (14)	26 (13)	39 (14)		4 (17)	
60-69	60 (13)	24 (12)	36 (13)		4 (17)	
70-79	33 (7)	11 (5)	22 (8)		4 (17)	
IPAQ						
Very active	58 (12)	30 (15)	29 (11)	< 0.01		
Active	226 (48)	78 (38)	149 (55)			
Irregularly active A	77 (16)	36 (18)	41 (15)			
Irregularly active B	74 (16)	39 (19)	35 (13)			
Sedentary	39 (8)	22 (11)	17 (6)			

[a]Values expressed as n (%) or mean ± SD. WC: waist circumference; LRLL: length of right lower limb; TC: thigh circumference; CC: calf circumference; and IPAQ: International Physical Activity Questionnaire.

study be used in order to interpret the results of the 6MST. To show the clinical application of our normative values, the number of steps was expressed as a proportion of the normative values in the present study. It is important to mention that, although the limit of 85% of the maximum HR predicted to stop the test was not adopted in the present study, this may be an important criterion to ensure safety in some clinical populations (e.g., patients with cardiac comorbidities).

The predicted equation accurately estimated the number of steps. Sex, age, weight, and height were the independent variables that remained in the equation. In general, men have less body fat and greater aerobic capacity than do women.[31,32] It should be noted that if a clinician/researcher wants to verify whether the performance of an individual (for example, a patient with a respiratory problem) on the 6MST can be classified as reduced functional exercise capacity, the lower limit of normal for that individual must be calculated. This can be done using the predicted mean value of the equation (1.64 × SEE)[33] or using the 10th percentile.[34] In the present study, men performed better than women by an average of 26 steps. Some physiological differences between the sexes, such as body composition, cardiovascular function, lung function, substrate metabolism, and thermoregulation, may influence exercise performance.[35] As previously mentioned, aging leads to changes in body structure and function.

Table 2. Normative values for the six-minute step test (in number of steps), by sex and age.

Age range, years	Total (N = 468)		Male (n = 198)		Female (n = 270)		Mean difference (95%CI)
	n ± SD (95%CI)	10th percentile	n ± SD (95%CI)	10th percentile	n ± SD (95%CI)	10th percentile	
18-28 (n = 135)	203 ± 36 (197-209)	158	217 ± 38 (207-227)	171	190 ± 28 (183-196)	150	27 (16-38)*
29-39 (n = 110)	191 ± 36 (185-198)	145	200 ± 34 (190-209)	159	185 ± 36 (176-194)	137	14 (0.7-27.0)*
40-49 (n = 66)	168 ± 36 (159-177)	125	177 ± 22 (168-186)	141	163 ± 42 (149-176)	113	14 (3.8-32.0)*
50-59 (n = 67)	163 ± 33 (154-171)	123	176 ± 34 (162-190)	137	154 ± 30 (144-164)	122	21 (5.6-38.0)*
60-69 (n = 60)	137 ± 42 (126-148)	99	153 ± 49 (132-174)	91	127 ± 32 (116-138)	96	26 (5-47)*
70-79 (n = 33)	118 ± 43 (103-133)	68	147 ± 25 (130-164)	107	104 ± 43 (85-123)	80	43 (14-72)*

*p < 0.05 for the difference between male and female.

Table 3. Correlation between the outcome variable (total number of steps) on the better of the two six-minute step tests) and dependent variables.

Independent variable	Best test result	
	R	p
Age, years	−0.60	< 0.01
Sex	0.28	< 0.01
Weight, kg	0.13	0.01
Height, cm	0.41	< 0.01
BMI, kg/m²	−0.22	< 0.01
WC, cm	−0.22	< 0.01
LRLL, cm	0.04	0.37
TC, cm	0.15	0.01
CC, cm	0.14	0.01
FVC, L	0.54	< 0.01
FVC, % predicted	0.23	< 0.01
FEV_1, L	0.01	0.95
FEV_1, % predicted	0.03	0.53
FEV_1/FVC	0.01	0.95
Physical activity level	0.17	< 0.01

WC: waist circumference; LRLL: length of right lower limb; TC: thigh circumference; and CC: calf circumference.

Weight influences the performance on the 6MST, as it increases the workload due to horizontal and vertical displacements against gravity that occur when climbing the step.[36] Height was probably considered a factor because the taller the person is, the longer his/her legs are, allowing them to favor the climb mechanically and contributing to the execution of a greater number of steps during the test.[37] The fact that the coefficient of determination was moderate may suggest that other independent variables, such as muscle mass and motivation, may also contribute to determining the performance on the 6MST. However, the reference equation obtained in the present study is attractive, because the independent variables are easily available in clinical practice. In this context, Arcuri et al.[13] proposed the first reference equation for the 6MST, showing that age and sex accounted for 48% of the variation in test performance and that the increase in waist circumference accounted for 2% of the test variance. However, that study had some limitations that may restrict its external validity,[13] including the fact that the study was conducted in a small single-center sample (91 participants) and that the equation was not tested prospectively in an independent sample. Although it was not an aim of the present study, we tested the reliability of the equations proposed by Arcuri et al.[13] using the performance of our independent sample, and those equations produced a larger standard deviation of the differences and showed a tendency toward underestimating the prediction of performance on the 6MST. However, our proposed equation was considered valid, as there was no significant difference between the actual and predicted number of steps climbed by the independent sample, and the mean of the differences between both was lower than the MDC.

Although the 6MST is reliable, at present, there is no clear indication that one test is sufficient; therefore, two tests are recommended to account for any potential learning effect. Furthermore, the learning effect of the 6MST was considered small in healthy subjects but should be investigated in clinical conditions. An SEM of 7.79 and an MDC of 21 steps were also identified. Thus, in order to consider that there is an improvement in 6MST performance, the number of steps should increase by more than 21 steps. Our error rate and MDC were lower than the MDC of 27.26 steps and the SEM of 11.75 reported by Arcuri et al.[13] We believe that this difference is due to the methodological characteristics of the present study, in which a stratified sample enabled by a larger sample size was included and age groups were better distributed.

Research on the 6MST has been desirable and timely. It is expected that the 6MST will be more frequently used with advances in new intervention strategies, such as telerehabilitation and home-based rehabilitation. In the current scenario, only 5% of individuals with an indication for pulmonary rehabilitation have access to

Table 4. Stepwise multiple linear regression model for the six-minute step test.

Variable	Unstandardized coefficient (B)	95% CI	SEE	p	Standardized coefficient (Beta)
Constant	106	20.45 to 191.85	43.611	0.015	
Sex	17.02	8.30 to 25.73	0.108	< 0.001	0.185
Age	−1.24	−1.58 to −1.16	4.435	< 0.001	−0.522
Height, cm	0.8	0.29 to 1.46	0.299	< 0.001	0.194
Weight, kg	−0.39	−0.77 to −0.005	0.196	0.04	−0.110

SEE: standard error of the estimate. Sex code: [0: woman; 1: man].

the 6MST and complete it with good adherence.[38] The reasons behind this fact are multifactorial, including logistical issues, socioeconomic barriers, and family dependency. However, traditional assessment tests such as the six-minute walk test and the shuttle walk test are difficult to apply at home because of the need for physical space. In this context, the 6MST is a potential alternative method for the evaluation of this population.

This study has some limitations. There were fewer participants in the older age group. However, a statistical difference could still be observed in the performance of this group when compared with other age groups. More recent data from the United Nations have shown that the world population still has a higher proportion of young people (> 15 years of age), estimated at 65.3% of the total population, than that of older people (> 65 years of age), who account for 9.1% of the total population.[39] The proportions of participants by age group in our study corresponded with the proportions in the real world. Although participants were provided with a structured questionnaire about their health condition at the time of screening (the exception being spirometry), they did not undergo physical examinations, and medical records were not reviewed. It is therefore possible that some of the self-reported "healthy" participants had a disqualifying medical condition. Regarding PA, our results show estimates of participants categorized as more physically active than the general population. This may have happened for two reasons: i) the assessment of active/inactive physical behavior was performed using a questionnaire, which is known not to be as reliable as activity monitors; and ii) bias associated with voluntarism, which tends to attract more people who are physically active in studies involving exercise/PA. There were few variable adjustments in the models. The small size of the independent sample, recruited from a single center, was not calculated a priori to test the accuracy of the equation, which is also a limitation. However, the reliability of the equation must be confirmed in future studies involving other populations.

In conclusion, this study has provided accurate normative values and a reference equation for the 6MST based on a large sample of healthy individuals within an age range between 18 and 79 years in Brazil. These findings might facilitate the identification, quantification, and interpretation of functional impairments with a quick, easy-to-perform test for use in clinical practice and research.

ACKNOWLEDGEMENTS

We would like to thank Polyana F Carvalho, undergraduate student at the *Universidade Federal do Rio Grande do Norte*, as well as Ynaê P Cabreira, Jullyane Maria Lima, Douglas O Marques and Rayssa C R Nascimento, undergraduate students at the *Universidade Federal do Pará*.

AUTHOR CONTRIBUTIONS

VSA and CM: guarantors of the data, the data analysis, and the study. SDC, DPA, TMDO, GFS, AKM, PDL, MLRD, IFC, AJ, GFBC, FM, and RRB: study design; data analysis and interpretation; drafting and review of the manuscript. All authors have read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Dechman G, Aceron R, Beauchamp M, Bhutani M, Bourbeau J, Brooks D, et al. Delivering pulmonary rehabilitation during the COVID-19 pandemic: A Canadian Thoracic Society position statement. Can J Respir Crit Care Sleep Med. 2020;23(4):232-5. https://doi.org/10.1080/24745332.2020.1828683
2. Garvey CNP, Holland APT, Corn J. Pulmonary rehabilitation resources in a complex and rapidly changing world. American Thoracic Society [serial on the Internet] 2020 Mar 30. [4 p.]. Available from: https://www.thoracic.org/members/assemblies/assemblies/pr/resources/pr-resources-in-a-complex-and-rapidly-changing-world-3-27-2020.pdf
3. Holland AE, Mahal A, Hill CJ, Lee AL, Burge AT, Cox NS, et al. Home-based rehabilitation for COPD using minimal resources: a randomised, controlled equivalence trial. Thorax. 2017;72(1):57-65. https://doi.org/10.1136/thoraxjnl-2016-208514
4. Andrade GN, Umeda IIK, Fuchs ARCN, Mastrocola LE, Rossi-Neto JM, Moreira DAR,, et al. Home-based training program in patients with chronic heart failure and reduced ejection fraction: a randomized pilot study. Clinics (Sao Paulo). 2021;76:e2550. https://doi.org/10.6061/clinics/2021/e2550
5. Bui KL, Nyberg A, Maltais F, Saey D. Functional Tests in Chronic Obstructive Pulmonary Disease, Part 2: Measurement Properties. Ann Am Thorac Soc. 2017;14(5):785-794. https://doi.org/10.1513/AnnalsATS.201609-734AS

6. Dal Corso S, Duarte SR, Neder JA, Malaguti C, de Fuccio MB, de Castro Pereira CA, et al. A step test to assess exercise-related oxygen desaturation in interstitial lung disease. Eur Respir J. 2007;29(2):330-336. https://doi.org/10.1183/09031936.00094006
7. Holland AE, Malaguti C, Hoffman M, Lahham A, Burge AT, Dowman L, et al. Home-based or remote exercise testing in chronic respiratory disease, during the COVID-19 pandemic and beyond: A rapid review. Chron Respir Dis. 2020;17:1479973120952418. https://doi.org/10.1177/1479973120952418
8. da Silva TD, Raimundo RD, Ferreira C, Torriani-Pasin C, Monteiro CB, Theodoro Júnior OA, et al. Comparison between the six-minute walk test and the six-minute step test in post stroke patients. Int Arch Med. 2013;6:31. https://doi.org/10.1186/1755-7682-6-31
9. Fioritto AP, Oliveira CC, Albuquerque VS, Almeida LB, Granger CL, Denehy L, et al. Individualized in-hospital exercise training program for people undergoing hematopoietic stem cell transplantation: a feasibility study. Disabil Rehabil. 2021;43(3):386-392. https://doi.org/10.1080/09638288.2019.1626493
10. Travensolo CF, Arcuri JF, Polito MD. Validity and reliability of the 6-min step test in individuals with coronary artery disease. Physiother Res Int. 2020;25(1):e1810. https://doi.org/10.1002/pri.1810
11. Marinho RS, Jürgensen SP, Arcuri JF, Goulart CL, Santos PBD, Roscani MG, et al. Reliability and validity of six-minute step test in patients with heart failure. Braz J Med Biol Res. 2021;54(10):e10514. https://doi.org/10.1590/1414-431x2020e10514
12. Magalhães MGS, Teixeira JB, Santos AMB, Clímaco DCS, Silva TNS, Lima AMJ. Construct validity and reproducibility of the six-minute step test in subjects with obstructive sleep apnea treated with continuous positive airway pressure. J Bras Pneumol. 2020;46(3):e20180422. https://doi.org/10.36416/1806-3756/e20180422
13. Arcuri JF, Borghi-Silva A, Labadessa IG, Sentanin AC, Candolo C, Pires Di Lorenzo VA. Validity and Reliability of the 6-Minute Step Test in Healthy Individuals: A Cross-sectional Study. Clin J Sport Med. 2016;26(1):69-75. https://doi.org/10.1097/JSM.0000000000000190
14. Gräsbeck R. The evolution of the reference value concept. Clin Chem Lab Med. 2004;42(7):692-697. https://doi.org/10.1515/CCLM.2004.118
15. von Elm E, Altman DG, Egger M, Pocock SJ, Gotzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies [Article in Spanish]. Rev Esp Salud Publica. 2008;82(3):251-259. https://doi.org/10.1016/j.jclinepi.2007.11.008
16. Sociedade Brasileira de Pneumologia e Tisiologia (SBPT). Diretrizes para testes de função pulmonar. J Bras Pneumol. 2002;28(Suppl 3):S1-S238.
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. Matsudo S, Araújo T, Matsudo V, Andrade D, Andrade E, Oliveira LC, et al. International physical activity questionnaire (IPAQ): study of validity and reliability in Brazil. Rev Bras Ativ Fis Saude. 2001;6(2):5-18. https://doi.org/10.12820/rbafs.v.6n2p5-18
19. Lee PH, Macfarlane DJ, Lam TH, Stewart SM. Validity of the International Physical Activity Questionnaire Short Form (IPAQ-SF): a systematic review. Int J Behav Nutr Phys Act. 2011;8:115. https://doi.org/10.1186/1479-5868-8-115
20. da Costa JN, Arcuri JF, Goncalves IL, Davi SF, Pessoa BV, Jamami M, et al. Reproducibility of cadence-free 6-minute step test in subjects with COPD. Respir Care. 2014;59(4):538-542. https://doi.org/10.4187/respcare.02743
21. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446. https://doi.org/10.1183/09031936.00150314
22. Borg G. Psychophysical scaling with applications in physical work and the perception of exertion. Scand J Work Environ Health. 1990;16 Suppl 1:55-58. https://doi.org/10.5271/sjweh.1815
23. Cecins N, Landers H, Jenkins S. Community-based pulmonary rehabilitation in a non-healthcare facility is feasible and effective. Chron Respir Dis. 2017;14(1):3-10. https://doi.org/10.1177/1479972316654287
24. Tabachnick BG, Fidell LS. Using Multivariate Statistics. 6th ed. Boston: Prentice Hall; 2013.
25. de Vet HC, Terwee CB, Knol DL, Bouter LM. When to use agreement versus reliability measures. J Clin Epidemiol. 2006;59(10):1033-1039. https://doi.org/10.1016/j.jclinepi.2005.10.015
26. Weir JP. Quantifying test-retest reliability using the intraclass correlation coefficient and the SEM. J Strength Cond Res. 2005;19(1):231-240. https://doi.org/10.1519/00124278-200502000-00038
27. Vatcheva KP, Lee M, McCormick JB, Rahbar MH. Multicollinearity in Regression Analyses Conducted in Epidemiologic Studies. Epidemiology (Sunnyvale). 2016;6(2):227. https://doi.org/10.4172/2161-1165.1000227
28. Hawkins S, Wiswell R. Rate and mechanism of maximal oxygen consumption decline with aging: implications for exercise training. Sports Med. 2003;33(12):877-888. https://doi.org/10.2165/00007256-200333120-00002
29. Wanderley FA, Silva G, Marques E, Oliveira J, Mota J, Carvalho J. Associations between objectively assessed physical activity levels and fitness and self-reported health-related quality of life in community-dwelling older adults. Qual Life Res. 2011;20(9):1371-1378. https://doi.org/10.1007/s11136-011-9875-x
30. Iwama AM, Andrade GN, Shima P, Tanni SE, Godoy I, Dourado VZ. The six-minute walk test and body weight-walk distance product in healthy Brazilian subjects [published correction appears in Braz J Med Biol Res. 2010 Mar;43(3):324]. Braz J Med Biol Res. 2009;42(11):1080-1085. https://doi.org/10.1590/S0100-879X2009005000032
31. Blaak E. Gender differences in fat metabolism. Curr Opin Clin Nutr Metab Care. 2001;4(6):499-502. https://doi.org/10.1097/00075197-200111000-00006
32. Cureton K, Bishop P, Hutchinson P, Newland H, Vickery S, Zwiren L. Sex difference in maximal oxygen uptake. Effect of equating haemoglobin concentration. Eur J Appl Physiol Occup Physiol. 1986;54(6):656-660. https://doi.org/10.1007/BF00943356
33. Machado FVC, Bisca GW, Morita AA, Rodrigues A, Probst VS, Furlanetto KC, et al. Agreement of different reference equations to classify patients with COPD as having reduced or preserved 6MWD. Pulmonology. 2017;S2173-5115(17)30151-3. https://doi.org/10.1016/j.rppnen.2017.08.007
34. Furlanetto KC, Correia NS, Mesquita R, Morita AA, do Amaral DP, Mont'Alverne DGB, et al. Reference Values for 7 Different Protocols of Simple Functional Tests: A Multicenter Study. Arch Phys Med Rehabil. 2022;103(1):20-28.e5. https://doi.org/10.1016/j.apmr.2021.08.009
35. Harms CA, Cooper D, Tanaka H. Exercise physiology of normal development, sex differences, and aging. Compr Physiol. 2011;1(4):1649-1678. https://doi.org/10.1002/cphy.c100065
36. REEDY JD, SAIGER GL, HOSLER RH. Evaluation of the Harvard Step Test with respect to factors of height and weight. Int Z Angew Physiol. 1958;17(2):115-119. https://doi.org/10.1007/BF00695202
37. Nyberg LA, Hellénius ML, Wändell P, Kowalski J, Sundberg CJ. Maximal step-up height as a simple and relevant health indicator: a study of leg muscle strength and the associations to age, anthropometric variables, aerobic fitness and physical function. Br J Sports Med. 2013;47(15):992-997. https://doi.org/10.1136/bjsports-2013-092577
38. An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation [published correction appears in Am J Respir Crit Care Med. 2014 Jun 15;189(12):1570]. Am J Respir Crit Care Med. 2013;188(8):e13-e64.
39. United Nations. Department of Economic and Social Affairs [homepage on the Internet]. New York City: United Nations [updated 2019 Aug 28; cited 2021 Nov 1]. World Population Prospects 2019. Available from: https://population.un.org/wpp

J Bras Pneumol. 2022;48(4):e20220015
https://dx.doi.org/10.36416/1806-3756/e20220015

Incidental chest findings on coronary CT angiography: a pictorial essay and management proposal

Erique Pinto[1], Diana Penha[1,2], Bruno Hochhegger[3], Colin Monaghan[2], Edson Marchiori[4,5], Luís Taborda-Barata[1], Klaus Irion[2]

1. Faculdade de Ciências da Saúde, Universidade da Beira Interior, Covilhã, Portugal.
2. Imaging Department, Liverpool Heart and Chest Hospital NHS Foundation Trust, Liverpool, United Kingdom.
3. Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
4. Faculdade de Medicina, Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
5. Faculdade de Medicina, Universidade Federal Fluminense, Niterói (RJ) Brasil.

Submitted: 18 January 2022.
Accepted: 7 March 2022.

Study carried out at the Liverpool Heart and Chest Hospital, NHS Foundation Trust, Liverpool, United Kingdom.

ABSTRACT

Many health systems have been using coronary CT angiography (CCTA) as a first-line examination for ischaemic heart disease patients in various countries. The rising number of CCTA examinations has led to a significant increase in the number of reported incidental extracardiac findings, mainly in the chest. Pulmonary nodules are the most common incidental findings on CCTA scans, as there is a substantial overlap of risk factors between the population seeking to exclude ischaemic heart disease and those at risk of developing lung cancer (i.e., advanced age and smoking habits). However, most incidental findings are clinically insignificant and actively pursuing them could be cost-prohibitive and submit the patient to unnecessary and potentially harmful examinations. Furthermore, there is little consensus regarding when to report or actively exclude these findings and how to manage them, that is, when to trigger an alert or to immediately refer the patient to a pulmonologist, a thoracic surgeon or a multidisciplinary team. This pictorial essay discusses the current literature on this topic and is illustrated with a review of CCTA scans. We also propose a checklist organised by organ and system, recommending actions to raise awareness of pulmonologists, thoracic surgeons, cardiologists and radiologists regarding the most significant and actionable incidental findings on CCTA scans.

Keywords: Incidental findings; Cardiac-gated imaging techniques; Coronary angiography; Lung neoplasms.

INTRODUCTION

Coronary CT angiography (CCTA) has recently been included in the guidelines for the diagnosis and management of coronary artery disease by several international cardiological societies, such as the American Heart Association/American College of Cardiology, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery.[1] In addition, the National Institute for Health and Care Excellence also recommends CCTA as a first-line test for evaluating stable angina based on cost-effectiveness and diagnostic accuracy.[2,3]

Numerous incidental findings (IFs) can be documented by CCTA, despite the small field of view (FOV) and optimised protocol for cardiac anatomy and function. A systematic review by Kay et al.[4] reported IFs in 45% of CCTA scans (7-100%).

Most IFs are clinically insignificant and pursuing them can add unnecessary costs and occasionally harmful evaluations. However, some IFs might present an alternative explanation for symptoms often misinterpreted as ischaemic heart disease (IHD).[5] In addition, the opportunity for dual screening (i.e., screening for IHD and lung cancer) in a population that shares risk factors of both diseases (e.g., advanced age and smoking habits) is appealing and could be achieved by using the full FOV.[6]

CCTA services have been successfully implemented worldwide, being most often the result of a partnership between radiologists and cardiologists. However, the service provision, multidisciplinary support, referral pathways and even access to relevant clinical information or previous examinations are very dependent on local practice, expertise and resources.[2] Therefore, clear guidelines for reporting and managing IFs are challenging to be implemented, but the need for multidisciplinary collaboration, including pulmonologists and thoracic surgeons, is widely recognised.

This pictorial essay reviews the most common IFs on CCTA scans, organised by organ and structure (Table 1) and discusses their clinical significance and proposed management.

Lung

IFs of the lung are the most common ones, with pulmonary nodules (PNs) or masses occurring in 14% to 38% of CCTA scans.[4,5] Multiple international societies provide guidelines for investigating and managing PNs that exceed 5 mm in diameter (or 80 mm^3 in volume) or show suspicious features.[7-11] Suspicious

Correspondence to:
Erique Pinto. Rua Luís de Camões, 102, lt 8, 3º esq, 1300-356, Lisboa, Portugal.
Tel: 44 749290-9500 or 351 96 1174460. E-mail: ericguedespinto@gmail.com
Financial support: None.

ISSN 1806-3756

Table 1. Checklist of incidental findings on coronary CT angiography per organ/system.

- Lung
  - Solid pulmonary nodule
    - < 5 mm or < 80 mm^3 with no suspicious features (e.g., granulomas, IPLNs)
      - → Reporting is optional, and no follow-up is required
    - > 5 mm, previously unknown or with suspicious features
      - → Report and alert the respiratory team
      - 5-8 mm → Baseline LDCT and provide an LDCT follow-up schedule
        - 5-6 mm: LDCT within one year
        - 6-8 mm: LDCT within three months
      - > 8 mm or > 300 mm^3 → Assess the risk of cancer (Brock model)
        - < 10% risk of cancer: baseline LCDT and follow-up LDCT within one year
        - ≥ 10% risk of cancer: referral to lung cancer MDT
  - Subsolid pulmonary nodule
    - ≥ 5 mm → Report to and alert the respiratory team
      - → Baseline LDCT and provide a follow-up schedule within three months
      - Stable after ≥ 3 months: assess the risk of cancer (Brock model)
        - < 10% risk of cancer: follow-up LDCT within one year
        - ≥ 10% risk of cancer: referral to lung cancer MDT
      - Growing or altered morphology → Referral to lung cancer MDT
  - Pulmonary emboli → Report and urgent referral to the respiratory team
  - ILAs → Report to and alert the respiratory team
    - In the presence of respiratory symptoms, physiological abnormalities, gas transfer abnormalities and extensive CT changes → Referral to the respiratory team/ILD MDT meeting
    - In the presence of risk factors for progression → Follow-up may be appropriate even after exclusion of ILD (the optimal interval for follow-up CT scanning is unknown)
  - Infection/Consolidation
    - → Report and referral to the respiratory team if not already under their care
    - → CT reassessment after therapy
  - Emphysema → Report and grade severity
  - Bronchiectasis, atelectasis → Report
- Pleura
  - Pneumothorax (rare) → Report and urgent referral to the medical emergency team
  - Pleural plaques → Report
    - in lung cancer patients: differentiate pleural plaques from pleural metastases
    - in asbestos exposure: assess signs suspicious for mesothelioma
  - Pleural effusion → Report
    - in cardiac patients it may be related to heart failure: trigger an alert
- Mediastinum
  - Pneumomediastinum (rare) → Report and urgent referral to the medical emergency team
  - Mediastinal nodule or mass → Report
    - if presenting suspicious features → Referral to the cardiothoracic surgical team
    - if benign-looking → Suggest annual CT follow-up or MRI characterisation
  - Aorta and pulmonary vessels → Report abnormalities in the context of the patient's cardiovascular disease
  - Lymphadenopathy → Report
    - if suspicious features or absence of an explaining disease to justify lymphadenopathy → Consider providing a follow-up schedule or suggest further characterisation with PET-CT or biopsy
  - Oesophageal hiatus hernia → Report
    - In the presence of heartburn (confounding symptom) → Referral to gastrointestinal evaluation
- Chest wall
  - Bone
    - 'Do not touch' lesions → Report but no follow-up required
    - Degenerative bony changes → Report (may cause atypical chest pain)
    - Suspicious bone lesions → Report and trigger an alert
  - Skin, subcutaneous and muscle lesions → Report new or previously undiagnosed lesions
  - Breast → Report new or previously undiagnosed lesions and alert breast team

Continue...▶

Table 1. Checklist of incidental findings on coronary CT angiography per organ/system. (Continued...)

Upper abdomen
Liver
Simple hepatic cysts → Reporting is optional, and no follow-up is required
Other focal parenchymal lesions → Report if previously undiagnosed and suggest further evaluation with triple-phase CT or MRI
Biliary system
Abnormal appearance of the gallbladder wall, biliary obstruction or pneumobilia → Report and suggest further evaluation
Gallstones → Reporting is optional, and no follow-up is required
Adrenal glands, pancreas, stomach and spleen
Any cystic or solid lesions, or splenomegaly → Report and suggest further evaluation if previously undiagnosed
Kidneys
Simple or minimally complex renal cysts (Bosniak I and II) → Reporting is optional, and no follow-up is required
Complex renal cysts → Report and suggest further evaluation
Solid renal masses → Report and trigger an alert
Peritoneum
Nodules, infiltrative masses, haziness, ascites, peritoneal thickening or implants → Report, alert and suggest further evaluation
Lymphadenopathy → Report and suggest further evaluation

IPLNs: intrapulmonary lymph nodes; LDCT: low-dose CT; MDT: multidisciplinary team; ILAs: interstitial lung abnormalities; and ILD: interstitial lung disease.

features of malignancy in PNs include the diameter-volume ratio, growth, distance from the pleura (if more than 10 mm), spiculation, ground-glass appearance, pleural indentation, vascular convergence, circumference-diameter ratio (roundness), upper lobe location, presence of air bronchogram, presence of lymphadenopathy and cavity wall thickness. Benign features include some patterns of nodule calcification (diffuse, central, laminated or popcorn pattern), smooth border, cavitation, satellite lesions and perifissural location.[8]

The British Thoracic Society[8,9] recommends the Brock model for estimating the risk of lung cancer in any solid nodule greater than 8 mm in diameter (or 300 mm^3 in volume) and in subsolid nodules larger than 5 mm if they are stable after three months. The decision between CT surveillance or further characterisation (i.e., PET-CT, biopsy, excision or non-surgical treatment) depends on this risk estimate, so the report should include it.[9] However, physicians should note that the Brock model was validated for low-dose CT scans and not for CCTA scans.[12,13] For solid, noncalcified PNs measuring between 5 and 8 mm in diameter, their growth rate is better at distinguishing malignancy from benign pathology than are morphological features. Because of this, the Fleischner Society recommends performing a baseline low-dose chest CT as soon as possible and a subsequent follow-up low-dose chest CT for any indeterminate PNs between 5 and 8 mm in diameter.[10,11]

The prevalence of IFs of malignancy in all patients undergoing CCTA is small (estimated at 0.7%), and most of them (72%) will be lung cancer (primary or secondary).[4,5] Even in patients with known cancer elsewhere, incidental small PNs are often benign and should not preclude treatment for the primary malignancy until proven to be metastases. Likewise, second primary lung cancer may have a better prognosis than may metastatic lung cancer and still be a candidate for treatment. The report should include any incidental and previously undocumented lung lesions larger than 5 mm and a proposed follow-up schedule. Lesions larger than 8 mm in diameter, growing or presenting suspicious features (Figure 1), should trigger an alert and referral for a lung cancer team so that they can be reviewed by a pulmonologist, an oncologist and a thoracic surgeon.[11]

Pulmonary emboli (Figure 2) are rare, identified in just 0.2% of CCTA scans, but should be reported and trigger an urgent referral, as the patient will benefit from a timely start of therapy.[14]

Pulmonary consolidation should trigger a referral to the respiratory team and a post-treatment imaging reassessment, as the differential diagnosis is vast and includes infection, alveolar haemorrhage, organising pneumonia and malignancy, among others.[15]

Interstitial lung abnormalities (ILAs) are imaging findings potentially compatible with interstitial lung disease (ILD) in patients with no prior history of ILD.[16] These findings are unexpected and incidental, common in the older (above 60 years of age) smoking population (4-9%). ILAs are often asymptomatic but may be related to mild ILD with potential functional impairment, risk of progressing disease and increased mortality risk.[17] Some imaging patterns, such as subpleural reticulations, basal predominance and honeycombing, are more strongly associated with progression.[16] Others, such as centrilobular nodules, are less likely to progress. Likewise, imaging patterns of pulmonary fibrosis are related to increased all-cause

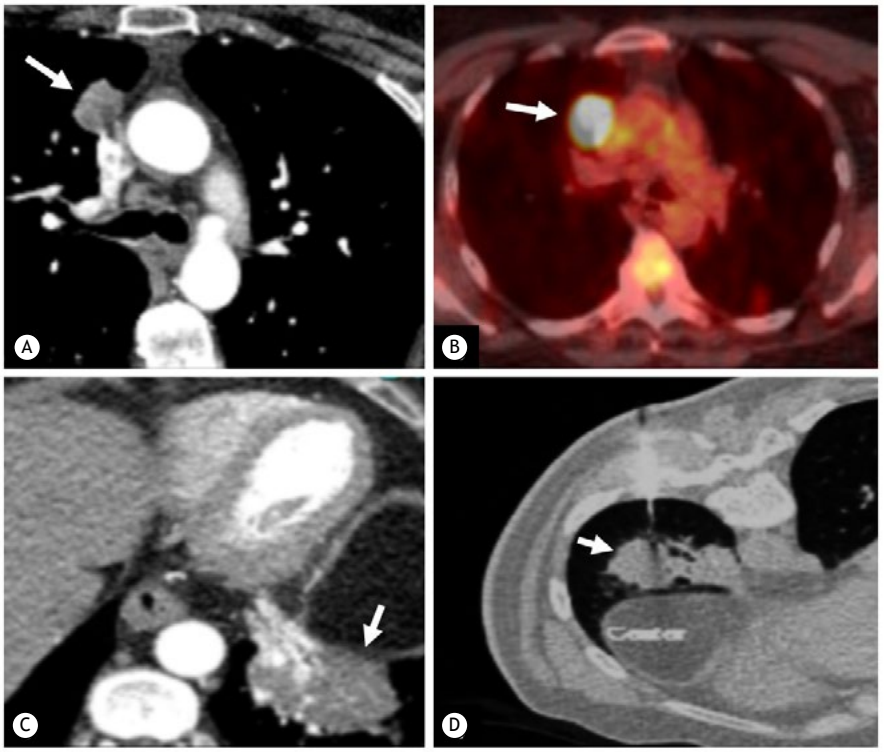


Figure 1. In A, an axial CT scan with a mediastinal window setting shows an incidental 20-mm nodule (arrow) in the right upper lobe. As per the British Thoracic Society guidelines,[8,9] this finding requires further evaluation and therefore was highlighted in the report. In B, a PET-CT scan of the same patient showed a standardised uptake value (SUV) of 12. This lesion was confirmed as a metastasis from a previously unknown melanoma on histology. In C, an axial CT scan with a mediastinal window setting shows an incidental left basal consolidation (arrow) and atelectasis in another patient. This area demonstrated an increased uptake (SUV = 3.4) on PET-CT (in D) and was proven to be an adenocarcinoma on histology. The staging after the multidisciplinary team meeting was T3N1M0.

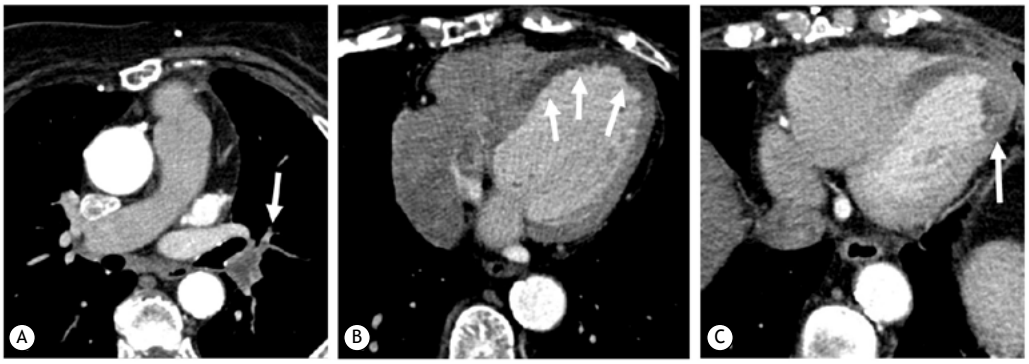


Figure 2. CT scans of a patient with acute chest pain and cardiac arrest. In A, an axial scan with a mediastinal window setting shows bilateral pulmonary emboli with the biggest thrombus occluding the left lower lobar artery (arrow). In B, a scan shows that the patient had an infarct of the left anterior descending coronary artery's territory with perfusion defects of the mid-cavity and apical walls (arrows). In C, a left ventricular thrombus in the apex (arrow) is also noted.

mortality. There are no clear guidelines for reporting or managing ILAs. Still, the Fleischner Society proposes that patients with respiratory symptoms, physiological abnormalities, gas transfer abnormalities and extensive CT changes should be referred for pulmonary evaluation and to a respective multidisciplinary team if available (Figure 3).[16] Follow-up of ILAs may still be appropriate after the exclusion of ILD but in the presence of risk factors for progression, even if the optimal interval for follow-up CT scanning is unknown.[16,18]

Other findings in the lung parenchyma include bronchial wall thickening in patients with COPD, emphysema, bronchiectasis and atelectasis (Figure 4).[4]

Intrapulmonary lymph nodes (IPLNs) are common on chest CT (prevalence of up to 66%) but under-represented on IF studies and do not require follow-up. The morphological criteria for IPLNs (Figure 5) are solid, homogeneous and noncalcified nodules with less than 12 mm in diameter. IPLNs may have an oval, lentiform,

or triangular shape, have regular and smooth margins, and be located primarily in the middle or lower lobes within 15 mm of the pleura.[19] Half of the cases show a connection between IPLNs and the pleura. In addition, IPLNs may present single or multiple attachments with veins but not with arteries, which can be useful in differentiating adenocarcinomas from IPLNs.[19]

Pleural space

Pleural effusion should be reported and related to heart failure in cardiac patients. Pleural plaques (Figure 6) are also common and under-reported IFs, linked to asbestos exposure and increased risk of mesothelioma.[5] The report should differentiate them from pleural metastases in patients with lung cancer. In addition, the presence of pleural plaques is also a marker for increased mortality in a history of asbestos exposure, and the report should document them for surveillance and legal compensation.[4,5,20]

Pneumothorax is rarely seen or reported on CCTA scans, likely because of the reduced FOV of CCTA scans and the outpatient setting. However, its clinical presentation can range from asymptomatic to life-threatening, and, when present, it should be reported and the patient should urgently be referred to the respiratory team or emergency room.

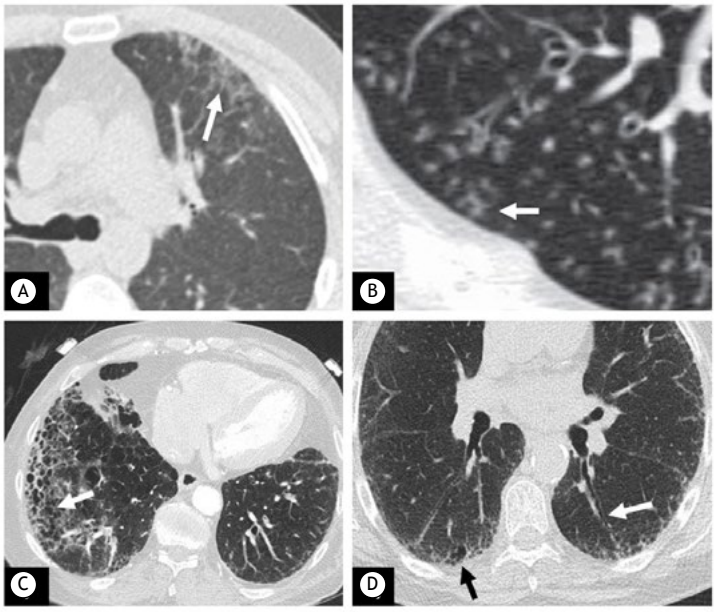


Figure 3. CT scans of a patient with atypical chest pain. Subpleural ground-glass opacities in the left upper lobe (arrow in A) and focal areas with tree-in-bud pattern (arrow in B) in the right lower lobe are seen. The patient was diagnosed with a lower tract respiratory infection. In another patient with a history of previous severe right lower lobe pneumonia, opening the field of view (FOV) allowed the visualisation of interstitial lung changes in the right lower lobe with asymmetric subpleural honeycombing and ground-glass patterns and bronchiectasis (arrow in C), residual to the previous infection. Likewise, using a large FOV in another patient, the scan shows the incidental finding of ILD (in D), characterised by subpleural reticulation with honeycombing (black arrow) and traction bronchiectasis (white arrow) affecting the lower lobes. These were further investigated with HRCT, and the diagnosis of the multidisciplinary team was probable usual interstitial pneumonia.

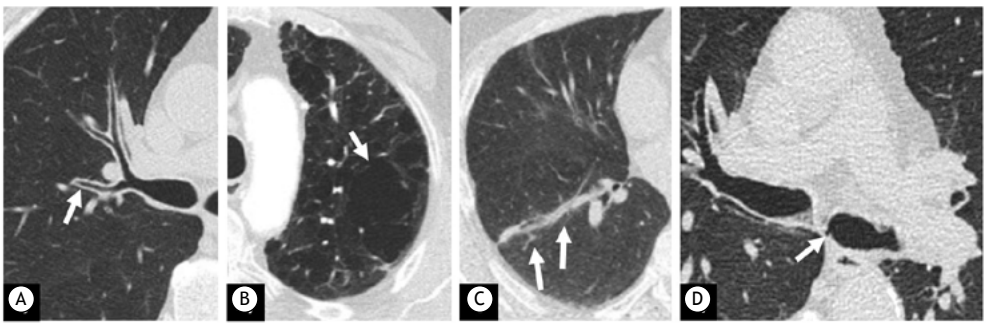


Figure 4. CT scans of a current smoker diagnosed with COPD, using the calcium score acquisition with a large field of view show bronchial thickening noted mainly in the lobar (arrow) and central segmental bronchi (in A) and centrilobular and paraseptal emphysema, forming a left upper lobe emphysematous bulla (arrow in B). Likewise, in another patient with COPD, an axial image shows linear atelectasis in the left lower lobe and mucous plugging (arrows in C). In D, a bronchial diverticulum is seen at the origin of the left main bronchus (arrow).

Mediastinum

Mediastinal lesions have a comprehensive list of differential diagnoses, including benign pathology (e.g., pericardial, bronchogenic or oesophageal duplication cysts; diving goitre) and malignancy (e.g., thymoma, thyroid malignancy, germ cell tumours, neurogenic tumours, oesophageal cancer and lymphoma; Figures 7 and 8).[4,5,21]

Most lesions in the anterior mediastinum will have attenuation compatible with a soft tissue lesion, with larger lesions more likely representing early-stage thymic epithelial tumours and smaller lesions likely expressing benign cysts.[22] On follow-up evaluation, most lesions are stable or slowly growing, and the absence of growth cannot distinguish between benignity and malignancy. While long-term follow-up may be appropriate, a purely cystic lesion is most commonly a benign thymic cyst and does not need follow-up. Thoracic MRI scanning is far superior to CT in distinguishing simple or complex cystic lesions from solid lesions, identifying fatty, cystic or necrotic components within solid lesions, as well as septations or soft tissue components within cystic lesions. In addition, MRI may be appropriate to alleviate patient anxiety.[22]

Mediastinal teratoma is the most common mediastinal germ cell tumour. Mature teratomas usually present multiple densities, including fat, cystic spaces, homogeneous soft tissue and calcification. Conversely, immature teratomas usually present as solid heterogeneous lesions. Mature and most immature teratomas are benign but some immature teratomas may have a malignant germ cell tumour component and even mature teratomas may undergo malignant transformation of non-germ cell components (usually squamous component).

Both inflammatory and malignant diseases may cause mediastinal lymphadenopathy. Examples of the former include tuberculosis, fungal infection, sarcoidosis,

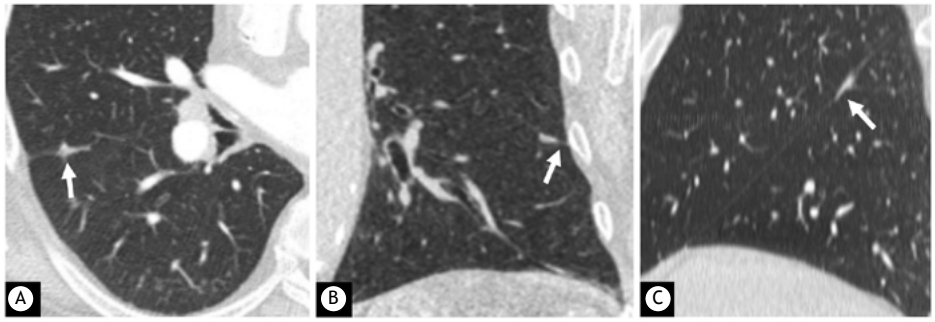


Figure 5. In A, an axial CT scan using the full field of view shows an oval-shaped, lentiform nodule in contact with the fissure (arrow). Coronal (in B) and sagittal (in C) CT scans show that the nodule adopts a more triangular shape and a linear contact with the fissure and adjacent pleura (arrows). These findings meet the criteria for benign intrapulmonary lymph nodes, and no follow-up is required.

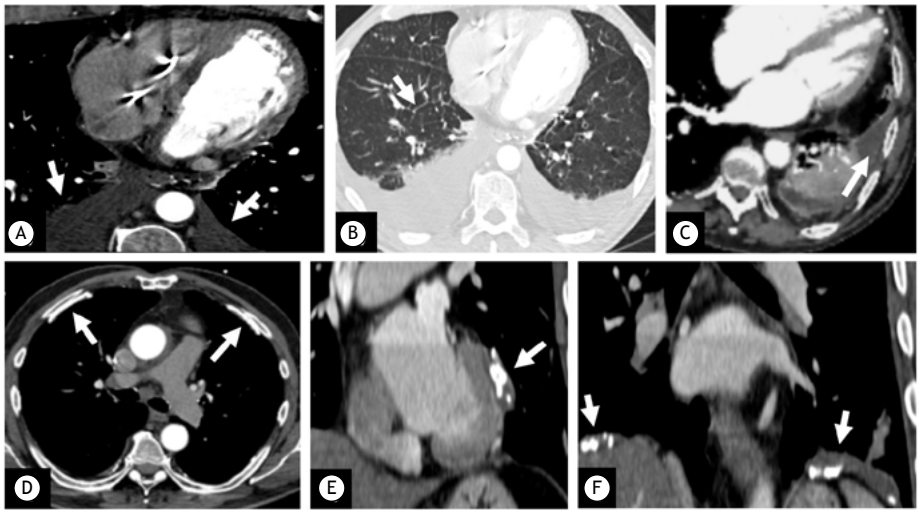


Figure 6. In A, bilateral pleural effusion (arrows) can be seen in the cardiac field of view (FOV) on a CT scan. In a reconstructed, wider FOV with a lung window setting (in B), the effusions are confirmed, and signs of pulmonary oedema with interlobular thickening (arrow) are also seen. In another patient, incidental left pleural effusion can be noted in C. The pleural layers were enhanced and showed areas of focal nodular thickening (arrows in D). Mesothelioma was diagnosed in this patient after further evaluation. CT scans of a patient with known exposure to asbestos reveal bilateral calcified pleural plaques (arrows), including the mediastinal (arrows in E) and diaphragmatic layers (arrows in F).

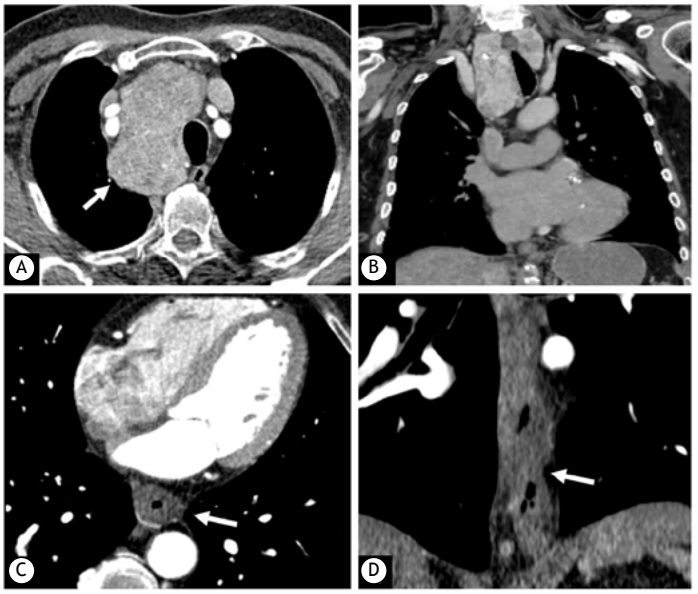


Figure 7. Coronary CT angiography performed for graft assessment (full chest coverage with wide field of view) shows an incidental finding of an anterior and heterogeneous mid-mediastinal soft-tissue mass (arrow in A), corresponding to diving goitre with a deviation of the trachea also depicted in a coronal view (in B). This patient was referred to the neck team for medical and surgical evaluation. Life-threatening severe complications, such as airway obstruction and neurovascular compression, can arise suddenly in these cases, usually secondary to intrathyroidal bleeding from trauma or infection. In another patient, axial (in C) and coronal (in D) scans show circumferential irregular thickening of the thoracic oesophagus (arrow) with adjacent enlarged lymph nodes. The patient was immediately referred to the upper gastrointestinal team, and upper endoscopy was performed. An adenocarcinoma was confirmed on histology.

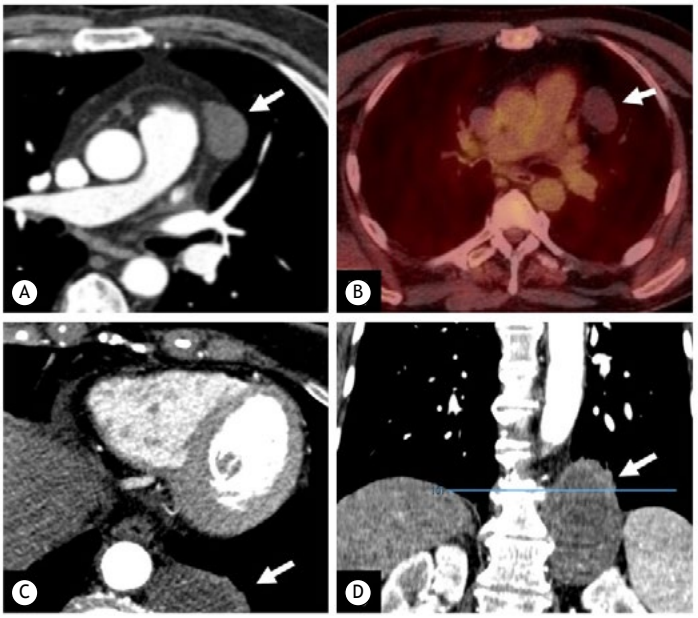


Figure 8. In A, an axial CT scan with a mediastinal window setting shows the incidental finding of a rounded lesion with fluid density (arrow). In B, a PET-CT scan shows that the lesion has no uptake (arrow) and is likely to represent a benign pericardial cyst. Surgical resection or percutaneous drainage is reserved for symptomatic individuals when complications are observed or when the diagnosis is uncertain. In another patient, an axial CT scan shows a heterogeneous left retrocrural mass (arrow in C) seen in the cardiac field of view. In D, a coronal CT scan confirms the left paraspinal location (arrow) of the lesion that was later confirmed as a neurogenic tumour. This finding requires an alert on the report as the patient will benefit from further evaluation and treatment.

silicosis, drug reactions, amyloidosis, Castleman's disease, ILD and COPD. Examples of the latter include lung cancer, lymphoproliferative disease and metastases (Figure 9). The criteria for lymphadenopathy include a short-axis diameter larger than 10 mm, changes to its usual ovoid shape or usual attenuation, coalescence

with adjacent enlarged lymph nodes or an invasive behaviour into the surrounding mediastinal fat.[19] Mediastinal lymph node enlargement is the third most common IF reported in the literature (1.7%) after lung nodules and parenchymal abnormalities.[4,19,23]

In the absence of suspicious features, lymph nodes smaller than 15 mm in the short-axis are overwhelmingly reactive lymph nodes and, if few, do not need follow-up.[21] The shape and number of lymph nodes, the presence of a fatty hilum, enhancement or calcifications, as well as previous history of diseases potentially explaining the enlarged lymph nodes are also important when considering follow-up or further characterisation with PET-CT or biopsy.[21]

Abnormalities of the aorta (Figure 10) and pulmonary arteries should be considered an integral part of the cardiac or coronary assessment in the context of the cardiovascular disease being evaluated, such as in cases of congenital abnormalities or pre-transcatheter aortic valve replacement.

Oesophageal hiatus hernia is very common and may cause chest pain (heartburn) as a confounding symptom behind the CCTA request. These patients will benefit from gastrointestinal evaluation and treatment.[4]

Similarly to pneumothorax, pneumomediastinum is infrequent and under-represented in systematic reviews of IFs on CCTA. However, these should be reported and trigger an urgent referral to the respiratory team or emergency department.

Chest wall

Degenerative bony changes are widespread in older patients and could cause atypical chest pain.[5] Metastatic disease, multiple myeloma, lymphoma, and leukaemia account for more than 99% of malignant bone lesions in the chest wall. Therefore, the report should distinguish them from common benign bony lesions (e.g., bone islands and haemangiomas) that do not require further assessment.[24]

The skin, muscles and subcutaneous fat tissue are sometimes the site of metastases and should be reviewed.[5] Despite the low predictive value for breast lesions on CCTA, it may be the first study to demonstrate a previously undiagnosed lesion. Incidental breast lesions first detected on CCTA prove to be cancer in 24-70% of the cases; therefore, any breast lesion not previously demonstrated to be benign (Figure 11) should be reported and trigger an alert for an appointment and further evaluation with a specialist.[25]

Abdominal cavity

A CCTA study usually includes some slices through the upper abdomen. The most common abdominal IFs are simple hepatic cysts, reported in 5% of CCTA scans as lesions with uniform fluid attenuation, no visible wall and no contrast enhancement.[5] These are benign and require no further imaging. However, the complete characterisation of focal liver lesions is often impossible to be obtained from a CCTA scan and may require a targeted protocol (e.g., triple-phase CT scan or liver MRI).[26] Hence, the report should include any new focal liver lesion apart from simple cysts, and further characterisation should be suggested. Likewise, biliary obstruction, pneumobilia and focal or diffuse thickening of the gallbladder wall should be alerted if previously undiagnosed. Renal cysts are also common and frequently benign IFs that do not require follow-up in the absence of suspicious features (e.g., septations, internal density, enhancement, calcification, and solid

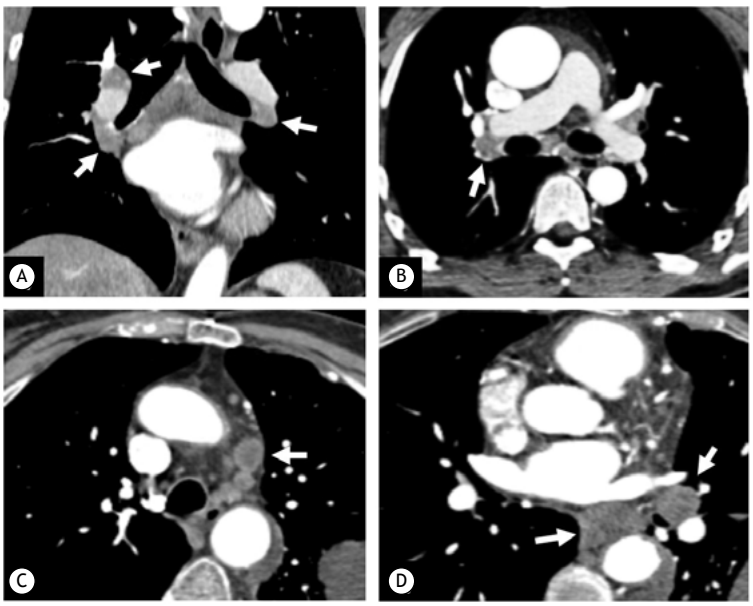


Figure 9. Coronal (in A) and axial (in B) CT scans show bilateral enlarged hilar lymph nodes (arrows), the biggest of them in the right hilum measuring 15 mm in the short axis. EBUS confirmed sarcoidosis. CT scans of another patient (in C and D) present several mediastinal and left hilar lymph nodes with a hypodense centre. The report alerted these findings, and EBUS later confirmed metastatic small cell carcinoma.

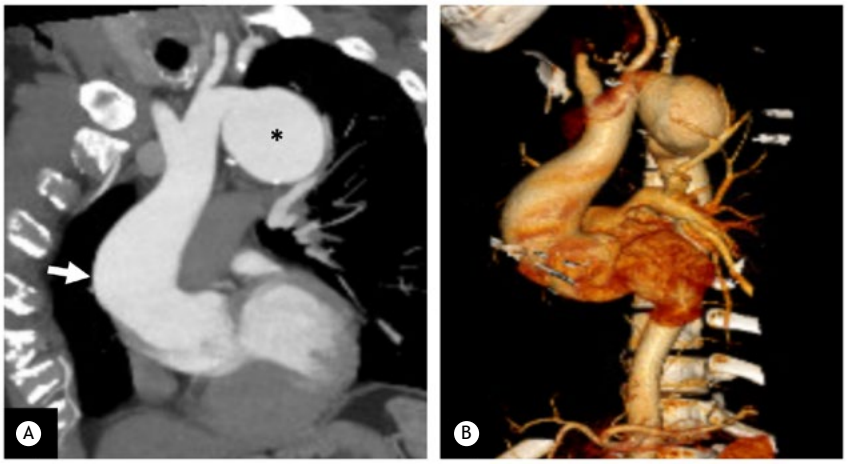


Figure 10. In A, coronal maximum-intensity projection reconstruction of the thoracic aorta of a young patient admitted with chest pain shows an incidental finding of an ascending aorta aneurysm (arrow) with distal aortic arch coarctation and a proximal descending saccular thoracic aorta aneurysm (asterisk). The congenital anatomical change and aneurysm are depicted in the 3D reconstruction (in B). The clinical information provided referred to a bicuspid aortic valve, which justified tailoring the imaging protocol to include the aortic arch.

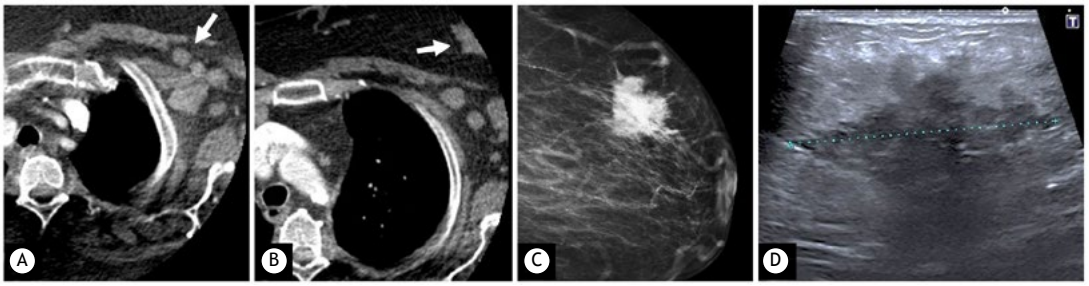


Figure 11. Axial CT images show an incidental finding of multiple left axillary adenopathy (arrow in A) and a left breast mass, partially included in the cardiac field of view (arrow in B). In C, a mammogram showed a suspicious spiculated lesion with a significant amount of microcalcifications. In D, the lesion was confirmed malignant on ultrasound-guided biopsy.

components). However, any solid renal nodule or mass should be reported and further characterised.[5,27]

Coverage of the adrenal glands, pancreas, spleen, and stomach are limited to the FOV and the patient's anatomy. However, any previously undiagnosed solid or cystic mass in these organs, splenomegaly, peritoneal disease (e.g., nodules, haziness and omental cake) and ascites should also be reported and further evaluated.[28,29]

FINAL CONSIDERATIONS

Clinically significant IFs are common in the evaluation of IHD using CCTA. Although their detection has the potential for additional costs and patient harm, it also presents opportunities for intervening to benefit patients. Therefore, radiologists and cardiologists reporting CCTA findings should be familiar with IFs.

AUTHOR CONTRIBUTIONS

EP and DP: study conception and design, data collection, drafting and review of the manuscript. CM, EM, BH, KI and LTB: review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, et al. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes [published correction appears in Eur Heart J. 2020 Nov 21;41(44):4242]. Eur Heart J. 2020;41(3):407-477. https://doi.org/10.1093/eurheartj/ehz425
2. Tzolos E, Newby DE. Coronary Computed Tomography Angiography Improving Outcomes in Patients with Chest Pain. Curr Cardiovasc Imaging Rep. 2019;12:15. https://doi.org/10.1007/s12410-019-9492-6
3. Moss AJ, Williams MC, Newby DE, Nicol ED. The Updated NICE Guidelines: Cardiac CT as the First-Line Test for Coronary Artery Disease. Curr Cardiovasc Imaging Rep. 2017;10(5):15. https://doi.org/10.1007/s12410-017-9412-6

4. Kay FU, Canan A, Abbara S. Common Incidental Findings on Cardiac CT: a Systematic Review. Curr Cardiovasc Imaging Rep. 2019;12(6):21. doi: 10.1007/s12410-019-9494-4 https://doi.org/10.1007/s12410-019-9494-4
5. Macmillan MT, Williams MC. Incidental Non-cardiac Findings in Cardiovascular Imaging. Curr Treat Options Cardiovasc Med. 2018;20(12):93. https://doi.org/10.1007/s11936-018-0700-5
6. Chao H, Shan H, Homayounieh F, Singh R, Khera RD, Guo H, et al. Deep learning predicts cardiovascular disease risks from lung cancer screening low dose computed tomography. Nat Commun. 2021;12(1):2963. https://doi.org/10.1038/s41467-021-23235-4
7. Ito M, Miyata Y, Okada M. Management pathways for solitary pulmonary nodules. J Thorac Dis. 2018;10(Suppl 7):S860-S866. https://doi.org/10.21037/jtd.2018.01.07
8. Graham RN, Baldwin DR, Callister ME, Gleeson FV. Return of the pulmonary nodule: the radiologist's key role in implementing the 2015 BTS guidelines on the investigation and management of pulmonary nodules. Br J Radiol. 2016;89(1059):20150776. https://doi.org/10.1259/bjr.20150776
9. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules [published correction appears in Thorax. 2015 Dec;70(12):1188]. Thorax. 2015;70 Suppl 2:ii1-ii54. https://doi.org/10.1136/thoraxjnl-2015-207168
10. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-243. https://doi.org/10.1148/radiol.2017161659
11. Bueno J, Landeras L, Chung JH. Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: Common Questions and Challenging Scenarios. Radiographics. 2018;38(5):1337-1350. https://doi.org/10.1148/rg.2018180017
12. Fox AH, Tanner NT. Approaches to lung nodule risk assessment: clinician intuition versus prediction models. J Thorac Dis. 2020;12(6):3296-3302. https://doi.org/10.21037/jtd.2020.03.68
13. Nair VS, Sundaram V, Desai M, Gould MK. Accuracy of Models to Identify Lung Nodule Cancer Risk in the National Lung Screening Trial. Am J Respir Crit Care Med. 2018;197(9):1220-1223. https://doi.org/10.1164/rccm.201708-1632LE
14. Williams MC, Hunter A, Shah ASV, Dreisbach J, Weir McCall JR, Macmillan MT, et al. Impact of noncardiac findings in patients undergoing CT coronary angiography: a substudy of the Scottish computed tomography of the heart (SCOT-HEART) trial. Eur Radiol. 2018;28(6):2639-2646. https://doi.org/10.1007/s00330-017-5181-5
15. Munden RF, Black WC, Hartman TE, MacMahon H, Ko JP, Dyer DS, et al. Managing Incidental Findings on Thoracic CT: Lung Findings. A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2021;18(9):1267-1279. https://doi.org/10.1016/j.jacr.2021.04.014
16. Hatabu H, Hunninghake GM, Richeldi L, Brown KK, Wells AU, Remy-Jardin M, et al. Interstitial lung abnormalities detected incidentally on CT: a Position Paper from the Fleischner Society. Lancet Respir Med. 2020;8(7):726-737. https://doi.org/10.1016/S2213-2600(20)30168-5
17. Putman RK, Hatabu H, Araki T, Gudmundsson G, Gao W, Nishino M, et al. Association Between Interstitial Lung Abnormalities and All-Cause Mortality. JAMA. 2016;315(7):672-681. https://doi.org/10.1001/jama.2016.0518
18. Putman RK, Gudmundsson G, Axelsson GT, Hida T, Honda O, Araki T, et al. Imaging Patterns Are Associated with Interstitial Lung Abnormality Progression and Mortality. Am J Respir Crit Care Med. 2019;200(2):175-183. https://doi.org/10.1164/rccm.201809-1652OC
19. Schreuder A, Jacobs C, Scholten ET, van Ginneken B, Schaefer-Prokop CM, Prokop M. Typical CT Features of Intrapulmonary Lymph Nodes: A Review. Radiol Cardiothorac Imaging. 2020;2(4):e190159. https://doi.org/10.1148/ryct.2020190159
20. Mazzei MA, Contorni F, Gentili F, Guerrini S, Mazzei FG, Pinto A, et al. Incidental and Underreported Pleural Plaques at Chest CT: Do Not Miss Them-Asbestos Exposure Still Exists. Biomed Res Int. 2017;2017:6797826. https://doi.org/10.1155/2017/6797826
21. Munden RF, Carter BW, Chiles C, MacMahon H, Black WC, Ko JP, et al. Managing Incidental Findings on Thoracic CT: Mediastinal and Cardiovascular Findings. A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2018;15(8):1087-1096. https://doi.org/10.1016/j.jacr.2018.04.029
22. Yoon SH. Management of incidental anterior mediastinal lesions: summary of relevant studies. Mediastinum. 2019;3:9. https://doi.org/10.21037/med.2019.03.01
23. Nin CS, de Souza VV, do Amaral RH, Schuhmacher Neto R, Alves GR, Marchiori E, et al. Thoracic lymphadenopathy in benign diseases: A state of the art review. Respir Med. 2016;112:10-17. https://doi.org/10.1016/j.rmed.2016.01.021
24. Bernard S, Walker E, Raghavan M. An Approach to the Evaluation of Incidentally Identified Bone Lesions Encountered on Imaging Studies. AJR Am J Roentgenol. 2017;208(5):960-970. https://doi.org/10.2214/AJR.16.17434
25. Son JH, Jung HK, Song JW, Baek HJ, Doo KW, Kim W, et al. Incidentally detected breast lesions on chest CT with US correlation: a pictorial essay. Diagn Interv Radiol. 2016;22(6):514-518. https://doi.org/10.5152/dir.2016.15539
26. Gore RM, Pickhardt PJ, Mortele KJ, Fishman EK, Horowitz JM, Fimmel CJ, et al. Management of Incidental Liver Lesions on CT: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14(11):1429-1437. https://doi.org/10.1016/j.jacr.2017.07.018
27. Herts BR, Silverman SG, Hindman NM, Uzzo RG, Hartman RP, Israel GM, et al. Management of the Incidental Renal Mass on CT: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2018;15(2):264-273. https://doi.org/10.1016/j.jacr.2017.04.028
28. Megibow AJ, Baker ME, Morgan DE, Kamel IR, Sahani DV, Newman E, et al. Management of Incidental Pancreatic Cysts: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14(7):911-923. https://doi.org/10.1016/j.jacr.2017.03.010
29. Mayo-Smith WW, Song JH, Boland GL, Francis IR, Israel GM, Mazzaglia PJ, et al. Management of Incidental Adrenal Masses: A White Paper of the ACR Incidental Findings Committee. J Am Coll Radiol. 2017;14(8):1038-1044. https://doi.org/10.1016/j.jacr.2017.05.001

J Bras Pneumol. 2022;48(4):e20220106
https://dx.doi.org/10.36416/1806-3756/e20220106

Brazilian Thoracic Association Consensus on Sleep-disordered Breathing

Ricardo Luiz de Menezes Duarte[1], Sonia Maria Guimarães Pereira Togeiro[2,3], Luciana de Oliveira Palombini[3], Fabíola Paula Galhardo Rizzatti[4], Simone Chaves Fagondes[5], Flavio José Magalhães-da-Silveira[6], Marília Montenegro Cabral[7], Pedro Rodrigues Genta[8], Geraldo Lorenzi-Filho[8], Danielle Cristina Silva Clímaco[9], Luciano Ferreira Drager[10], Vitor Martins Codeço[11], Carlos Alberto de Assis Viegas[12], Marcelo Fouad Rabahi[13]

1. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
2. Disciplina de Clínica Médica, Escola Paulista de Medicina – EPM – Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
3. Instituto do Sono, São Paulo (SP) Brasil.
4. Disciplina de Pneumologia, Departamento de Medicina, Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.
5. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
6. SleepLab – Laboratório de Estudo dos Distúrbios do Sono, Rio de Janeiro (RJ) Brasil.
7. Universidade de Pernambuco, Recife (PE) Brasil.
8. Laboratório de Investigação Médica 63 – LIM 63 (Laboratório do Sono) – Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.
9. Serviço de Pneumologia, Hospital Otávio de Freitas, Recife (PE) Brasil.
10. Unidade de Hipertensão, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo – HCFMUSP – São Paulo (SP) Brasil.
11. Hospital Regional da Asa Norte, Secretaria de Estado de Saúde do Distrito Federal, Brasília (DF) Brasil.
12. Faculdade de Medicina, Universidade de Brasília, Brasília (DF) Brasil.
13. Faculdade de Medicina, Universidade Federal de Goiás – UFG – Goiânia (GO) Brasil.

Submitted: 24 March 2022.
Accepted: 23 May 2022.

ABSTRACT

Sleep is essential for the proper functioning of all individuals. Sleep-disordered breathing can occur at any age and is a common reason for medical visits. The objective of this consensus is to update knowledge about the main causes of sleep-disordered breathing in adult and pediatric populations, with an emphasis on obstructive sleep apnea. Obstructive sleep apnea is an extremely prevalent but often underdiagnosed disease. It is often accompanied by comorbidities, notably cardiovascular, metabolic, and neurocognitive disorders, which have a significant impact on quality of life and mortality rates. Therefore, to create this consensus, the Sleep-Disordered Breathing Department of the Brazilian Thoracic Association brought together 14 experts with recognized, proven experience in sleep-disordered breathing.

Keywords: Sleep apnea syndromes/diagnosis; Sleep apnea syndromes/therapy; Hypoventilation.

INTRODUCTION

Sleep is essential for the health and well-being of children, adolescents, and adults, being important for cognitive function, as well as for mental, cardiovascular, cerebrovascular, and metabolic health.[1] Sleep can be affected by various respiratory disorders. Among the causes of sleep-disordered breathing (SDB), the most prevalent is obstructive sleep apnea (OSA), which is characterized by frequent upper airway (UA) collapse during sleep, resulting in intermittent hypoxia and sleep fragmentation.[2] In most cases, OSA has cardiovascular, metabolic, and neurocognitive consequences, with a significant decrease in quality of life,[2,3] as well as increasing the risk of death.[4] When left untreated, OSA constitutes a health risk, with economic costs that affect the individuals with the condition, their families, and society.[5,6]

OBSTRUCTIVE SLEEP APNEA

Prevalence

Data from the Wisconsin Sleep Cohort Study, which involved workers between 30 and 60 years of age, demonstrated that the prevalence of OSA in men and women was 24% and 9%, respectively, when the criterion was an apnea-hypopnea index (AHI) ≥ 5 events/h, compared with 9% and 4%, respectively, when the criterion was an AHI ≥ 15 events/h.[7] However, in recent years, there has been a clear increase in the prevalence of OSA,[8-10] possibly due to the aging of the population, higher rates of obesity, the development of methods of detection that are more sensitive, such as the use of nasal-cannula-pressure-transducer systems (instead of the exclusive use of thermistors), and more "tolerant" hypopnea criteria (desaturation of 3% rather than 4%). In a study conducted in the city of São Paulo, Brazil, involving 1,042 volunteers representative of the adult population,

Correspondence to:
Ricardo L. M. Duarte. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro, Rua Professor Rodolpho Paulo Rocco, 255, 1° andar, Sala 01D 58/60, CEP 21941-913, Rio de Janeiro, RJ, Brasil.
Tel.: 55 21 3938-2887. E-mail: rlmduarte@gmail.com
Financial support: None.

ISSN 1806-3756

32.8% of the participants were diagnosed with OSA syndrome, which is characterized by an AHI ≥ 5 events/h with symptoms or an AHI ≥ 15 events/h irrespective of symptoms.[11] Another study found that the prevalence of an AHI ≥ 5 events/h ranged from 9% to 38% in the general population, reaching rates as high as 90% and 78% among men and women, respectively, in certain elderly populations.[12] In one study comparing White and Asian subjects matched for age, sex, and BMI, the severity of OSA was found to be greater in the latter, probably due to differences in craniofacial anatomy.[13]

Recent estimates suggest that, worldwide, nearly one billion people have OSA, moderate/severe OSA affecting an estimated 425 million individuals between 30 and 69 years of age.[14] Brazil is among the ten countries with the highest estimated number of individuals with OSA[14]: 49 million with an AHI ≥ 5 events/h; and 25 million with an AHI ≥ 15 events/h. In certain population groups, OSA is highly prevalent, such groups including individuals in the preoperative period of bariatric surgery,[15,16] those with resistant hypertension,[17,18] those with atrial fibrillation,[19] and those who have had a stroke.[20]

Insomnia and OSA are highly prevalent sleep disorders. The combination of the two diseases, which is also common and is known as comorbid insomnia and sleep apnea, impairs quality of life and reduces adherence to positive airway pressure treatment, as well as increasing mortality rates.[21-23]

Pathophysiology

In humans, the UAs are responsible for speech, swallowing, and ventilation; because they are composed of numerous muscles and soft parts that do not have a protective bone framework, they are predisposed to collapse.[24] Although that ability is essential for speech and swallowing when an individual is awake, it also allows the UAs to collapse during sleep, resulting in OSA.[24] The pathophysiology of OSA is complex and may involve four main phenotypes (Chart 1).[25]

Another factor that plays a role in the genesis of OSA is unstable ventilatory control, which can lead to cyclical respiratory effort and periodic breathing. This abnormal respiratory effort can produce variable levels of negative intraluminal pressure and an inadequate compensatory response from the dilator muscles, predisposing to UA collapse. Brief arousals followed by apnea cause increased respiratory effort and changes in ventilation, resulting in fluctuations in PaO_2 and $PaCO_2$ levels and instability of respiratory control centers, perpetuating a cyclical breathing pattern.[26]

Episodes of obstructive apnea can lead to intermittent hypoxia and mild CO_2 retention, disrupting normal autonomic and hemodynamic responses during sleep.[27] Occurring repeatedly during the night and accompanied by a chemoreceptor-mediated increase in sympathetic activity, episodes of obstructive apnea increase the sympathetic activity of peripheral blood vessels, with consequent vasoconstriction.[27] That hemodynamic stress occurs when there is severe hypoxemia and hypercapnia, and it may initiate pathophysiological mechanisms that promote various diseases, via sympathetic activation, increased release of vasoactive substances, systemic inflammation, and oxidative stress.[27]

Obesity is the main cause of UA narrowing and is therefore a major predictor of OSA.[25] The pathophysiology of OSA in obesity is a multifactorial process, in which the main mechanism may be the deposition of adipose tissue in the structures of the neck, leading to luminal narrowing and UA collapse.[15,16] In addition, obese individuals with OSA often have more tongue fat than do similarly obese individuals without OSA.[28] Increasing body weight accelerates the progression of OSA, whereas weight loss reduces in its severity.[29] Obesity can also reduce lung volume, promoting UA collapse,[30] and is often associated with greater neck circumference (NC). A larger NC is associated with an increased risk of OSA.[31,32] The NC, which is typically larger in men than in women, correlates with waist circumference, BMI, metabolic syndrome, and cardiovascular risk factors.[32-34] The nocturnal displacement of fluid from the legs to the neck may contribute to UA collapse, and that displacement has been shown to correlate significantly with the AHI, NC, and time spent sitting when awake.[35]

It is known that OSA is more common in men than in women, and that its prevalence is higher in postmenopausal women than in those who are

Chart 1. Four major phenotypes associated with the pathophysiology of obstructive sleep apnea.

Impaired UA anatomy (i.e., UA narrowing/collapse)
Inefficiency of the UA dilator muscles
Low arousal threshold
Unstable ventilatory control (i.e., high loop gain)

Adapted from Eckert.[25] UA: upper airway. UA narrowing/collapse is the major cause of obstructive sleep apnea (OSA), given that all patients with OSA have some anatomical alteration in their UA. However, the anatomical factors depend on the balance between forces that promote UA collapse (i.e., negative intraluminal pressure generated by the diaphragm during inspiration and pressure from the tissues "involving" the UA) and UA dilatation (i.e., contraction of the pharyngeal dilator [genioglossus] muscle and longitudinal traction caused by changes in lung volume). During sleep, there is a reduction in the activity of the muscles involved in UA opening. In individuals with OSA, there is an imbalance between opening and closing forces, leading to recurrent UA obstruction. In addition, there is muscle damage in the area as a result of the constant vibration of its structures, predisposing to or worsening OSA.

premenopausal.[36,37] In comparison with women, men have a longer pharyngeal airway and a greater cross-sectional area of the soft palate, indicating that the UA is more collapsible in men than in women.[38] Other potential contributing factors include the deleterious effects of male sex hormones and the protective effects of female sex hormones.[39] Progesterone stimulates the UA muscles and ventilation and may contribute to the lower prevalence of OSA in premenopausal women,[40] whereas higher testosterone levels (due to androgen supplementation or polycystic ovary disease) can worsen OSA.[41,42]

The prevalence of OSA increases with age,[10,43] possibly due to the following mechanisms[44,45]: increased fat deposition around the pharynx; loss of tissue elasticity; lengthening of the soft palate; and decreased respiratory chemoreceptor responses. In elderly individuals, OSA may go undiagnosed because of the common misperception that the symptoms are due to aging rather than to OSA. The prevalence of OSA tends to be similar among aging men and women, especially among those over 60 years of age.[10,43]

Clinical consequences

In individuals with OSA, there can cardiovascular, metabolic, and neurocognitive consequences, as well as other, less common, repercussions (Chart 2).[2,46-50] Especially in its more severe forms, OSA is associated with several cardiovascular comorbidities, such as stroke,[20,51] coronary artery disease,[52] hypertension,[18] and arrhythmias (notably atrial fibrillation).[19] Regular treatment with CPAP can reduce cardiovascular risk.[53-55]

The increased production of oxidants and inflammatory mediators, caused by obstructive events, together with the increase in left ventricular afterload, also contribute to altering cardiac electrophysiology, with remodeling of the heart chambers and a consequent increase in the risk of arrhythmias, especially atrial fibrillation. Bradyarrhythmias, ventricular arrhythmias, and atrioventricular conduction abnormalities may also occur, especially when OSA and hypoxemia are more severe.[56,57]

The prevalence of hypertension in individuals with OSA is significant (as high as 50%), and approximately 30% of patients with hypertension have OSA.[50] In individuals with resistant hypertension, the prevalence of OSA has been reported to be as high as 80%.[17] Constant activation of the sympathetic nervous system is the likely pathway responsible for the increase in blood pressure; intermittent hypoxia, negative intrathoracic pressure, and primary hyperaldosteronism may also be involved.[58,59] Many individuals with OSA do not show the expected nocturnal drop in blood pressure, being classified as having OSA with a "nondipping" pattern (a drop in blood pressure of less than 10% during sleep).[57,60]

Chart 2. Major clinical consequences of obstructive sleep apnea.

Hypertension
Stroke
Arrhythmia
Ischemic heart disease
Heart failure
Type 2 diabetes mellitus
Metabolic syndrome
Cognitive decline
Depression
Motor vehicle and occupational accidents

Adapted from various previous studies.[46-50]

Another aspect of OSA is its association with stroke. The reported prevalence of OSA in individuals who have a stroke ranges from 30% to 70%.[61] The chance of having a stroke has been shown to be higher among individuals with an AHI ≥ 20 events/h than among those with an AHI < 5 events/h, even after adjustment for confounders (OR = 4.33; 95% CI: 1.32-14.24).[62] The cascade of deleterious pathophysiological events that occurs in OSA probably contributes to the concomitant occurrence of arrhythmias, oxidative stress, endothelial dysfunction, atherosclerosis, hypertension, autonomic dysfunction, and hypercoagulability. In individuals who have had a stroke, OSA leads to worse clinical outcomes[61,63]: longer hospital stays and prolonged rehabilitation; increased risk of stroke recurrence, and a greater risk of death.

Metabolic syndrome is strongly associated with OSA, with a consequent increase in cardiovascular risk.[64] The clinical features of metabolic syndrome—central obesity, hypertension, insulin resistance, hyperglycemia, and dyslipidemia—are shared by patients with OSA.[65] A study encompassing two cohorts found an increased incidence of metabolic syndrome associated with OSA,[66] and treatment of OSA with CPAP may reduce some components of metabolic syndrome, such as blood pressure and triglyceride levels.[67] In a recent randomized study of patients with OSA and metabolic syndrome, the proportion of patients in whom metabolic syndrome was reversed was greater among those who were treated with CPAP than among those who were not, although that reversal occurred in only a minority of the patients, suggesting that there is a need for combined treatments.[68] Despite robust evidence of the interplay between the two conditions, OSA is still underdiagnosed in individuals with the metabolic syndrome.[64,69] A diagnosis of OSA is a risk factor for the development of type 2 diabetes mellitus, and OSA leads to poorer glycemic control in individuals who develop the disease.[70]

Residual excessive sleepiness, even after adequate treatment with CPAP, occurs in 12% to 30% of patients with OSA.[71] Other causes of excessive daytime sleepiness (EDS) should always be investigated, such as insufficient sleep, inadequate sleep hygiene, and restless legs syndrome, as well as clinical conditions such as hypothyroidism, depression, and narcolepsy.[72] When CPAP is the treatment for OSA, optimization is

essential, because nonadherence to CPAP treatment is a major cause of residual sleepiness. In addition, OSA can result in a neurocognitive decline (mainly in executive functions, attention, and memory).[73] Although symptoms of depression are prevalent in patients with OSA, such depression may be associated with comorbidities such as obesity and metabolic syndrome.[74]

Another important complication is the increase in the frequency of automobile accidents in which individuals with OSA are at fault, mainly attributable to EDS. In the case of professional drivers, the risk of an automobile accident is even higher than in the general population, because they are more likely to have comorbidities, such as obesity, cardiovascular disease, diabetes mellitus, and metabolic syndrome.[75] The chance of causing an automobile accident is two to three times higher in individuals with untreated OSA than in individuals without OSA.[76]

In recent studies of the combination of OSA and cancer, the severity of OSA and intermittent nocturnal hypoxemia was found to be associated with increased tumor growth and aggressiveness, notably in cases of melanoma.[77,78]

Association with chronic lung diseases

In many cases, OSA occurs in conjunction with chronic lung diseases, including interstitial lung disease, bronchial asthma (BA), COPD, and pulmonary hypertension. A systematic review and meta-analysis involving a collective total of 569 patients with interstitial lung disease showed that the prevalence of OSA in that population was 61%.[79] In another study, the prevalence of moderate-to-severe OSA was found to be higher in patients with idiopathic pulmonary fibrosis and a diagnosis of severe OSA was found to be strongly associated with the presence of cardiovascular disease, especially ischemic heart disease.[80] The combination of OSA and idiopathic pulmonary fibrosis worsens the prognosis, increases cardiovascular risk, and increases the risk of death; however, when individuals are regularly treated with CPAP (> 4 h/night), there is a significant improvement in EDS and sleep quality, as well as a reduction in the mortality rate.[80-82]

The prevalence of OSA can be high in patients with BA, ranging from 19% to 60% and being as high as 95% in those with severe BA.[83] In BA, inflammatory infiltration of the UAs and the increase in fat deposition on the walls of the pharynx, due to the use of corticosteroids or to obesity, lead to a reduced transverse UA diameter, thus favoring the occurrence of OSA.[83] In one study, the rate of decline in FEV_1 was shown to be higher in patients with BA and OSA than in those with BA alone, the AHI being found to be the only independent risk factor for a decline in lung function.[84] However, among the patients with severe OSA, the rate of decline in FEV_1 was found to be significantly lower in those who were treated with CPAP than in those who were not.[84] Another study evaluated the impact of prolonged CPAP treatment on clinical symptoms in individuals with BA and OSA: there was a significant reduction in BA symptoms and a reduction in the use of rescue medication.[85] A multicenter prospective study evaluating a collective total of 99 patients with BA and OSA demonstrated that, after 6 months of CPAP use, there were significant improvements in BA control, quality of life, and pulmonary function.[86] A systematic review of patients with BA and OSA treated with CPAP also documented improved quality of life, especially in those with severe OSA or uncontrolled BA.[87]

Prevalence studies of overlap syndrome (COPD in conjunction with OSA) tend to report a wide variation in results, mainly due to differences in definitions and in the populations studied, the reported prevalence of the syndrome ranging from 10% to 65%.[88] The different clinical phenotypes of COPD influence the chance of having OSA[89]: increased lung volume and low BMI are associated with the emphysema phenotype and protect against OSA, whereas peripheral edema and high BMI, often associated with the chronic bronchitis phenotype, increase the risk of OSA.[89] Narrowing of the UAs, due to a fluid shift from the lower limbs (edema) to the neck (especially in those with cor pulmonale), and UA myopathy, due to COPD itself or the use of corticosteroids, are both factors that contribute to OSA.[89]

Classic OSA symptoms (e.g., snoring, morning headache, and EDS) and traditional risk factors for OSA (e.g., male gender, advanced age, and increased NC) are not helpful in confirming the suspicion of OSA in patients with COPD, particularly in those with moderate or severe COPD.[90,91] Therefore, in patients with COPD, polysomnography (PSG) is indicated when there is clinical suspicion of OSA, hypoxemic complications (cor pulmonale and polycythemia), or pulmonary hypertension disproportionate to the degree of airflow impairment.[92] Because OSA and COPD are clinical conditions associated with hypoxia and systemic inflammation, they increase cardiovascular risk and worsen other comorbidities, such as pulmonary hypertension; it is therefore to be expected that morbidity and mortality rates will be higher in patients with overlap syndrome than in those with COPD or OSA alone.[90,93] In an observational study of patients with overlap syndrome, the risk of COPD exacerbation and the mortality rate were both found to be lower among those who were treated with CPAP,[94] which is therefore indicated for the treatment of overlap syndrome. Similarly, CPAP treatment has been associated with increased survival in patients with moderate-to-severe OSA and COPD with hypoxemia who were on long-term supplemental oxygen therapy.[95]

Although there are limited data, it seems likely that SDB is more prevalent in adults with pulmonary hypertension than in the general adult population.[96-98] In individuals with OSA alone, there is a small increase in pulmonary artery pressure, usually

without clinical significance.[99] In contrast, OSA in combination with obesity hypoventilation syndrome or COPD contributes to the development of significant pulmonary hypertension, which can be severe.[99] The population of patients with pulmonary hypertension typically differs from the general population with suspected OSA in that it has a predominance of women and a smaller proportion of individuals who are obese, those with nocturnal hypoxemia also having lower survival rates.[100] When indicated, CPAP treatment has the potential to improve pulmonary hemodynamics, although the decrease achieved in pulmonary artery pressure is minimal.[96]

Clinical suspicion

The main risk factors for OSA are male gender, obesity, advanced age, and craniofacial abnormalities.[2,101,102] Anamnesis should be performed in order to investigate snoring/observed apnea (mainly in men) and tiredness/fatigue/morning headache/insomnia (mainly in women), as well as EDS.[101,103] One of the main daytime symptoms of OSA is EDS, which is often accompanied by cognitive and functional changes (difficulty concentrating, irritability, and impaired memory and work ability), as well as being associated with a higher rate of automobile accidents,[2,101] as detailed in Chart 3.

As part of the physical examination, clinicians should routinely evaluate blood pressure (to identify hypertension), BMI, NC, and craniofacial abnormalities (micrognathia, retrognathia, alterations of the soft palate, lateral narrowing of the oropharynx, hypertrophy of tonsils, and macroglossia), as well as the Mallampati score and nasal obstruction.[2,101,102] Systematic assessment of the pharynx using Friedman staging, including the modified Mallampati score and tonsil size,[104] is generally recommended as a predictor of success in soft tissue surgical treatment,[105,106] as shown in Chart 4.

The various screening instruments for OSA are based on clinical, demographic, and anthropometric data, with the aim of identifying adult individuals at high risk for the disorder. It should be noted that no single instrument is capable of ruling in or ruling out OSA without an objective sleep study. The sensitivity and specificity of a screening instrument are inversely related.[107] In the case of OSA, a highly prevalent and often underdiagnosed disorder, it is perhaps more important that a screening instrument has high sensitivity and does not fail to diagnose patients with OSA, rather than having high specificity.[107] Due to the lack of a clear benefit in treating asymptomatic individuals, screening for OSA is not recommended in such individuals.[108]

One possible use of OSA screening instruments is to identify patients classified as being at high risk for OSA so that they can be referred for portable or home diagnostic methods, thus trimming the waiting lists at sleep laboratories.[109-111] Another possible use is in individuals in the preoperative period, given that patients with OSA are at increased risk of respiratory and cardiovascular complications in the postoperative period.[112,113] Comparing the performance of screening instruments can be particularly difficult because it depends on the type of objective sleep study used for diagnosis, the type of population studied, and the AHI cutoff used for diagnosis.[114,115]

Chief among the various screening instruments are the Berlin questionnaire,[116] the STOP-Bang

Chart 3. Clinical suspicion of obstructive sleep apnea in adults.

Risk factors
Male gender
Obesity
Advanced age
Craniofacial abnormalities
Nighttime symptoms
Loud, disturbing snoring
Witnessed episodes of apnea
Gasping or a choking sensation
Nocturia
Nasal congestion
Night sweats
Excessive salivation
Daytime symptoms
Excessive daytime sleepiness
Memory impairment
Worsening concentration
Irritability
Mood changes
Morning headaches
Depressive symptoms
Complications
Cardiovascular complications
Metabolic complications
Neurocognitive complications
Motor vehicle and occupational accidents

Adapted from various previous studies.[2,101,102] Didactically, the symptoms associated with obstructive sleep apnea can be divided into nighttime and daytime symptoms. Because the nighttime symptoms may not be perceived by the patient, it is always desirable that the initial visit be conducted in the presence of the bed partner.

Chart 4. Friedman classification.

Stage I	Mallampati 1 or 2 + Tonsil 3 or 4
Stage II	Mallampati 1 or 2 + Tonsil 1 or 2 OR Mallampati 3 or 4 + Tonsil 3 or 4
Stage III	Mallampati 3 or 4 + Tonsil 0 or 1 or 2
Stage IV	Any patient with a BMI > 40 kg/m^2

Adapted from various previous studies.[104-106] The Friedman classification takes into account the palatine tonsils, the modified Mallampati score, and the BMI. Thus, four stages (I, II, III, and IV) are defined. Patients classified into lower stages are more likely to have a successful outcome after uvulopalatopharyngoplasty for the treatment of obstructive sleep apnea.

questionnaire,[117] the NoSAS score,[118] and the GOAL questionnaire,[119] all of which are detailed in Chart 5.

The Epworth Sleepiness Scale (ESS), developed several decades ago,[120] is widely used in clinical practice. However, it is generally of low utility as a screening model for OSA, possibly because patients with OSA may not necessarily have EDS and because EDS may have many causes other than OSA,[121,122] as well as because the ESS is not reliably reproducible when applied sequentially.[123] The ESS has been validated for use in Brazil.[124]

Another OSA screening tool is the Berlin questionnaire,[116] which has also been validated for use in Brazil.[125] In a systematic review and meta-analysis, this instrument was found to have moderate sensitivity and low specificity for OSA in individuals evaluated at sleep clinics,[107] potentially performing better in a primary care setting than in sleep laboratories.[126]

The STOP-Bang questionnaire[117] has been widely validated: in a meta-analysis of studies involving individuals referred to sleep laboratories,[127] the questionnaire presented a sensitivity of 90%, 94%, and 96%, respectively, for the detection of any OSA, moderate/severe OSA, and severe OSA, whereas its specificity for those same parameters was 49%, 34%, and 25%, respectively. The STOP-Bang questionnaire has also been validated for use in Brazil.[128]

The NoSAS score was derived from a cohort in Switzerland and externally validated in a cohort in Brazil.[118] In both cohorts, NoSAS performed significantly better than did the STOP-Bang and Berlin questionnaires.[118] The NoSAS has been validated in various clinical settings, having proved to be a useful screening tool in all of those settings.[129]

The GOAL questionnaire, which uses only four dichotomous clinical parameters, was originally developed and validated for use in Brazil.[119] In the original study,[119] the GOAL questionnaire showed satisfactory performance in screening for OSA, with a discriminatory capacity similar to that obtained with the three other instruments evaluated (the No-Apnea score, STOP-Bang questionnaire, and NoSAS score). It was subsequently validated in other clinical contexts, always showing satisfactory performance.[130,131]

Laboratory diagnosis

The various types of objective sleep studies are described in Chart 6. A type 1 sleep study (attended PSG) is considered the gold standard for the diagnosis of OSA and stratification of its severity.[57,132] However, it must be performed in a sleep laboratory by trained technical personnel, therefore being inherently costly, and is not widely available.[2,133] There can be night-to-night variability in the AHI data obtained by PSG, which may be related to the time spent in the supine position (in which the AHI is typically greater than in the lateral position) or to the use of alcohol and drugs that act on the central nervous system.[134,135]

The combination of electroencephalography, electrooculography, and electromyography allows the staging of rapid eye movement (REM) sleep and non-REM sleep (subdivided into stages N1, N2, and N3),[133] as outlined in Chart 7. Respiratory parameters such as episodes of apnea, hypopnea, and respiratory effort-related arousals are measured with airflow sensors (a nasal-cannula-pressure-transducer system or an oronasal thermistor), through the quantification of respiratory effort (with chest straps and abdomen), and by determination of the degree of oxygenation (pulse oximetry). For certain diagnoses, it may be necessary to employ other techniques in order to measure some optional parameters, such as video monitoring, the use of an esophageal balloon to accurately determine the respiratory effort, and the measurement of expired CO_2 (by capnography) or transcutaneous CO_2 in cases of suspected hypoventilation.[57,132,133]

The results of a PSG are analyzed by a professional certified in the area, who stages sleep and evaluates respiratory events in accordance with the rules

Chart 5. Clinical parameters of screening instruments for obstructive sleep apnea in adults.

Instruments
• ESS(probability of dozing in eight different day-to-day situations): each item is scored from 0 to 3 (ranging from no chance to high chance of dozing, respectively); and high risk is defined as a score ≥ 11 points (maximum possible score of 24 points)
• Berlin questionnaire, comprising three categories—snoring; fatigue and sleepiness; and obesity and hypertension—high risk being defined as at least two positive categories
• STOP-Bang questionnaire, comprising eight questions (1 point for each positive answer)—loud snoring, tiredness, observed apnea, hypertension, BMI > 35 kg/m^2, age > 50 years, NC > 40 cm, and male gender—high risk being defined as a score ≥ 3 points (maximum possible score of 8 points)
• NoSAS score—4 points for an NC > 40 cm; 3 points for a BMI 25-29 kg/m^2 or 5 points for a BMI ≥ 30 kg/m^2; 2 points for snoring; 4 points for being > 55 years of age; and 2 points for being male—high risk being defined as a score ≥ 8 points (maximum possible score of 17 points)
• GOAL questionnaire, comprising four questions (1 point for each affirmative answer)—male gender; BMI ≥ 30 kg/m^2; age ≥ 50 years; and loud snoring— high risk being defined as a score ≥ 2 points (maximum possible score of 4 points)

Adapted from various previous studies.[116-120] ESS: Epworth Sleepiness Scale; and NC: neck circumference. Although the ESS is a screening tool for excessive daytime sleepiness, rather than for obstructive sleep apnea, it is widely used in clinical practice, being a scale for subjective assessment of daytime sleepiness, which is considered excessive if the score is ≥ 11.

Chart 6. Classification of objective sleep studies.

Objective sleep studies
Type 1: Full, in-laboratory, attended PSG (≥ 7 channels)
Type 2: Full, unattended PSG (≥ 7 channels)
Type 3: Portable monitoring with 4-7 channels
Type 4: Portable monitoring with 1-2 channels, including noninvasive oximetry

Adapted from various previous studies.[2,57,132,133] PSG: polysomnography. Objective sleep studies are used for the diagnosis and stratification of the severity of obstructive sleep apnea (OSA), being classified, in decreasing order of complexity, as type 1, type 2, type 3, and type 4. A type 1 sleep study is a full, in-laboratory, attended PSG in which a technologist monitors a minimum of 7 channels, including electroencephalogram electrooculogram, chin electromyogram, electrocardiogram, respiratory monitoring (airflow, effort [respiratory effort bands]), and pulse oximetry, and may also include anterior tibial electromyogram and monitoring of body position (sensors). A type 1 sleep study is considered the gold standard for the diagnosis and stratification of the severity of OSA because it makes it possible to gather detailed information on sleep stages and respiratory abnormalities. A type 2 sleep study has the same parameters as type 1 test but is not attended by a technologist. A type 3 sleep study, or home cardiopulmonary monitoring, offers a minimum of 4 channels, whereas a type 4 sleep study consists of continuous overnight recording of 1 to 2 channels, one of which must be oximetry, with or without heart rate recording. Despite being a very promising method, especially in selected cases, oximetry alone should be currently considered a screening rather than a diagnostic tool for OSA. Actigraphy is a noninvasive method that measures sleep-wake patterns through sensors that detect movement, being widely used to help diagnose insomnia and circadian rhythm disorders. However, actigraphy alone is not indicated for diagnosing OSA, although it can be an adjunct to portable monitoring (an optional recommendation by the American Academy of Sleep Medicine).

established by the American Academy of Sleep Medicine (AASM),[133] as detailed in Chart 8.

The currently recommended definition of hypopnea is at least a 30% reduction in flow, accompanied by 3% desaturation or a microarousal. However, there is an alternative definition that allows 4% desaturation without a microarousal. Therefore, variability of the hypopnea index in the same patient may result from the use of different criteria, and it is essential to describe which criteria were used to define hypopnea in the PSG report.[136] Differences in the definition of hypopnea can affect the AHI, and a lack of consistency in the definition of these events makes it difficult to interpret the results of a sleep study.[136,137]

Based on the degree of evidence established by the *Grading of Recommendations Assessment, Development, and Evaluation* (GRADE) method, the AASM has made a number of recommendations. 1) A PSG or home monitoring using portable polygraphy can be used for diagnosis in uncomplicated patients who have signs and symptoms that are indicative of moderate or high risk of OSA (strong recommendation). 2) A PSG should be performed when home testing is negative, inconclusive, or technically inappropriate (strong recommendation). 3) In the presence of significant cardiopulmonary disease, neuromuscular disease, waking hypoventilation (or suspected sleep hypoventilation), chronic opioid use, severe insomnia, or a history of stroke, a PSG should be performed (strong recommendation—preferred over home testing). It should be noted that, in relation to the use of home methods in the diagnosis of SDB in patients with neuromuscular diseases, there are studies that suggest that even nocturnal oximetry would be sufficient to assess these patients, especially when PSG is not feasible.[138,139] 4) A second PSG should be performed if the first is negative and a strong suspicion of OSA remains (weak recommendation). 5) Questionnaires alone should not be used for the diagnosis of OSA, an objective sleep test (PSG or polygraphy; strong recommendation) always being recommended.[2]

Split-night PSG is a diagnostic method in which, in the same examination, a baseline PSG is initially performed, followed by CPAP titration in the second half of the night. The AASM suggests that, if clinically appropriate, a split-night study can be used instead of a full-night PSG for the diagnosis of OSA (weak recommendation).[2] For a split-night study to be acceptable, CPAP titration should be initiated only when moderate or severe OSA is detected during at least 2 h of the diagnostic recording time, followed by at least 3 h of CPAP titration.[2]

Home diagnosis

As described in Chart 9, portable OSA diagnostic devices were developed to reduce cost, increase patient comfort, and simplify the diagnostic process. As can be seen in Figure 1, type 3 handheld devices are recommended for the diagnosis of OSA in individuals with a high pretest probability for moderate-to-severe OSA who do not have severe or decompensated comorbidities[2,140] and should be managed at facilities with experience in sleep medicine, under the supervision of physicians certified in the specialty.[2]

The home examination consists of measurements of airflow, respiratory effort, and SpO_2. The sensors are applied by the patients themselves, following the instructions of a PSG technician or provided in an instructional video. Home devices must allow manual or automatic collection of data, which must always be reviewed by a specialist in sleep medicine and must always be read manually.[141,142] In comparison with a type 1 sleep study (attended PSG), type 3 (portable monitoring) sleep studies will typically underestimate the AHI, because they measure total recording time rather than total sleep time, as well as because they register only episodes of hypopnea that are accompanied by desaturation.

Chart 7. Parameters recorded during type 1 polysomnography.

Neurological parameters
Total sleep time
Sleep efficiency
Number of arousals
Sleep latency
REM sleep latency
Total wake time after sleep onset
Sleep stages
N1
N2
N3
R
Number of microarousals
Spontaneous microarousals
Microarousals associated with respiratory events
Microarousals associated with leg movement
Periodic leg movements
Additional data that can be reported on a type 1 study (polysomnography): bruxism, abnormal behaviors during video monitoring, epileptiform activity, loss of REM sleep atonia, changes in sleep microstructure such as alpha-delta intrusion, increased REM density, and increases in sleep spindles
Cardiopulmonary parameters
Apnea-hypopnea index
Apnea index
Hypopnea index
Respiratory effort-related arousal index
Respiratory disturbance index
SpO_2
Baseline
Mean
Minimum
Oxygen desaturation index
SpO_2 time < 90%
SpO_2 time < 80%
Heart rate (minimum, mean, and maximum)
Electrocardiogram
Additional parameters (capnography)

Adapted from Berry et al.[133] REM: rapid eye movement; N1, etc.: non-REM sleep stages; and R: REM sleep stage. The oxygen desaturation index cutoff can be 2%, 3%, or 4%. The respiratory disturbance index consists of the sum of the apnea index, hypopnea index, and respiratory effort-related arousal index.

This underestimation of the AHI by polygraphy does not seem to be clinically relevant.[143] However, it can be especially problematic for patients with mild OSA and for patients who frequently experience respiratory events unaccompanied by desaturation, including young people, women, and normal-weight individuals.

One systematic review evaluated validation studies of type 3 sleep studies versus type 1 sleep studies and found the accuracy of the former, in high-risk patients, to be as follows[2]: 84-91% (AHI > 5 events/h); 65-91% (AHI > 15 events/h); and 81-94% (AHI > 30 events/h). Portable home methods showed excellent agreement and correlated well with the values obtained by complete, supervised PSG, especially in individuals with the more severe forms of OSA.[2] That same systematic review included studies aimed at comparing clinical outcomes when the diagnosis was made using a type 3 (portable monitoring) device versus a type 1 (PSG) device, and no differences were found in the EDS (assessed by the ESS), quality of life, or adherence to CPAP treatment.[2] However, it should be noted that, in that review,[2] the studies evaluated were limited to patients with a high probability of moderate-to-severe OSA, without significant comorbidities, and without other sleep disorders; in addition, they were conducted at centers with extensive experience in sleep medicine.

Due to their greater practicality and availability, portable devices allow more frequent reassessment of patients under treatment. Although routine reassessment is not indicated for all patients, those receiving treatments considered alternatives to CPAP, such as the use of a mandibular advancement device,

Chart 8. Definition of terms.

Term	Definition
Apnea	A reduction in airflow (≥ 90%) lasting for at least 10 seconds
Hypopnea	A reduction in airflow (≥ 30%) lasting for at least 10 seconds and accompanied by microarousal or desaturation (≥ 3%)
Obstructive apnea	Apnea that is accompanied by thoracoabdominal motion
Central apnea	Apnea that is unaccompanied by thoracoabdominal motion
Mixed apnea	A combination of central and obstructive apnea
Cheyne-Stokes respiration	Periodic breathing characterized by a crescendo-decrescendo pattern of breathing between episodes of central apnea or central hypopnea
AIH	Number of episodes of apnea + hypopnea/TST (events/h)
RDI	Number of episodes of apneas + hypopnea + RERAs/TST (events/h)
OSA	An RDI ≥ 5.0 events/h together with symptoms or an RDI > 15.0 events/h regardless of symptoms
Severity assessment	
No OSA	AHI < 5.0 events/h
Mild OSA	AHI 5.0-14.9 events/h
Moderate OSA	AHI 15.0-29.9 events/h
Severe OSA	AHI ≥ 30.0 events/h

Adapted from Berry et al.[133] AHI: apnea-hypopnea index; TST: total sleep time; RDI: respiratory disturbance index; RERA: respiratory effort-related arousal; and OSA: obstructive sleep apnea. For defining OSA, the RDI is preferable to the AHI (an optional recommendation by the American Academy of Sleep Medicine). Severity assessment in adults, by either the AHI or the RDI, consists of the polysomnography criterion with the cutoff points of 5, 15, and 30 events/h.

Chart 9. Advantages and disadvantages of a type 3 sleep study (polygraphy) in comparison with a type 1 study (polysomnography).

Advantages of a type 3 sleep study
The comfort level is higher, it requires less monitoring, and the patient sleeps in his/her own bedroom.
The costs are lower: it does not require a sleep laboratory or polysomnography technologists.
Wait times for the test are shorter.
Report preparation takes less time.
Disadvantages of a type 3 sleep study
It does not assess the neurological portions of sleep.
It is not intended for assessing other sleep disorders.
It is an unattended test.
Sensors may be displaced, which may result in inadequate studies and the need for a repeat test.
It may underestimate the apnea-hypopnea index.

Adapted from two previous studies.[2,140] A portable (type 3) monitoring device may perform very poorly in patients with central sleep apnea, alveolar hypoventilation, or hypoxemia (e.g., those with congestive heart failure, COPD, neuromuscular disease, a history of stroke, or severe insomnia, as well as in those using opioids). A type 3 sleep study (polygraphy) is not indicated for patients who do not have a high pretest probability of moderate-to-severe obstructive sleep apnea.

positional therapy, surgery, or weight loss treatment, may benefit from a reassessment.[144]

High-resolution oximetry (a type 4 sleep study) detects cyclical oscillations in SpO_2 that typically accompany respiratory events. Recent studies demonstrate a strong correlation between the PSG-derived AHI and the oxygen desaturation index, whether the latter is analyzed as a PSG-independent channel or through a high-resolution oximeter.[145-147] Nocturnal oximetry has clear advantages[2]: it is an inexpensive, easily applied, noninvasive method; and there is robust evidence for its validity as a screening test for OSA, as well as in documenting the resolution of hypoxemia after treatment.[2] However, the method can produce false-negative results, cannot distinguish between OSA and central sleep apnea (CSA), and its accuracy can be reduced by various clinical factors, such as anemia, hypotension, peripheral vascular disorders, obesity, COPD, and frequent movements during sleep.[148,149] Therefore, further studies are needed in order to support the use of nocturnal home oximetry as a stand-alone diagnostic test for OSA, particularly in children and in individuals with significant comorbidities.[148]

The use of type 3 (portable monitoring) devices for the diagnosis of OSA in patients considered to be at high risk for moderate-to-severe OSA, without other suspected sleep disorders or significant cardiopulmonary or neurological comorbidities, is largely supported by validation studies and analyses of clinical outcomes. The use of such devices can reduce the huge demand for assessments in sleep laboratories.

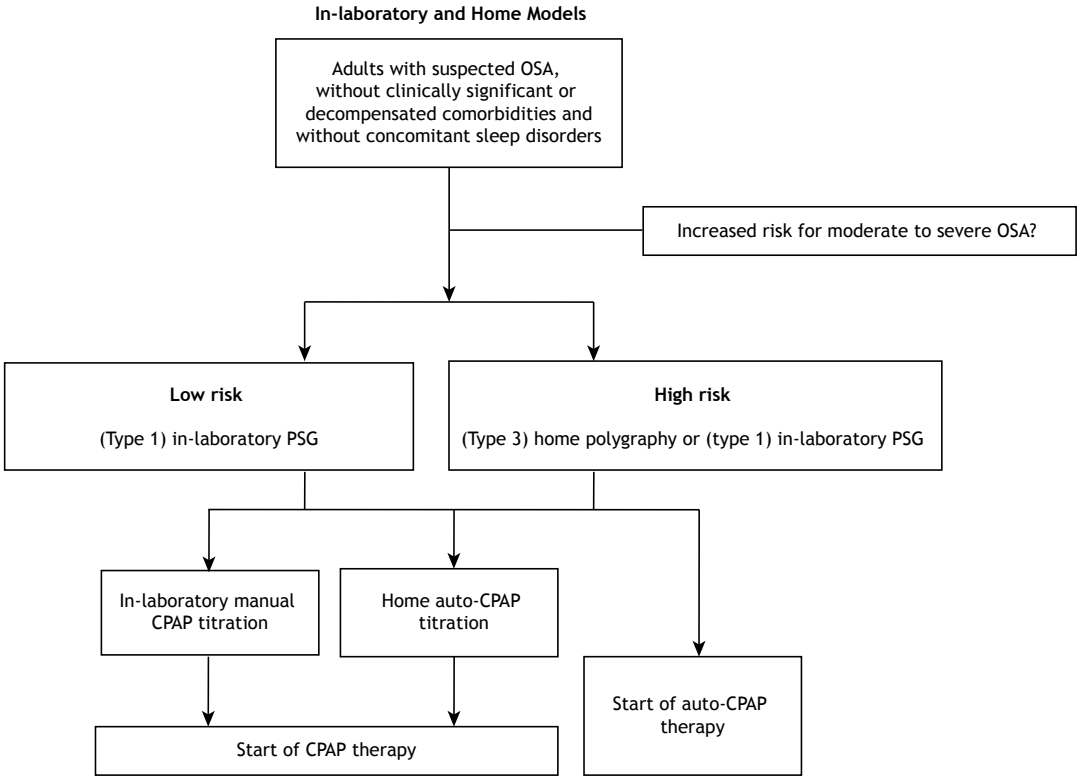


Figure 1. Diagnostic algorithm for adults with suspected sleep-disordered breathing (SDB). OSA: obstructive sleep apnea; and PSG: polysomnography. Adapted from Kapur et al.[2] High pretest probability (i.e., increased risk of moderate to severe OSA) can be estimated by the presence of excessive daytime sleepiness (EDS) and two of the three following criteria: loud, frequent snoring; witnessed episodes of apnea or episodes of a choking sensation; and hypertension. Individuals classified as being at low risk should be tested in the sleep laboratory, whereas those classified as being at high risk can be tested either at home or in the sleep laboratory. In patients with a high degree of clinical suspicion for OSA, a technically inadequate or negative home sleep study should be followed by in-laboratory PSG (a type 1 sleep study) to exclude OSA and to assess alternative causes of EDS. In patients with suspected central disorders of hypersomnolence, parasomnias, or sleep-related movement disorders, as well as in those with severe insomnia or who have difficulty in assembling the equipment at home, PSG, rather than home sleep testing, should be the first choice. The flow chart shows that titration in those individuals with an indication for positive pressure therapy can also involve, as is the case for diagnosis, the sleep laboratory and the home. Home sleep studies should be managed at facilities with experience in sleep medicine and should be supervised by physicians certified in the specialty.

Titration with positive pressure

Positive pressure therapy is the treatment of choice for individuals with moderate-to-severe OSA.[150,151] The individualization of that therapy involves the determination of the ideal pressure to be applied in the UAs in order to control the obstructive respiratory events presented by the patient. This important part of positive pressure therapy can be performed in the sleep laboratory, under supervision (with the help of a full- or split-night PSG) or unsupervised at home.[150,151]

The gold standard for determining the optimal pressure to be applied in positive pressure therapy is manual titration during an overnight PSG in a sleep laboratory.[57,151,152] In that procedure, patients should receive educational information about the device, interfaces, beneficial effects, and the potential side effects of positive pressure therapy.The various interfaces (nasal mask, nasal pillow, and full face mask) and accessories (chin strap and heated humidifier) must be available on the night of the titration, and the patient must undergo desensitization, trying the interfaces connected to the device while it is turned on, before recording begins. This is an opportunity for patient education and due correction of any issues that may arise during the examination.[57] Nasal masks or nasal pillows should be considered the first choice of interface during titration because full face masks generally lead to a higher residual AHI, higher therapeutic pressure level, and greater leakage, which could reduce adherence to the treatment proposed.[153-156]

The manual titration protocols for CPAP and BiPAP follow the AASM algorithms,[152] as outlined in Figures 2 and 3.The titration is classified as optimal when there is complete control of respiratory events (AHI < 5 events/h and $SpO_2 \geq 90\%$) for ≥ 15 min of REM sleep in the supine position. It is classified as good if the final respiratory disturbance index (RDI) is ≤ 10 or 50% lower than the baseline RDI if the latter was < 15 for ≥ 15 min of REM sleep in the supine position. It is classified as appropriate if the final RDI

is not ≤ 10 but is ≥ 75% lower than the baseline RDI or if criteria for optimal or good titration are met but there was no REM sleep in the supine position. The titration is considered unacceptable if none of the criteria described above are met.[152]

In patients presenting with hypoventilation or a history of hypoxemic lung disease, CPAP titration with supplemental oxygen may be necessary. Oxygen supplementation should be considered for patients who have a room-air SpO_2 ≤ 88% while awake and in the supine position before titration. In addition, oxygen supplementation is used when the patient maintains a room-air SpO_2 ≤ 88% for more than 5 min, even if there is complete control of obstructive events. Oxygen should be started at 1 L/min and titrated to maintain the SpO_2 at 88-94%.[152]

During a CPAP titration study, some patients may develop treatment-emergent central sleep apnea (formerly known as complex sleep apnea syndrome), which is characterized by episodes of central sleep apnea in patients diagnosed with OSA.[157] In most cases, episodes of central apnea during an initial titration are transient and may disappear after continuous use of CPAP for 4-8 weeks, and it may be necessary to reduce the pressure level that was determined to be optimal during the titration.[158] When CPAP treatment fails to correct treatment-emergent central sleep apnea, it may be necessary to use adaptive servo-ventilation.[159]

Although the gold-standard practice involves manual titration of pressure during PSG performed in a sleep laboratory, that practice is laborious and costly. Therefore, the decision can be made to use auto-adjusting positive airway pressure (APAP) devices for automatic pressure titration, in a sleep laboratory or at home.[150,151] That decision should be based on access, cost, patient preference, and clinical judgment. Titration with automatic devices should not be performed in patients with hypoventilation, heart failure, COPD, neuromuscular disease, or nocturnal hypoxemia, as well as being inappropriate for use in non-snorers or in patients with CSA.[160] The potential benefits of home titration include its lower cost and faster initiation of treatment, due to easier access to the examination. For this type of titration, the patient must receive adequate educational guidance, problems must be quickly identified and corrected, and the physician must closely monitor the response to treatment.

Various studies have shown that there are no statistically significant differences between the mean treatment pressure obtained by home titration with APAP and that obtained by manual titration in a sleep laboratory.[110,161-163] A meta-analysis encompassing 10 randomized controlled trials compared the use of positive pressure using home titration with APAP and in-laboratory positive pressure titration[150]: there were no clinically significant differences between the groups in adherence, sleepiness, or quality of life. A randomized clinical trial assessed patient preference for diagnostic/therapeutic management in the laboratory versus at home, showing that 62% of the participants

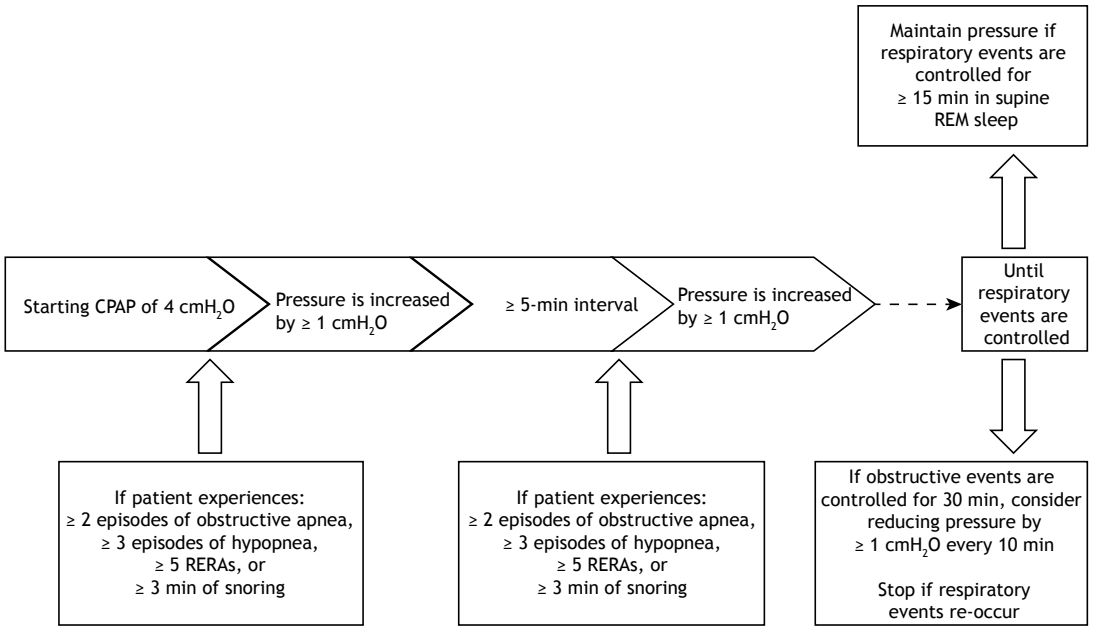


Figure 2. Algorithm for manual CPAP titration in adults during overnight polysomnography or split-night polysomnography. REM: rapid eye movement; and RERA: respiratory effort-related arousal. Adapted from Kushida et al.[152] A higher starting CPAP may be used in patients with a high BMI or for retitration studies. CPAP should be increased until all respiratory events are eliminated. The maximum CPAP is 20 cmH_2O; however, if pressures greater than 15 cmH_2O are needed or if the patient is uncomfortable or intolerant of high pressures on CPAP, BiPAP should be tried. The titration algorithm for split-night CPAP titration studies should be identical to that of overnight CPAP titration studies. For split-night CPAP titration studies, it is prudent to consider larger pressure increments (i.e., 2.0-2.5 cmH_2O) given the shorter titration duration.

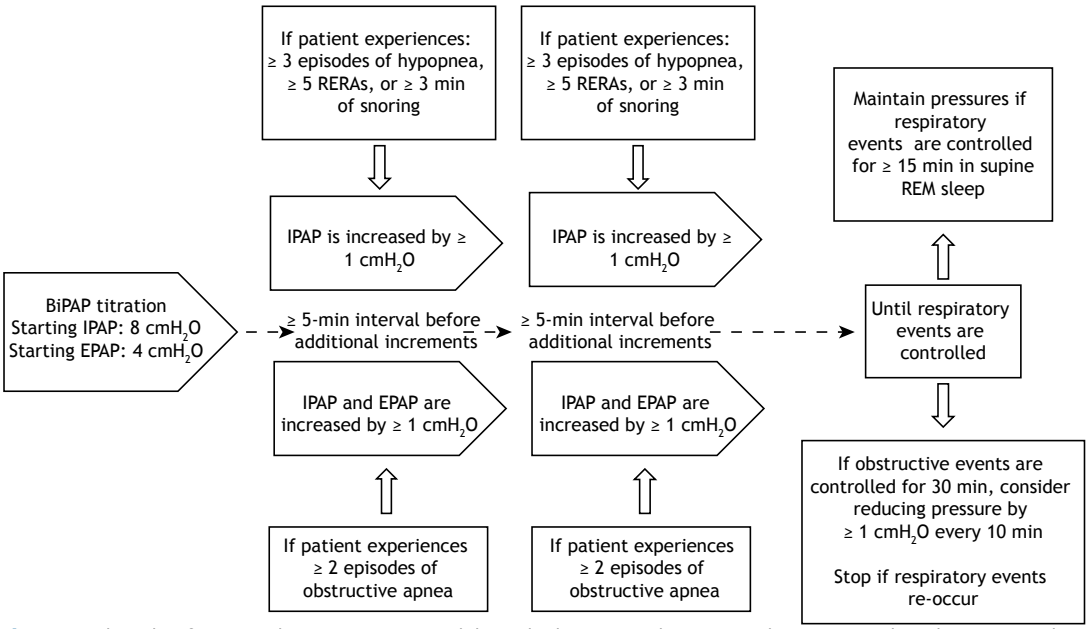


Figure 3. Algorithm for manual BiPAP titration in adults with obstructive sleep apnea during overnight polysomnography or split-night polysomnography. RERA: respiratory effort-related arousal; REM: rapid eye movement; IPAP: inspiratory positive airway pressure; and EPAP: expiratory positive airway pressure. Adapted from Kushida et al.[152] For manual BiPAP titration, the recommended minimum starting IPAP and EPAP should be 8 cmH_2O and 4 cmH_2O, respectively. These starting pressures will be adjusted according to the obstructive breathing events observed. If there are ≥ 2 episodes of obstructive apnea during titration, IPAP and EPAP should both be increased by ≥ 1 cmH_2O. If there are any other respiratory events (≥ 3 episodes of hypopnea, ≥ 5 RERAs, or ≥ 3 min of snoring), only IPAP should be increased by ≥ 1 cmH_2O. An interval of at least 5 min should be allowed before additional pressure increases are made. The recommended maximum starting IPAP should not exceed 30 cmH_2O because of the risk of barotrauma, and the recommended IPAP-EPAP differential should be 4-10 cmH_2O. The titration algorithm for split-night BiPAP titration studies should be identical to that of overnight BiPAP titration studies, but one may consider increasing IPAP and EPAP in larger increments (2.0-2.5 cmH_2O) to control breathing events.

randomized to in-laboratory management would have preferred home management, whereas only 6% of those randomized home management would have preferred in laboratory management.[164]

Positive pressure therapy

Positive pressure therapy is currently recommended for patients with an AHI ≥ 15 events/h, as well as for those with an AHI of 5-14 events/h and EDS, cognitive impairment, mood disorders, insomnia, or coexisting conditions, such as hypertension, ischemic heart disease, and a history of stroke.[150,160] Although CPAP treatment significantly improves several clinical outcomes, adherence to the treatment is suboptimal in some cases.[165] Although CPAP adherence is defined as the use of CPAP for ≥ 4 h/night for at least 70% of the nights, there is a dose-response relationship between CPAP use and several clinical outcomes (Chart 10), a greater number of hours per night translating to a greater benefit.[53,55,166-170] Positive pressure devices provide pressure through a mask, preventing upper airway collapse and normalizing the AHI in more than 90% of users.[150] In a study analyzing data from more than 2.6 million patients initiating PAP therapy between 2014 and 2017, the aforementioned level of adherence was achieved by 75% within the first 90 days of treatment.[171] Of the patients who initiate PAP therapy, 65-80% are still using it 4 years later.[172,173] In a long-term follow-up study involving 107 patients with OSA, adequate adherence to PAP therapy (> 4 h/night) was observed in 57% of the patients in the first year, with no significant changes over the next 9 years.[174] Treatment adherence was found to correlate significantly with the severity of OSA (as assessed by the AHI) and ESS scores, although not with the pressure applied or the age of the patients.[174]

There are various approaches to positive pressure therapy, including BiPAP, APAP, and a reduction in pressure during the expiratory phase (expiratory pressure relief). In a meta-analysis of 23 randomized controlled trials, no clinically significant difference was observed between adults with OSA treated with APAP and those treated with CPAP regarding the mean number of hours of use.[151] Small clinical trials have shown that cognitive behavioral therapy or short-term use of a nonbenzodiazepine hypnotic can increase nocturnal CPAP use.[175,176] Patients with OSA who cannot tolerate positive pressure therapy are potential candidates for mandibular advancement devices, positional therapy (avoidance of the supine position during sleep), or surgery.[160]

In a randomized study comparing real and sham CPAP, real CPAP was found to improve vitality

Chart 10. Major beneficial and adverse effects of CPAP.

Beneficial effects
Improved cognitive function
Improved quality of life
Reduced arterial pressure
Improved nocturia
Reduced risk of acute myocardial infarction and stroke
Reduced excessive daytime sleepiness
Improved vitality
Reduced fatigue
Reduced risk of motor vehicle accidents
Reduced insulin resistance
Improved symptoms of depression
Adverse effects
Skin irritation
Conjunctivitis
Oropharyngeal dryness
Nasal congestion
Aerophagia
Claustrophobia
Air leaks through the interface

Adapted from various previous studies.[2,3,150,151]

significantly in comparison with the sham treatment.[177] In a study comparing CPAP and placebo, fatigue and EDS were both found to be lower in the patients treated with CPAP.[178] Among patients with OSA, the risk of motor vehicle accidents has been reported to decrease substantially after CPAP treatment, becoming similar to that among drivers without OSA.[179] Treatment for OSA has a positive impact on cardiovascular health; in a study involving patients with an AHI ≥ 15 events/h, 24-h systolic blood pressure was found to be lower (by 4 mmHg) in those receiving CPAP than in those receiving placebo.[180] Similar results have been found in patients with resistant hypertension,[168] as well as in those with type 2 diabetes mellitus and hypertension.[181]

The effects that OSA treatment has on cardiovascular events remain unclear. In a randomized clinical trial comparing CPAP treatment with no treatment, involving patients without EDS and with an AHI ≥ 20 events/h, no appreciable reduction in a composite outcome of hypertension or cardiovascular events was observed over a 4-year period.[182] In a randomized study comparing CPAP with the standard of care among patients with established cardiovascular disease and moderate-to-severe OSA without severe sleepiness, CPAP was found to have no major effect on cardiovascular outcomes.[183] However, it should be noted that the two aforementioned studies had two major limitations: they excluded patients with EDS, which is an established risk factor for cardiovascular disease,[184] and adherence to CPAP treatment was low in their samples.

There are a number of factors that improve adherence to CPAP treatment[3]: education regarding the risks of OSA and the expected benefits of positive pressure therapy; monitoring of CPAP use; and behavioral interventions, including cognitive behavioral therapy and motivational therapy. Technical solutions such as using humidifiers, automatic devices, and expiratory pressure relief devices to reduce side effects have shown no significant correlation with a increase in adherence to CPAP.[3,185,186]

Follow-up of patients receiving positive pressure therapy

Patients undergoing CPAP treatment are usually monitored by a clinician reading the data stored in the CPAP device memory card. Those data provide information on three major parameters: adherence (number of hours of CPAP use per night and percentage of days using CPAP for > 4 h/night); air leaks; and residual AHI. Telemedicine use has increased dramatically, having an impact on the management (diagnosis, treatment, and follow-up) of SDB.[187-189] Telemonitoring of CPAP treatment involves the use of digital technologies to collect data on air leaks, residual AHI, and treatment adherence, which are electronically transmitted to the health care professional from the home of the patient.[190]

One of the main advantages of telemonitoring is early detection of treatment-related problems (air leaks or persistent respiratory events), facilitating appropriate interventions and improving the initial experience of patients with CPAP.[190,191] This is important because a favorable initial experience greatly contributes to long-term adherence.[150,151,192]

Telemonitoring appears to be well accepted by patients.[193] In addition, two meta-analyses showed that adherence to CPAP is significantly higher in telemonitoring groups than in standard monitoring

groups.[194,195] In a study including a collective total of 4,181,490 patients in Brazil, Mexico, and the United States, more than 80% of the participants met the adherence criteria in the first 3 months (use of CPAP for ≥ 4 h/night for ≥ 70% of the nights), 1-year adherence rates being > 75%.[196]

Other treatments

Treatment for OSA can include behavioral measures, oral appliances (OAs), and surgical procedures. Behavioral measures include avoiding the supine position, avoiding the use of alcohol especially before bedtime, engaging in regular aerobic exercise, and promoting weight loss. Avoiding the supine position reduces the risk of UA collapse. Positional therapy can involve the use of various accessories with different types of technology.[197] Weight loss improves OSA, and there is no minimum weight loss required to achieve this benefit; however, greater weight loss translates to a greater benefit.[198] Physical exercise can also improve OSA, independently of weight loss; although the mechanism has yet to be well understood, it appears to involve fat redistribution, fluid reabsorption, and increased pharyngeal muscle tone.[199]

The use of OAs for the treatment of OSA is an effective option, especially in patients with mild to moderate OSA. The appliances can also be used in patients with OSA who cannot tolerate CPAP. Although there are different types of OAs, the ones most commonly used are mandibular advancement devices that promote mandibular protrusion by altering the position of the tongue, thus increasing the UA diameter. Such appliances are effective in treating snoring in patients without OSA, as well as in reducing the AHI in patients with OSA,[200] leading to resolution of OSA in 60-80% of patients with mild OSA and in 30-50% of those with severe OSA.[201] However, it is highly unlikely that the 30-50% can be achieved in patients with severe OSA who are obese, are elderly, or have severe hypoxemia during sleep. Although CPAP has been shown to be more effective than are OAs in reducing the AHI and improving oxygenation, rates of treatment adherence can be higher for the latter.[202] Respiratory variables should be assessed in order to confirm the efficacy of treatment with OAs. Although the use of OAs can lead to changes in dental occlusion, it does not lead to significant skeletal changes. Their use can also cause temporary discomfort in the temporomandibular joint, masticatory muscles, or both, especially at the beginning of treatment. Side effects, including occlusal changes and pain, rarely lead to treatment discontinuation.[200,203]

Assessment and (clinical or surgical) treatment of nasal obstruction play an essential role in the management of OSA. Although nasal surgery alone does not have a consistent, significant effect of decreasing the AHI,[59] it can be used as an adjuvant treatment to improve adherence to CPAP.[204]

Surgical treatment is indicated for selected patients with OSA and is often recommended for those who cannot tolerate CPAP treatment.[205] The most commonly performed procedures involve removal of UA soft tissues and include uvulopalatopharyngoplasty, tongue base surgery, and lateral pharyngeal wall surgery. Because uvulopalatopharyngoplasty has a low success rate, new surgical techniques have been described and used, including lateral pharyngoplasty and expansion sphincter pharyngoplasty. However, there is no consensus regarding the best surgical technique and additional studies are needed in order to establish long-term efficacy.[205]

Maxillomandibular advancement surgery is indicated in specific cases of maxillomandibular disproportion, its reported rate of success—defined as a > 50% reduction in the AHI after surgery (to < 20 events/h)—being 85.5%.[206] Despite that high success rate, maxillomandibular advancement surgery is a major surgical procedure requiring postoperative follow-up.[206] In addition, because there are not enough studies confirming that it is effective, it should be recommended with caution and only after evaluation by a surgeon with experience in OSA.

Hypoglossal nerve stimulation is a recently described surgical procedure aimed at increasing pharyngeal dilator muscle tone.[207] However, the procedure has yet to be approved for use in Brazil and is not yet even available in the country. It consists in placing an electrode around the hypoglossal nerve, a sensor between the intercostal muscles to detect inspiratory effort, and a pulse generator in the chest wall. Hypoglossal nerve stimulation has been reported to lead to a significant decrease in the median AHI at 12 months (from 29.3 events/h to 9.0 events/h).[207] However, because it is a surgical procedure, appropriate patient selection is required, and drug-induced sleep endoscopy can aid in excluding the procedure as a treatment option.[208]

Bariatric surgery is the most effective and long-lasting treatment for obesity, reducing the risk of obesity-related comorbidities, as well as significantly reducing the number of obstructive respiratory events, improving oxygenation, and reducing mortality.[209-211] Among patients with class III obesity (BMI > 40 kg/m^2) who undergo bariatric surgery, those with OSA appear to be at an increased risk of perioperative and postoperative complications.[212,213] Bariatric surgery effectively reduces body weight and significantly improves OSA, which can resolve completely in patients undergoing the procedure.[214,215]

Myofunctional therapy can also be used as an adjunct in the management of OSA.[216] This treatment modality consists of exercises targeting oral and oropharyngeal structures, and can lead to a reduction in the AHI in approximately 50% of patients with OSA.[216,217] In addition, it can improve oxygenation, snoring, and EDS,[216,217] and it can be used as an adjunct to other therapies.[217]

It is of note that the treatment of OSA is becoming more targeted to specific phenotypes, including

compromised UA anatomy (UA narrowing/collapse), UA dilator muscle dysfunction, low arousal threshold, and unstable ventilatory control (high loop gain), with the objective of increasing the therapeutic response.[25,218] However, analysis of the aforementioned phenotypes is currently unfeasible in clinical practice, requiring specialized equipment and methods.[25,218]

HYPOVENTILATION SYNDROMES

Hypoventilation is defined as an increase in $PaCO_2$ to a level above the normal value of 45 mmHg in individuals at rest and awake.[219] Chart 11 shows the diseases that are most commonly associated with sleep hypoventilation. Although no single specific test can determine the cause of hypoventilation, the combined use of clinical assessment, physical examination, and ancillary tests (arterial blood gas analysis, pulmonary function tests, radiological evaluation, nocturnal oximetry, and PSG) can aid in identifying the etiology.[220]

Obesity hypoventilation syndrome

Obesity hypoventilation syndrome (OHS) is defined as a combination of obesity (a BMI ≥ 30 kg/m^2) and daytime $PaCO_2$ > 45 mmHg at sea level in the absence of an alternative cause for hypercapnia, including lung disease, neuromuscular disease, metabolic disorders, and chest wall disease.[221-223] The AASM defines sleep hypoventilation as follows[123]: $PaCO_2$ (or transcutaneous/expired CO_2 as a surrogate) > 55 mmHg for ≥ 10 min during sleep; or an increase in $PaCO_2$ > 10 mmHg (in comparison with an awake supine value) to a value exceeding 50 mmHg for ≥ 10 min. In children, hypoventilation is defined as an increase in $PaCO_2$ (or a surrogate) > 50 mmHg for > 25% of total sleep time.[123] Approximately 90% of patients with OHS also have OSA because obesity is a risk factor for both, the former also being known as hypercapnic OSA; in the 10% who do not have OSA, the sleep hypoventilation is not explained by episodes of apnea or hypopnea.[221-223]

Unlike patients with OSA alone, patients with OHS can present with dyspnea, leg edema, daytime hypoventilation, signs of cor pulmonale, and facial plethora,[221-223] as well as nocturnal OSA-related symptoms such as snoring, gasping/choking, and witnessed episodes of apnea.

An SpO_2 < 93% and a venous serum bicarbonate concentration ≥ 27 mEq/L are suggestive of OHS,[223] and the differential diagnosis requires arterial blood gas analysis; pulmonary function testing and respiratory muscle strength (MIP and MEP) measurements; chest X-ray; electrocardiography; thyroid function testing; and PSG.

In patients with OHS, hypercapnia is multifactorial, including increased work of breathing; reduced central response to hypercapnia and hypoxemia; and reduced leptin activity. In comparison with other obese individuals, patients with OHS have decreased lung compliance, decreased functional residual capacity, and increased pulmonary resistance.[224]

The cornerstone of OHS treatment is weight loss, which can be achieved with bariatric surgery. Patients with OHS can benefit from CPAP treatment, which improves alveolar ventilation by reducing UA resistance, relieving respiratory muscle load, increasing central respiratory activity, or any combination of the three. Adult patients with OHS and concurrent severe OSA (AHI ≥ 30 events/h) presenting with stable chronic respiratory failure can be initially treated with CPAP rather than noninvasive ventilation (NIV).[222] It is of note that more than 70% of patients with OHS have severe OSA.[222] Therefore, this recommendation is applicable to the majority of patients with OHS.[222] However, there is less certainty in OHS patients without concomitant severe OSA.[222] Improvements in hypercapnia might be achieved more slowly with CPAP than with NIV during the initial weeks of treatment.[222] Patients with a higher degree of initial ventilatory failure, poorer lung function, advanced age, or OSA that is less severe might be less likely to respond to CPAP treatment.[222] Despite treatment adherence, hypercapnia and hypoxemia can persist in 20-50% of patients with OHS; in such cases, a switch to BiPAP is usually the next step.[224] Treatment with diuretics, medroxyprogesterone, acetazolamide, oxygen therapy alone, or tracheostomy is not currently recommended.[223]

Hypoventilation syndrome caused by neuromuscular disease

Several neuromuscular diseases can cause respiratory muscle weakness, affecting children and adults (Chart 11). Although those diseases differ in their pathogenesis, treatment, and course, the final

Chart 11. Major diseases associated with hypoventilation in sleep.

- Ventilatory control disorders: CCHS, brain injury (e.g., stroke, infection, and tumor), medication-induced disturbances, idiopathic alveolar hypoventilation
- Neuromuscular diseases: amyotrophic lateral sclerosis, poliomyelitis, Guillain-Barré syndrome, myasthenia gravis, spinal muscular atrophy, Lambert-Eaton myasthenic syndrome, botulism, muscular dystrophies (e.g., Duchenne and Becker), and inflammatory myopathies (e.g., dermatomyositis and polymyositis)
- Chest wall diseases: kyphoscoliosis, sequelae of thoracoplasty, fibrothorax, and OHS
- Lung diseases: COPD, overlap syndrome, and cystic fibrosis

Adapted from various previous studies.[219,220] CCHS: congenital central hypoventilation syndrome; and OHS: obesity hypoventilation syndrome.

common pathway is respiratory muscle weakness resulting in alveolar hypoventilation.[220] Although PSG with capnography is essential for assessing sleep in patients with neuromuscular disease, a night in a sleep laboratory can be especially difficult for such patients, particularly if they require a personal care assistant.[225] The approach to these patients includes treating ventilatory muscle dysfunction, ineffective cough, and swallowing dysfunction, with the objective of protecting the airways.[225] The objective of NIV is to stabilize the decrease in vital capacity, to correct hypoxemia/hypercapnia, and to improve quality of life.[226] For patients with neuromuscular disease, NIV is considered the best treatment, and oxygen therapy (with NIV) should be provided only in cases in which NIV alone is unable to correct hypoxemia. The combined use of NIV and oxygen therapy leads to an improvement in survival in comparison with the use of oxygen therapy alone,[226,227] and these patients should not receive oxygen therapy without ventilatory support, because it could worsen hypoventilation.

Congenital central hypoventilation syndrome

Congenital central hypoventilation syndrome (CCHS), also known as "Ondine's curse", is a rare condition characterized by disordered respiratory control. In addition to an abnormal respiratory drive, clinical manifestations include aganglionic megacolon, neural crest tumors, and autonomic nervous system abnormalities, including impaired heart rate control, impaired swallowing, gastroesophageal reflux, pupillary abnormalities, hypotonia, and profuse sweating.[219] The symptoms of CCHS typically appear in the first year of life, and diagnosis requires persistent evidence of hypoventilation in the absence of heart disease, lung disease, or neuromuscular disease.[219] Although CCHS primarily affects children, a small population of adults with mild, previously undetected CCHS has been identified.[220] The treatment of CCHS is based on ventilatory support.[228] Although NIV is ventilatory support of choice, electric stimulation of the diaphragm can also be used.[229,230]

Hypoventilation syndrome caused by lung disease

Individuals with COPD are particularly prone to nocturnal hypoventilation, especially during REM sleep, due to loss of muscle tone and of accessory muscle function. In addition, many such patients show hyperinflation, which reduces diaphragmatic efficiency. Hypoventilation is exacerbated by reduced ventilatory responsiveness to CO_2 during sleep, resulting in nocturnal oxygen desaturation and predisposing to pulmonary hypertension, cardiac arrhythmias, and reduced sleep quality, as well as being a marker of increased mortality.

In patients with COPD, resting daytime hypoxemia, and evidence of right ventricular dysfunction, oxygen therapy reduces mortality, reduces exacerbations, and improves quality of life, a greater number of hours of use translating to a greater benefit.[89,231,232] There is no consensus as to whether patients with nocturnal oxygen desaturation alone should use oxygen therapy or NIV.[89,231,232]

Patients with overlap syndrome have more significant nocturnal hypoventilation, as well as greater hypoxemia and hypercapnia, than do those with COPD or OSA alone.[231] The standard treatment for overlap syndrome is CPAP because it relieves UA obstruction, relieves the respiratory muscles, reduces hypoventilation, reduces oxygen consumption, and reduces CO_2 production by the respiratory muscles.[232] Because CPAP alone might not be able to correct hypoxemia fully, oxygen therapy is also required.[231,232]

CENTRAL SLEEP APNEA

It is known that CSA is much less common than is OSA.[233] Central apnea is the cessation of airflow with no respiratory effort; patients with an AHI ≥ 5 events/h, more than 50% of which are central respiratory events, are classified as having CSA.[233,234] Home polygraphs have yet to be validated for use in the diagnosis of CSA, PSG therefore continuing to be the gold standard.[234]

On the basis of its pathophysiology, CSA can be divided into two groups[235]: eucapnic CSA (the more common of the two, being accompanied by Cheyne-Stokes respiration and affecting patients with heart failure, acute ischemic stroke, and periodic breathing at high altitude); and hypercapnic CSA (which is observed in individuals with neuromuscular disease, rib cage abnormalities, or opioid intoxication). Hypercapnic CSA arises from changes in the respiratory center, chemoreceptors, or skeletal muscles, leading to hypoventilation.[235,236] In contrast, eucapnic CSA is caused by instability in the regulatory pathways that control ventilation[235,236]: disturbances such as hypoxemia or transitions from wakefulness to sleep are associated with periods of hyperventilation, which lead to increased minute ventilation and subsequent decreases in $PaCO_2$. When $PaCO_2$ falls below the apnea threshold, as determined by the central chemoreceptors, a central apnea occurs.[235,236]

Heart failure is perhaps the condition that is most commonly associated with CSA (or, more specifically, with Cheyne-Stokes respiration).[234] In a cross-sectional analysis of the Sleep Heart Health study, the overall prevalence of CSA in patients with heart failure was found to be 0.9%, and approximately half of the patients with CSA also had Cheyne-Stokes respiration.[237] Although Cheyne-Stokes respiration can occur during wakefulness and during sleep, it is more common during the latter: when Cheyne-Stokes respiration occurs during sleep, it is a form of CSA with prolonged hyperpnea and denotes low cardiac output.[234] The diagnostic criteria for Cheyne-Stokes respiration include at least three consecutive episodes of central apnea or hypopnea separated

by crescendo-decrescendo respirations with a cycle length of at least 40 s.[234]

Initial population-based studies reported that approximately 40% of men with systolic heart failure had CSA, and subsequent studies, some of which also included women, showed similar proportions.[238,239] Central events occur most frequently during the lighter stages of non-REM sleep, particularly after arousals and sleep stage changes.[238]

A form of Cheyne-Stokes respiration can also be observed during periodic breathing at high altitude. Altered breathing during non-REM sleep commonly occurs in this situation because of changes in neural signaling caused by hypoxia (attributed to a decrease in FiO_2) and hyperventilation-induced alkalosis. Although this can occur at elevations as low as 1,400 m, it rarely causes symptoms at elevations below 2,500 m.[240]

Although stroke has been considered a risk factor for CSA, an analysis of central and obstructive events in patients with stroke shows that OSA is much more common than is CSA in such patients.[241,242] Opioid intoxication is another risk factor for CSA because opioids decrease central and peripheral responsiveness to hypoxemia and hypercapnia during wakefulness and sleep.[243] Although the exact mechanism of CSA caused by chronic opioid use has yet to be understood, it might be partly due to a change in respiratory drive caused by reduced chemoreceptor sensitivity. The most common sleep-related disorder in chronic opioid users is CSA because although chronic opioid use can lead to worsening of obstructive events, it plays a greater role in the development of central events.[244]

The mainstay of the treatment of hypercapnic and eucapnic CSA is optimization in relation to the underlying cause.[234] For patients with an AHI > 15 events/h (with a predominance of central events) and significant symptoms, CPAP can be used.[245] If a decision is made to initiate positive pressure therapy, CPAP is the preferred choice because it has led to improvements in patients with heart failure.[246,247] The addition of oxygen therapy is indicated if PSG demonstrates episodes of nocturnal desaturation associated with central events.[234] If symptoms persist despite initiation of CPAP treatment or if patients cannot tolerate that treatment, other positive pressure modes can be used.[234] The most important determining factor of which mode to use in the treatment of CSA associated with heart failure is the ejection fraction; in patients with an ejection fraction < 45%, it remains unclear what the optimal treatment is. One study[248] showed that adaptive servo-ventilation should not be used in patients with an ejection fraction ≤ 45%, because, in comparison with guideline-based medical treatment alone, it was found to increase all-cause mortality (35% vs. 29%; hazard ratio, 1.28; 95% CI: 1.06-1.55) and cardiovascular mortality (30% vs. 24%; hazard ratio, 1.34; 95% CI: 1.09-1.65).

Oxygen therapy (if needed) combined with optimization of heart failure treatment can be the optimal approach for patients with CSA.[234] Adaptive servo-ventilation and BiPAP with a backup rate are available treatment options for patients who have an ejection fraction > 45% and who cannot tolerate CPAP treatment.[234] It has recently been shown that phrenic nerve stimulators ensure stable ventilation, improving physical performance and reducing hypoxemia.[249]

OBSTRUCTIVE SLEEP APNEA IN CHILDREN

In children, SDB ranges from primary snoring to OSA (Chart 12).[250] The estimated overall prevalence of OSA in children (of any age) is 1-4%, being significantly higher in obese children.[251] The incidence of OSA in children peaks between 2 and 8 years of age, which is the age range in which the pharyngeal and palatine tonsils are largest in relation to the UAs. It tends to be more common in children with a family history of OSA, in those of African or Asian descent, and in those with clinical conditions that lead to UA obstruction; those with craniofacial abnormalities; and those with lysosomal storage disorders.[251,252]

The pathophysiology of OSA in children is similar to that of OSA in adults in that UA narrowing occurs during sleep as a result of decreased muscle tone and, consequently, increased UA resistance caused by loss of the wakefulness stimuli. In pediatric patients, OSA is probably due to a combination of changes in UA structure and reduced neuromuscular control, together with genetic, hormonal, inflammatory, metabolic, and environmental factors (exposure to smoking and environmental pollution).[252,253]

The main predictors of OSA are snoring, witnessed episodes of apnea, and restless sleep. Screening for OSA in children should include questions regarding the following[250,254]: snoring (frequency, intensity, body position, persistence, and association with respiratory effort); behavior during sleep and upon waking; sleep position; enuresis; recurrent UA infections; mouth breathing; school performance; emotional lability; and comorbidities.

In the physical examination of children with suspected OSA, the following aspects should be investigated[253]: height and weight (because children with OSA tend to present with growth impairment and weigh less than expected for their age); evidence of chronic UA obstruction (signs of mouth breathing); enlarged palatine tonsils (in the transverse and anteroposterior diameters); craniofacial features (long, narrow facial features, receding chin, retrognathia, high-arched palate, elongated soft palate, and malocclusion); and signs of right ventricular overload and hypertension. Because the prevalence of OSA is high in patients with syndromes, neuromuscular disorders, and craniofacial (skeletal or soft-tissue) abnormalities, such patients should be carefully evaluated.[250]

For the diagnosis of OSA and the monitoring of patients under treatment for OSA, the standard test is PSG performed in a sleep laboratory. Infants ≤ 6 months of age can undergo daytime PSG (the

Chart 12. Characteristics of sleep-disordered breathing in children.

• Primary snoring: that occurring at least three nights/week without obstructive events, gas exchange abnormalities, or frequent arousals
• UA resistance syndrome: characterized by periods of increased UA resistance and increased work of breathing during sleep, accompanied by snoring and sleep fragmentation
• Obstructive hypoventilation: that resulting from snoring and hypercapnia in the absence of recognizable obstructive events
• Obstructive sleep apnea: characterized by episodes of partial or complete UA obstruction, interrupting ventilation during sleep and disrupting the normal pattern of sleep

Adapted from Kaditis et al.[250] UA: upper airway.

recommended recording time being 3-4 h). Unlike adult OSA, pediatric OSA can be diagnosed on the basis of 1 event/h of sleep, 1.5 events/h of sleep, or 2 events/h of sleep. An obstructive AHI > 5 events/h indicates moderate OSA, and an obstructive AHI ≥ 10 events/h indicates severe OSA.[250] In adolescents, OSA is diagnosed on the basis of the same criteria as those used for the diagnosis of OSA in adults because specific criteria have yet to be established.[255] Evaluation of CO_2 during PSG, by capnography or transcutaneous monitoring, plays an important role in identifying hypoventilation in children.[133] Although CO_2 measurement is highly recommended, it is not currently widely available in Brazil because there is a lack of CO_2 measurement devices approved for use by the Brazilian National Health Regulatory Agency. Although home sleep monitoring remains controversial, it has been used in settings in which access to PSG is limited and the results have been promising.[250]

Pediatric PSG should be performed in the following situations[250]: in children with symptoms of obstructive SDB before undergoing adenotonsillectomy, particularly in those with obesity, craniofacial abnormalities, neuromuscular disorders, or complex abnormalities (e.g., Chiari malformation, Down syndrome, and Prader-Willi syndrome), as well as in those in whom the need for treatment is unclear; in patients with persistent symptoms of OSA despite having undergone adenotonsillectomy; in those presenting with moderate-to-severe OSA in the preoperative period; and in those presenting with obesity, craniofacial abnormalities, neuromuscular disorders, or complex abnormalities (e.g., Chiari malformation, Down syndrome, and Prader-Willi syndrome); and before and after OSA treatment with rapid maxillary expansion, OAs, CPAP, or NIV.

Ancillary tests such as fiberoptic laryngoscopy, cephalometry, CT of the facial bones followed by three-dimensional reconstruction of the images, spirometry, and arterial blood gas analysis can be used depending on the clinical context. In patients with severe abnormalities who are candidates for surgery, echocardiography for assessment of the right heart and detection of pulmonary hypertension can be indicated.

Surgery (adenotonsillectomy) is still the treatment of first choice for patients with lymphoid tissue hypertrophy.[253] However, surgical treatment is more likely to fail or only partially succeed in infants, obese children, patients with genetic disorders that result in craniofacial abnormalities, and patients with severe OSA.[252]

Postoperative respiratory complications have been reported to be common in children with severe OSA, those < 3 years of age, and those with comorbidities. Such children should be continuously and noninvasively monitored for oxygen and CO_2 levels, preferably in the ICU.[253] Surgical procedures such as mandibular distraction osteogenesis, maxillomandibular advancement, and, in extreme cases, tracheostomy can be performed, especially in patients with craniofacial abnormalities. At some referral centers, bariatric surgery has been performed, albeit rarely, in obese adolescents.

In individuals with OSA, other treatment approaches can be used in isolation or in combination with adenotonsillectomy, including the use of topical nasal corticosteroids or leukotriene receptor antagonists; weight loss diets; orofacial myofunctional therapy; orthodontic and dentofacial orthopedic treatment; and CPAP. Older children and adolescents with OSA can have clinical characteristics that are similar to those of adults, the recommended therapeutic approach therefore being similar.[57]

There is increasing evidence of the cardiac impact of inadequately treated OSA, including hypertension, tachycardia, increased heart rate variability, right ventricular dysfunction, and pulmonary hypertension. Great emphasis has been given to neurocognitive impairments, with evidence that OSA can affect mood, language skills, visual perception, and memory.[252] The most significant neurocognitive and cardiovascular sequelae are described in Chart 13.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the conceptualization and planning of the study, as well as to the writing, reviewing, and revising of the manuscript, having approved the final version before submission.

CONFLICTS OF INTEREST

None declared.

Chart 13. Major neurological and cardiovascular complications of obstructive sleep apnea in children.

Neurological
Excessive daytime sleepiness
Attention deficit/hyperactivity
Cognitive deficit/learning difficulty
Behavioral problems
Cardiovascular
Hypertension (systemic)
Pulmonary hypertension and cor pulmonale

Adapted from Kaditis et al.[250]

REFERENCES

1. Ramar K, Malhotra RK, Carden KA, Martin JL, Abbasi-Feinberg F, Aurora RN, et al. Sleep is essential to health: an American Academy of Sleep Medicine position statement. J Clin Sleep Med. 2021;17(10):2115-2119. https://doi.org/10.5664/jcsm.9476
2. Kapur VK, Auckley DH, Chowdhuri S, Kuhlmann DC, Mehra R, Ramar K, et al. Clinical Practice Guideline for Diagnostic Testing for Adult Obstructive Sleep Apnea: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13(3):479-504. https://doi.org/10.5664/jcsm.6506
3. Gottlieb DJ, Punjabi NM. Diagnosis and Management of Obstructive Sleep Apnea: A Review. JAMA. 2020;323(14):1389-1400. https://doi.org/10.1001/jama.2020.3514
4. Dodds S, Williams LJ, Roguski A, Vennelle M, Douglas NJ, Kotoulas SC, et al. Mortality and morbidity in obstructive sleep apnoea-hypopnoea syndrome: results from a 30-year prospective cohort study. ERJ Open Res. 2020;6(3):00057-2020. https://doi.org/10.1183/23120541.00057-2020
5. Huyett P, Bhattacharyya N. Incremental health care utilization and expenditures for sleep disorders in the United States. J Clin Sleep Med. 2021;17(10):1981-1986. https://doi.org/10.5664/jcsm.9392
6. Lyons MM, Bhatt NY, Pack AI, Magalang UJ. Global burden of sleep-disordered breathing and its implications. Respirology. 2020;25(7):690-702. https://doi.org/10.1111/resp.13838
7. 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):1230-1235. https://doi.org/10.1056/NEJM199304293281704
8. Peppard PE, Young T, Barnet JH, Palta M, Hagen EW, Hla KM. Increased prevalence of sleep-disordered breathing in adults. Am J Epidemiol. 2013;177(9):1006-1014. https://doi.org/10.1093/aje/kws342
9. Heinzer R, Vat S, Marques-Vidal P, Marti-Soler H, Andries D, Tobback N, et al. Prevalence of sleep-disordered breathing in the general population: the HypnoLaus study. Lancet Respir Med. 2015;3(4):310-318. https://doi.org/10.1016/S2213-2600(15)00043-0
10. Fietze I, Laharnar N, Obst A, Ewert R, Felix SB, Garcia C, et al. Prevalence and association analysis of obstructive sleep apnea with gender and age differences - Results of SHIP-Trend. J Sleep Res. 2019;28(5):e12770. https://doi.org/10.1111/jsr.12770
11. Tufik S, Santos-Silva R, Taddei JA, Bittencourt LR. Obstructive sleep apnea syndrome in the Sao Paulo Epidemiologic Sleep Study. Sleep Med. 2010;11(5):441-446. https://doi.org/10.1016/j.sleep.2009.10.005
12. Senaratna CV, Perret JL, Lodge CJ, Lowe AJ, Campbell BE, Matheson MC, et al. Prevalence of obstructive sleep apnea in the general population: A systematic review. Sleep Med Rev. 2017;34:70-81. https://doi.org/10.1016/j.smrv.2016.07.002
13. Lam B, Ip MS, Tench E, Ryan CF. Craniofacial profile in Asian and white subjects with obstructive sleep apnoea. Thorax. 2005;60(6):504-510. https://doi.org/10.1136/thx.2004.031591
14. Benjafield AV, Ayas NT, Eastwood PR, Heinzer R, Ip MSM, Morrell MJ, et al. Estimation of the global prevalence and burden of obstructive sleep apnoea: a literature-based analysis. Lancet Respir Med. 2019;7(8):687-698. https://doi.org/10.1016/S2213-2600(19)30198-5
15. Kositanurit W, Muntham D, Udomsawaengsup S, Chirakalwasan N. Prevalence and associated factors of obstructive sleep apnea in morbidly obese patients undergoing bariatric surgery. Sleep Breath. 2018;22(1):251-256. https://doi.org/10.1007/s11325-017-1500-y
16. Ravesloot MJ, van Maanen JP, Hilgevoord AA, van Wagensveld BA, de Vries N. Obstructive sleep apnea is underrecognized and underdiagnosed in patients undergoing bariatric surgery. Eur Arch Otorhinolaryngol. 2012;269(7):1865-1871. https://doi.org/10.1007/s00405-012-1948-0
17. Muxfeldt ES, Margallo VS, Guimarães GM, Salles GF. Prevalence and associated factors of obstructive sleep apnea in patients with resistant hypertension. Am J Hypertens. 2014;27(8):1069-1078. https://doi.org/10.1093/ajh/hpu023
18. Pedrosa RP, Drager LF, Gonzaga CC, Sousa MG, de Paula LK, Amaro AC, et al. Obstructive sleep apnea: the most common secondary cause of hypertension associated with resistant hypertension. Hypertension. 2011;58(5):811-817. https://doi.org/10.1161/HYPERTENSIONAHA.111.179788
19. Youssef I, Kamran H, Yacoub M, Patel N, Goulbourne C, Kumar S, et al. Obstructive Sleep Apnea as a Risk Factor for Atrial Fibrillation: A Meta-Analysis. J Sleep Disord Ther. 2018;7(1):282. https://doi.org/10.4172/2167-0277.1000282
20. Li M, Hou WS, Zhang XW, Tang ZY. Obstructive sleep apnea and risk of stroke: a meta-analysis of prospective studies. Int J Cardiol. 2014;172(2):466-469. https://doi.org/10.1016/j.ijcard.2013.12.230
21. Zhang Y, Ren R, Lei F, Zhou J, Zhang J, Wing YK, et al. Worldwide and regional prevalence rates of co-occurrence of insomnia and insomnia symptoms with obstructive sleep apnea: A systematic review and meta-analysis. Sleep Med Rev. 2019;45:1-17. https://doi.org/10.1016/j.smrv.2019.01.004
22. Luyster FS, Buysse DJ, Strollo PJ Jr. Comorbid insomnia and obstructive sleep apnea: challenges for clinical practice and research. J Clin Sleep Med. 2010;6(2):196-204. https://doi.org/10.5664/jcsm.27772
23. Lechat B, Appleton S, Melaku YA, Hansen K, McEvoy RD, Adams R, et al. Co-morbid insomnia and obstructive sleep apnoea is associated with all-cause mortality. Eur Respir J. 2021;2101958. https://doi.org/10.1183/13993003.01958-2021
24. Eckert DJ, Malhotra A. Pathophysiology of adult obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):144-153. https://doi.org/10.1513/pats.200707-114MG
25. Eckert DJ. Phenotypic approaches to obstructive sleep apnoea - New pathways for targeted therapy. Sleep Med Rev. 2018;37:45-59. https://doi.org/10.1016/j.smrv.2016.12.003
26. Taranto-Montemurro L, Messineo L, Wellman A. Targeting Endotypic Traits with Medications for the Pharmacological Treatment of Obstructive Sleep Apnea. A Review of the Current Literature. J Clin Med. 2019;8(11):1846. https://doi.org/10.3390/jcm8111846
27. Somers VK, Dyken ME, Mark AL, Abboud FM. Sympathetic-nerve activity during sleep in normal subjects. N Engl J Med. 1993;328(5):303-307. https://doi.org/10.1056/NEJM199302043280502
28. Kim AM, Keenan BT, Jackson N, Chan EL, Staley B, Poptani H, et al. Tongue fat and its relationship to obstructive sleep apnea. Sleep. 2014;37(10):1639-1648. https://doi.org/10.5665/sleep.4072
29. Peppard PE, Young T, Palta M, Dempsey J, Skatrud J. Longitudinal

study of moderate weight change and sleep-disordered breathing. JAMA. 2000;284(23):3015-3021. https://doi.org/10.1001/jama.284.23.3015

30. Stanchina ML, Malhotra A, Fogel RB, Trinder J, Edwards JK, Schory K, et al. The influence of lung volume on pharyngeal mechanics, collapsibility, and genioglossus muscle activation during sleep. Sleep. 2003;26(7):851-856. https://doi.org/10.1093/sleep/26.7.851
31. Kawaguchi Y, Fukumoto S, Inaba M, Koyama H, Shoji T, Shoji S, et al. Different impacts of neck circumference and visceral obesity on the severity of obstructive sleep apnea syndrome. Obesity (Silver Spring). 2011;19(2):276-282. https://doi.org/10.1038/oby.2010.170
32. Dancey DR, Hanly PJ, Soong C, Lee B, Shepard J Jr, Hoffstein V. Gender differences in sleep apnea: the role of neck circumference. Chest. 2003;123(5):1544-1550. https://doi.org/10.1378/chest.123.5.1544
33. Onat A, Hergenç G, Yüksel H, Can G, Ayhan E, Kaya Z, et al. Neck circumference as a measure of central obesity: associations with metabolic syndrome and obstructive sleep apnea syndrome beyond waist circumference. Clin Nutr. 2009;28(1):46-51. https://doi.org/10.1016/j.clnu.2008.10.006
34. Shah N, Hanna DB, Teng Y, Sotres-Alvarez D, Hall M, Loredo JS, et al. Sex-Specific Prediction Models for Sleep Apnea From the Hispanic Community Health Study/Study of Latinos. Chest. 2016;149(6):1409-1418. https://doi.org/10.1016/j.chest.2016.01.013
35. Redolfi S, Yumino D, Ruttanaumpawan P, Yau B, Su MC, Lam J, et al. Relationship between overnight rostral fluid shift and Obstructive Sleep Apnea in nonobese men. Am J Respir Crit Care Med. 2009;179(3):241-246. https://doi.org/10.1164/rccm.200807-1076OC
36. Bixler EO, Vgontzas AN, Lin HM, Ten Have T, Rein J, Vela-Bueno A, et al. Prevalence of sleep-disordered breathing in women: effects of gender. Am J Respir Crit Care Med. 2001;163(3 Pt 1):608-613. https://doi.org/10.1164/ajrccm.163.3.9911064
37. Mirer AG, Young T, Palta M, Benca RM, Rasmuson A, Peppard PE. Sleep-disordered breathing and the menopausal transition among participants in the Sleep in Midlife Women Study. Menopause. 2017;24(2):157-162. https://doi.org/10.1097/GME.0000000000000744
38. Malhotra A, Huang Y, Fogel RB, Pillar G, Edwards JK, Kikinis R, et al. The male predisposition to pharyngeal collapse: importance of airway length. Am J Respir Crit Care Med. 2002;166(10):1388-1395. https://doi.org/10.1164/rccm.2112072
39. Jordan AS, McEvoy RD. Gender differences in sleep apnea: epidemiology, clinical presentation and pathogenic mechanisms. Sleep Med Rev. 2003;7(5):377-389. https://doi.org/10.1053/smrv.2002.0260
40. Caufriez A, Leproult R, L'Hermite-Balériaux M, Kerkhofs M, Copinschi G. Progesterone prevents sleep disturbances and modulates GH, TSH, and melatonin secretion in postmenopausal women. J Clin Endocrinol Metab. 2011;96(4):E614-E623. https://doi.org/10.1210/jc.2010-2558
41. Lin TY, Lin PY, Su TP, Li CT, Lin WC, Chang WH, et al. Risk of developing obstructive sleep apnea among women with polycystic ovarian syndrome: a nationwide longitudinal follow-up study. Sleep Med. 2017;36:165-169. https://doi.org/10.1016/j.sleep.2016.12.029
42. Liu PY, Yee B, Wishart SM, Jimenez M, Jung DG, Grunstein RR, et al. The short-term effects of high-dose testosterone on sleep, breathing, and function in older men. J Clin Endocrinol Metab. 2003;88(8):3605-3613. https://doi.org/10.1210/jc.2003-030236
43. Ernst G, Mariani J, Blanco M, Finn B, Salvado A, Borsini E. Increase in the frequency of obstructive sleep apnea in elderly people. Sleep Sci. 2019;12(3):222-226. https://doi.org/10.5935/1984-0063.20190081
44. Malhotra A, Huang Y, Fogel R, Lazic S, Pillar G, Jakab M, et al. Aging influences on pharyngeal anatomy and physiology: the predisposition to pharyngeal collapse. Am J Med. 2006;119(1):72.e9-72.e7.2E14. https://doi.org/10.1016/j.amjmed.2005.01.077
45. Gooneratne NS, Vitiello MV. Sleep in older adults: normative changes, sleep disorders, and treatment options. Clin Geriatr Med. 2014;30(3):591-627. https://doi.org/10.1016/j.cger.2014.04.007
46. Arnaud C, Bochaton T, Pépin JL, Belaidi E. Obstructive sleep apnoea and cardiovascular consequences: Pathophysiological mechanisms. Arch Cardiovasc Dis. 2020;113(5):350-358. https://doi.org/10.1016/j.acvd.2020.01.003
47. Reutrakul S, Mokhlesi B. Obstructive Sleep Apnea and Diabetes: A State of the Art Review. Chest. 2017;152(5):1070-1086. https://doi.org/10.1016/j.chest.2017.05.009
48. Li M, Li X, Lu Y. Obstructive Sleep Apnea Syndrome and Metabolic Diseases. Endocrinology. 2018;159(7):2670-2675. https://doi.org/10.1210/en.2018-00248
49. Dredla BK, Castillo PR. Cardiovascular Consequences of Obstructive Sleep Apnea. Curr Cardiol Rep. 2019;21(11):137. https://doi.org/10.1007/s11886-019-1228-3
50. Salman LA, Shulman R, Cohen JB. Obstructive Sleep Apnea, Hypertension, and Cardiovascular Risk: Epidemiology, Pathophysiology, and Management. Curr Cardiol Rep. 2020;22(2):6. https://doi.org/10.1007/s11886-020-1257-y
51. Yaggi HK, Concato J, Kernan WN, Lichtman JH, Brass LM, Mohsenin V. Obstructive sleep apnea as a risk factor for stroke and death. N Engl J Med. 2005;353(19):2034-2041. https://doi.org/10.1056/NEJMoa043104
52. Lee CH, Sethi R, Li R, Ho HH, Hein T, Jim MH, et al. Obstructive Sleep Apnea and Cardiovascular Events After Percutaneous Coronary Intervention. Circulation. 2016;133(21):2008-2017. https://doi.org/10.1161/CIRCULATIONAHA.115.019392
53. Marin JM, Carrizo SJ, Vicente E, Agusti AG. Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study. Lancet. 2005;365(9464):1046-1053. https://doi.org/10.1016/S0140-6736(05)71141-7
54. Campos-Rodriguez F, Martinez-Garcia MA, de la Cruz-Moron I, Almeida-Gonzalez C, Catalan-Serra P, Montserrat JM. Cardiovascular mortality in women with obstructive sleep apnea with or without continuous positive airway pressure treatment: a cohort study. Ann Intern Med. 2012;156(2):115-122. https://doi.org/10.7326/0003-4819-156-2-201201170-00006
55. Martínez-García MA, Campos-Rodríguez F, Catalán-Serra P, Soler-Cataluña JJ, Almeida-Gonzalez C, De la Cruz Morón I, et al. Cardiovascular mortality in obstructive sleep apnea in the elderly: role of long-term continuous positive airway pressure treatment: a prospective observational study. Am J Respir Crit Care Med. 2012;186(9):909-916. https://doi.org/10.1164/rccm.201203-0448OC
56. Mehra R. Sleep apnea and the heart. Cleve Clin J Med. 2019;86(9 Suppl 1):10-18. https://doi.org/10.3949/ccjm.86.s1.03
57. Epstein LJ, Kristo D, Strollo PJ Jr, Friedman N, Malhotra A, Patil SP, et al. Clinical guideline for the evaluation, management and long-term care of obstructive sleep apnea in adults. J Clin Sleep Med. 2009;5(3):263-276. https://doi.org/10.5664/jcsm.27497
58. Carnethon MR, Johnson DA. Sleep and Resistant Hypertension. Curr Hypertens Rep. 2019;21(5):34. https://doi.org/10.1007/s11906-019-0941-z
59. Van Ryswyk E, Mukherjee S, Chai-Coetzer CL, Vakulin A, McEvoy RD. Sleep Disorders, Including Sleep Apnea and Hypertension. Am J Hypertens. 2018;31(8):857-864. https://doi.org/10.1093/ajh/hpy082
60. Cai A, Wang L, Zhou Y. Hypertension and obstructive sleep apnea. Hypertens Res. 2016;39(6):391-395. https://doi.org/10.1038/hr.2016.11
61. Lyons OD, Ryan CM. Sleep Apnea and Stroke. Can J Cardiol. 2015;31(7):918-927. https://doi.org/10.1016/j.cjca.2015.03.014
62. Arzt M, Young T, Finn L, Skatrud JB, Bradley TD. Association of sleep-disordered breathing and the occurrence of stroke. Am J Respir Crit Care Med. 2005;172(11):1447-1451. https://doi.org/10.1164/rccm.200505-702OC
63. McKee Z, Auckley DH. A sleeping beast: Obstructive sleep apnea and stroke. Cleve Clin J Med. 2019;86(6):407-415. https://doi.org/10.3949/ccjm.86a.18033
64. Drager LF, Togeiro SM, Polotsky VY, Lorenzi-Filho G. Obstructive sleep apnea: a cardiometabolic risk in obesity and the metabolic syndrome. J Am Coll Cardiol. 2013;62(7):569-576. https://doi.org/10.1016/j.jacc.2013.05.045
65. Gaines J, Vgontzas AN, Fernandez-Mendoza J, Bixler EO. Obstructive sleep apnea and the metabolic syndrome: The road to clinically-meaningful phenotyping, improved prognosis, and personalized treatment. Sleep Med Rev. 2018;42:211-219. https://doi.org/10.1016/j.smrv.2018.08.009
66. Hirotsu C, Haba-Rubio J, Togeiro SM, Marques-Vidal P, Drager LF,

Vollenweider P, et al. Obstructive sleep apnoea as a risk factor for incident metabolic syndrome: a joined Episono and HypnoLaus prospective cohorts study. Eur Respir J. 2018;52(5):1801150. https://doi.org/10.1183/13993003.01150-2018

67. Dorkova Z, Petrasova D, Molcanyiova A, Popovnakova M, Tkacova R. Effects of continuous positive airway pressure on cardiovascular risk profile in patients with severe obstructive sleep apnea and metabolic syndrome. Chest. 2008;134(4):686-692. https://doi.org/10.1378/chest.08-0556
68. Giampá SQC, Furlan SF, Freitas LS, Macedo TA, Lebkuchen A, Cardozo KHM, et al. Effects of CPAP on Metabolic Syndrome in Patients With OSA: A Randomized Trial. Chest. 2022;161(5):1370-1381. https://doi.org/10.1016/j.chest.2021.12.669
69. Chaudhary P, Goyal A, Pakhare A, Goel SK, Kumar A, Reddy MA, et al. Metabolic syndrome in non-obese patients with OSA: learning points of a cross-sectional study from a tertiary care hospital in Central India. Sleep Breath. 2022;26(2):681-688. https://doi.org/10.1007/s11325-021-02401-4
70. Yu Z, Cheng JX, Zhang D, Yi F, Ji Q. Association between Obstructive Sleep Apnea and Type 2 Diabetes Mellitus: A Dose-Response Meta-Analysis. Evid Based Complement Alternat Med. 2021;2021:1337118. https://doi.org/10.1155/2021/1337118
71. Panossian LA, Veasey SC. Daytime sleepiness in obesity: mechanisms beyond obstructive sleep apnea–a review. Sleep. 2012;35(5):605-615. https://doi.org/10.5665/sleep.1812
72. Chapman JL, Serinel Y, Marshall NS, Grunstein RR. Residual Daytime Sleepiness in Obstructive Sleep Apnea After Continuous Positive Airway Pressure Optimization: Causes and Management. Sleep Med Clin. 2016;11(3):353-363. https://doi.org/10.1016/j.jsmc.2016.05.005
73. Vanek J, Prasko J, Genzor S, Ociskova M, Kantor K, Holubova M, et al. Obstructive sleep apnea, depression and cognitive impairment. Sleep Med. 2020;72:50-58. https://doi.org/10.1016/j.sleep.2020.03.017
74. BaHammam AS, Kendzerska T, Gupta R, Ramasubramanian C, Neubauer DN, Narasimhan M, et al. Comorbid depression in obstructive sleep apnea: an under-recognized association. Sleep Breath. 2016;20(2):447-456. https://doi.org/10.1007/s11325-015-1223-x
75. Schiza SE, Bouloukaki I. Screening for obstructive sleep apnoea in professional drivers. Breathe (Sheff). 2020;16(1):29364. https://doi.org/10.1183/20734735.0364-2019
76. Strohl KP, Brown DB, Collop N, George C, Grunstein R, Han F, et al. An official American Thoracic Society Clinical Practice Guideline: sleep apnea, sleepiness, and driving risk in noncommercial drivers. An update of a 1994 Statement. Am J Respir Crit Care Med. 2013;187(11):1259-1266. https://doi.org/10.1164/rccm.201304-0726ST
77. Marrone O, Bonsignore MR. Obstructive sleep apnea and cancer: a complex relationship. Curr Opin Pulm Med. 2020;26(6):657-667. https://doi.org/10.1097/MCP.0000000000000729
78. Gozal D, Farré R, Nieto FJ. Obstructive sleep apnea and cancer: Epidemiologic links and theoretical biological constructs. Sleep Med Rev. 2016;27:43-55. https://doi.org/10.1016/j.smrv.2015.05.006
79. Cheng Y, Wang Y, Dai L. The prevalence of obstructive sleep apnea in interstitial lung disease: a systematic review and meta-analysis [published correction appears in Sleep Breath. 2021 Mar 23;:]. Sleep Breath. 2021;25(3):1219-1228. https://doi.org/10.1007/s11325-020-02282-z
80. Gille T, Didier M, Boubaya M, Moya L, Sutton A, Carton Z, et al. Obstructive sleep apnoea and related comorbidities in incident idiopathic pulmonary fibrosis. Eur Respir J. 2017;49(6):1601934. https://doi.org/10.1183/13993003.01934-2016
81. Li D, Wang B, Liu Y, Wang H. Prevalence and impact of comorbid obstructive sleep apnoea in diffuse parenchymal lung diseases. PLoS One. 2021;16(2):e0246878. https://doi.org/10.1371/journal.pone.0246878
82. Papadogiannis G, Bouloukaki I, Mermigkis C, Michelakis S, Ermidou C, Mauroudi E, et al. Patients with idiopathic pulmonary fibrosis with and without obstructive sleep apnea: differences in clinical characteristics, clinical outcomes, and the effect of PAP treatment. J Clin Sleep Med. 2021;17(3):533-544. https://doi.org/10.5664/jcsm.8932
83. Damianaki A, Vagiakis E, Sigala I, Pataka A, Rovina N, Vlachou A, et al. The Co-Existence of Obstructive Sleep Apnea and Bronchial Asthma: Revelation of a New Asthma Phenotype?. J Clin Med. 2019;8(9):1476. https://doi.org/10.3390/jcm8091476
84. Wang TY, Lo YL, Lin SM, Huang CD, Chung FT, Lin HC, et al. Obstructive sleep apnoea accelerates FEV1 decline in asthmatic patients. BMC Pulm Med. 2017;17(1):55. https://doi.org/10.1186/s12890-017-0398-2
85. Kauppi P, Bachour P, Maasilta P, Bachour A. Long-term CPAP treatment improves asthma control in patients with asthma and obstructive sleep apnoea. Sleep Breath. 2016;20(4):1217-1224. https://doi.org/10.1007/s11325-016-1340-1
86. Serrano-Pariente J, Plaza V, Soriano JB, Mayos M, López-Viña A, Picado C, et al. Asthma outcomes improve with continuous positive airway pressure for obstructive sleep apnea. Allergy. 2017;72(5):802-812. https://doi.org/10.1111/all.13070
87. Davies SE, Bishopp A, Wharton S, Turner AM, Mansur AH. Does Continuous Positive Airway Pressure (CPAP) treatment of obstructive sleep apnoea (OSA) improve asthma-related clinical outcomes in patients with co-existing conditions?- A systematic review. Respir Med. 2018;143:18-30. https://doi.org/10.1016/j.rmed.2018.08.004
88. Brennan M, McDonnell MJ, Walsh SM, Gargoum F, Rutherford R. Review of the prevalence, pathogenesis and management of OSA-COPD overlap [published online ahead of print, 2022 Jan 16]. Sleep Breath. 2022;10.1007/s11325-021-02540-8. https://doi.org/10.1007/s11325-021-02540-8
89. McNicholas WT. COPD-OSA Overlap Syndrome: Evolving Evidence Regarding Epidemiology, Clinical Consequences, and Management. Chest. 2017;152(6):1318-1326. https://doi.org/10.1016/j.chest.2017.04.160
90. Adler D, Bailly S, Benmerad M, Joyeux-Faure M, Jullian-Desayes I, Soccal PM, et al. Clinical presentation and comorbidities of obstructive sleep apnea-COPD overlap syndrome. PLoS One. 2020;15(7):e0235331. https://doi.org/10.1371/journal.pone.0235331
91. Soler X, Liao SY, Marin JM, Lorenzi-Filho G, Jen R, DeYoung P, et al. Age, gender, neck circumference, and Epworth sleepiness scale do not predict obstructive sleep apnea (OSA) in moderate to severe chronic obstructive pulmonary disease (COPD): The challenge to predict OSA in advanced COPD. PLoS One. 2017;12(5):e0177289. https://doi.org/10.1371/journal.pone.0177289
92. Chaouat A, Bugnet AS, Kadaoui N, Schott R, Enache I, Ducoloné A, et al. Severe pulmonary hypertension and chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;172(2):189-194. https://doi.org/10.1164/rccm.200401-006OC
93. Kendzerska T, Leung RS, Aaron SD, Ayas N, Sandoz JS, Gershon AS. Cardiovascular Outcomes and All-Cause Mortality in Patients with Obstructive Sleep Apnea and Chronic Obstructive Pulmonary Disease (Overlap Syndrome). Ann Am Thorac Soc. 2019;16(1):71-81. https://doi.org/10.1513/AnnalsATS.201802-136OC
94. Marin JM, Soriano JB, Carrizo SJ, Boldova A, Celli BR. Outcomes in patients with chronic obstructive pulmonary disease and obstructive sleep apnea: the overlap syndrome. Am J Respir Crit Care Med. 2010;182(3):325-331. https://doi.org/10.1164/rccm.200912-1869OC
95. Machado MC, Vollmer WM, Togeiro SM, Bilderback AL, Oliveira MV, Leitão FS, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxaemic COPD. Eur Respir J. 2010;35(1):132-137. https://doi.org/10.1183/09031936.00192008
96. Adir Y, Humbert M, Chaouat A. Sleep-related breathing disorders and pulmonary hypertension. Eur Respir J. 2021;57(1):2002258. https://doi.org/10.1183/13993003.02258-2020
97. Jilwan FN, Escourrou P, Garcia G, Jaïs X, Humbert M, Roisman G. High occurrence of hypoxemic sleep respiratory disorders in precapillary pulmonary hypertension and mechanisms. Chest. 2013;143(1):47-55. https://doi.org/10.1378/chest.11-3124
98. Prisco DL, Sica AL, Talwar A, Narasimhan M, Omonuwa K, Hakimisefat B, et al. Correlation of pulmonary hypertension severity with metrics of comorbid sleep-disordered breathing. Sleep Breath. 2011;15(4):633-639. https://doi.org/10.1007/s11325-010-0411-y
99. Wong HS, Williams AJ, Mok Y. The relationship between pulmonary hypertension and obstructive sleep apnea. Curr Opin Pulm Med. 2017;23(6):517-521. https://doi.org/10.1097/

MCP.0000000000000421

100. Nagaoka M, Goda A, Takeuchi K, Kikuchi H, Finger M, Inami T, et al. Nocturnal Hypoxemia, But Not Sleep Apnea, Is Associated With a Poor Prognosis in Patients With Pulmonary Arterial Hypertension. Circ J. 2018;82(12):3076-3081. https://doi.org/10.1253/circj.CJ-18-0636
101. Myers KA, Mrkobrada M, Simel DL. Does this patient have obstructive sleep apnea?: The Rational Clinical Examination systematic review. JAMA. 2013;310(7):731-741. https://doi.org/10.1001/jama.2013.276185
102. Zonato AI, Martinho FL, Bittencourt LR, de Oliveira Camponês Brasil O, Gregório LC, Tufik S. Head and neck physical examination: comparison between nonapneic and obstructive sleep apnea patients. Laryngoscope. 2005;115(6):1030-1034. https://doi.org/10.1097/01.MLG.0000163494.19965.DC
103. Basoglu OK, Tasbakan MS. Gender differences in clinical and polysomnographic features of obstructive sleep apnea: a clinical study of 2827 patients. Sleep Breath. 2018;22(1):241-249. https://doi.org/10.1007/s11325-017-1482-9
104. Yu JL, Rosen I. Utility of the modified Mallampati grade and Friedman tongue position in the assessment of obstructive sleep apnea. J Clin Sleep Med. 2020;16(2):303-308. https://doi.org/10.5664/jcsm.8188
105. Esteller E, Carrasco M, Díaz-Herrera MÁ, Vila J, Sampol G, Juvanteny J, et al. Clinical Practice Guideline recommendations on examination of the upper airway for adults with suspected obstructive sleep apnoea-hypopnoea syndrome. Acta Otorrinolaringol Esp (Engl Ed). 2019;70(6):364-372. https://doi.org/10.1016/j.otorri.2018.06.008
106. Friedman M, Ibrahim H, Joseph NJ. Staging of obstructive sleep apnea/hypopnea syndrome: a guide to appropriate treatment. Laryngoscope. 2004;114(3):454-459. https://doi.org/10.1097/00005537-200403000-00013
107. Senaratna CV, Perret JL, Matheson MC, Lodge CJ, Lowe AJ, Cassim R, et al. Validity of the Berlin questionnaire in detecting obstructive sleep apnea: A systematic review and meta-analysis. Sleep Med Rev. 2017;36:116-124. https://doi.org/10.1016/j.smrv.2017.04.001
108. Jonas DE, Amick HR, Feltner C, Weber RP, Arvanitis M, Stine A, et al. Screening for Obstructive Sleep Apnea in Adults: Evidence Report and Systematic Review for the US Preventive Services Task Force [published correction appears in JAMA. 2017 Mar 28;317(12):1278]. JAMA. 2017;317(4):415-433. https://doi.org/10.1001/jama.2016.19635
109. Andrade L, Paiva T. Ambulatory Versus Laboratory Polysomnography in Obstructive Sleep Apnea: Comparative Assessment of Quality, Clinical Efficacy, Treatment Compliance, and Quality of Life. J Clin Sleep Med. 2018;14(8):1323-1331. https://doi.org/10.5664/jcsm.7264
110. Rosen IM, Kirsch DB, Carden KA, Malhotra RK, Ramar K, Aurora RN, et al. Clinical Use of a Home Sleep Apnea Test: An Updated American Academy of Sleep Medicine Position Statement. J Clin Sleep Med. 2018;14(12):2075-2077. https://doi.org/10.5664/jcsm.7540
111. Bernhardt L, Brady EM, Freeman SC, Polmann H, Réus JC, Flores-Mir C, et al. Diagnostic accuracy of screening questionnaires for obstructive sleep apnoea in adults in different clinical cohorts: a systematic review and meta-analysis. Sleep Breath. 2021;1-26. https://doi.org/10.1007/s11325-021-02450-9
112. Kaw R, Michota F, Jaffer A, Ghamande S, Auckley D, Golish J. Unrecognized sleep apnea in the surgical patient: implications for the perioperative setting. Chest. 2006;129(1):198-205. https://doi.org/10.1378/chest.129.1.198
113. Mutter TC, Chateau D, Moffatt M, Ramsey C, Roos LL, Kryger M. A matched cohort study of postoperative outcomes in obstructive sleep apnea: could preoperative diagnosis and treatment prevent complications?. Anesthesiology. 2014;121(4):707-718. https://doi.org/10.1097/ALN.0000000000000407
114. Abrishami A, Khajehdehi A, Chung F. A systematic review of screening questionnaires for obstructive sleep apnea. Can J Anaesth. 2010;57(5):423-438. https://doi.org/10.1007/s12630-010-9280-x
115. Ramachandran SK, Josephs LA. A meta-analysis of clinical screening tests for obstructive sleep apnea. Anesthesiology. 2009;110(4):928-939. https://doi.org/10.1097/ALN.0b013e31819c47b6
116. 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):485-491. https://doi.org/10.7326/0003-4819-131-7-199910050-00002
117. Chung F, Yegneswaran B, Liao P, Chung SA, Vairavanathan S, Islam S, et al. STOP questionnaire: a tool to screen patients for obstructive sleep apnea. Anesthesiology. 2008;108(5):812-821. https://doi.org/10.1097/ALN.0b013e31816d83e4
118. Marti-Soler H, Hirotsu C, Marques-Vidal P, Vollenweider P, Waeber G, Preisig M, et al. The NoSAS score for screening of sleep-disordered breathing: a derivation and validation study. Lancet Respir Med. 2016;4(9):742-748. https://doi.org/10.1016/S2213-2600(16)30075-3
119. Duarte RL, Magalhães-da-Silveira FJ, Oliveira-E-Sá TS, Silva JA, Mello FC, Gozal D. Obstructive Sleep Apnea Screening with a 4-Item Instrument, Named GOAL Questionnaire: Development, Validation and Comparative Study with No-Apnea, STOP-Bang, and NoSAS. Nat Sci Sleep. 2020;12:57-67. https://doi.org/10.2147/NSS.S238255
120. Johns MW. A new method for measuring daytime sleepiness: the Epworth sleepiness scale. Sleep. 1991;14(6):540-545. https://doi.org/10.1093/sleep/14.6.540
121. Panchasara B, Poots AJ, Davies G. Are the Epworth Sleepiness Scale and Stop-Bang model effective at predicting the severity of obstructive sleep apnoea (OSA); in particular OSA requiring treatment?. Eur Arch Otorhinolaryngol. 2017;274(12):4233-4239.
122. Grewe FA, Roeder M, Bradicich M, Schwarz EI, Held U, Thiel S, et al. Low repeatability of Epworth Sleepiness Scale after short intervals in a sleep clinic population. J Clin Sleep Med. 2020;16(5):757-764. https://doi.org/10.5664/jcsm.8350
123. Campbell AJ, Neill AM, Scott DAR. Clinical Reproducibility of the Epworth Sleepiness Scale for Patients With Suspected Sleep Apnea. J Clin Sleep Med. 2018;14(5):791-795. https://doi.org/10.5664/jcsm.7108
124. 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):877-883. https://doi.org/10.1590/S1806-37132009000900009
125. 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;60:182-187. https://doi.org/10.1016/j.sleep.2019.03.022
126. Ahmadi N, Chung SA, Gibbs A, Shapiro CM. The Berlin questionnaire for sleep apnea in a sleep clinic population: relationship to polysomnographic measurement of respiratory disturbance. Sleep Breath. 2008;12(1):39-45. https://doi.org/10.1007/s11325-007-0125-y
127. Nagappa M, Liao P, Wong J, Auckley D, Ramachandran SK, Memtsoudis S, et al. Validation of the STOP-Bang Questionnaire as a Screening Tool for Obstructive Sleep Apnea among Different Populations: A Systematic Review and Meta-Analysis. PLoS One. 2015;10(12):e0143697. https://doi.org/10.1371/journal.pone.0143697
128. Duarte RLM, Fonseca LBM, Magalhães-da-Silveira FJ, Silveira EAD, Rabahi MF. Validation of the STOP-Bang questionnaire as a means of screening for obstructive sleep apnea in adults in Brazil. J Bras Pneumol. 2017;43(6):456-463. https://doi.org/10.1590/s1806-37562017000000139
129. Chen H, Zheng Z, Chen R, Zeng Y, Li N, Zhu J, et al. A meta-analysis of the diagnostic value of NoSAS in patients with sleep apnea syndrome. Sleep Breath. 2022;26(2):519-531. https://doi.org/10.1007/s11325-021-02410-3
130. Duarte RLM, Magalhães-da-Silveira FJ, Gozal D. Validation of the GOAL Questionnaire as an Obstructive Sleep Apnea Screening Instrument in Bariatric Surgery Candidates: a Brazilian Single-Center Study. Obes Surg. 2020;30(12):4802-4809. https://doi.org/10.1007/s11695-020-04888-4
131. Duarte RLM, Magalhães-da-Silveira FJ, Gozal D. Prediction of obstructive sleep apnea using GOAL questionnaire in adults with or without excessive daytime sleepiness: A cross-sectional study. Sleep Health. 2021;7(2):212-218. https://doi.org/10.1016/j.sleh.2021.01.003
132. Kushida CA, Littner MR, Morgenthaler T, Alessi CA, Bailey D,

Coleman J Jr, et al. Practice parameters for the indications for polysomnography and related procedures: an update for 2005. Sleep. 2005;28(4):499-521. https://doi.org/10.1093/sleep/28.4.499

133. 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. https://doi.org/10.5664/jcsm.2172
134. Chediak AD, Acevedo-Crespo JC, Seiden DJ, Kim HH, Kiel MH. Nightly variability in the indices of sleep-disordered breathing in men being evaluated for impotence with consecutive night polysomnograms. Sleep. 1996;19(7):589-592. https://doi.org/10.1093/sleep/19.7.589
135. Roeder M, Bradicich M, Schwarz EI, Thiel S, Gaisl T, Held U, et al. Night-to-night variability of respiratory events in obstructive sleep apnoea: a systematic review and meta-analysis. Thorax. 2020;75(12):1095-1102. https://doi.org/10.1136/thoraxjnl-2020-214544
136. Duce B, Milosavljevic J, Hukins C. The 2012 AASM Respiratory Event Criteria Increase the Incidence of Hypopneas in an Adult Sleep Center Population. J Clin Sleep Med. 2015;11(12):1425-1431. https://doi.org/10.5664/jcsm.5280
137. Ho V, Crainiceanu CM, Punjabi NM, Redline S, Gottlieb DJ. Calibration Model for Apnea-Hypopnea Indices: Impact of Alternative Criteria for Hypopneas. Sleep. 2015;38(12):1887-1892. https://doi.org/10.5665/sleep.5234
138. Khan Y, Heckmatt JZ. Obstructive apnoeas in Duchenne muscular dystrophy. Thorax. 1994;49(2):157-161. https://doi.org/10.1136/thx.49.2.157
139. Rodrigues Filho JC, Neves DD, Moreira GA, Viana ADC Jr, Araújo-Melo MH. Nocturnal oximetry in the diagnosis of obstructive sleep apnea syndrome in potentially hypoxic patients due to neuromuscular diseases. Sleep Med. 2021;84:127-133. https://doi.org/10.1016/j.sleep.2021.05.009
140. Collop NA, Anderson WM, Boehlecke B, Claman D, Goldberg R, Gottlieb DJ, et al. Clinical guidelines for the use of unattended portable monitors in the diagnosis of obstructive sleep apnea in adult patients. Portable Monitoring Task Force of the American Academy of Sleep Medicine. J Clin Sleep Med. 2007;3(7):737-747. https://doi.org/10.5664/jcsm.27032
141. Nigro CA, Dibur E, Aimaretti S, González S, Rhodius E. Comparison of the automatic analysis versus the manual scoring from ApneaLink™ device for the diagnosis of obstructive sleep apnoea syndrome. Sleep Breath. 2011;15(4):679-686. https://doi.org/10.1007/s11325-010-0421-9
142. Labarca G, Dreyse J, Salas C, Contreras A, Nazar G, Gaete MI, et al. Differences between manual and automatic analysis in determining the severity of obstructive sleep apnea using home sleep apnea testing. Sleep Med. 2018;47:66-71. https://doi.org/10.1016/j.sleep.2018.03.015
143. Zancanella E, do Prado LF, de Carvalho LB, Machado Júnior AJ, Crespo AN, do Prado GF. Home sleep apnea testing: an accuracy study. Sleep Breath. 2022;26(1):117-123. https://doi.org/10.1007/s11325-021-02372-6
144. Caples SM, Anderson WM, Calero K, Howell M, Hashmi SD. Use of polysomnography and home sleep apnea tests for the longitudinal management of obstructive sleep apnea in adults: an American Academy of Sleep Medicine clinical guidance statement. J Clin Sleep Med. 2021;17(6):1287-1293. https://doi.org/10.5664/jcsm.9240
145. Behar JA, Palmius N, Zacharie S, Chocron A, Penzel T, Bittencourt L, et al. ingle-channel oximetry monitor versus in-lab polysomnography oximetry analysis: does it make a difference?. Physiol Meas. 2020;41(4):044007. https://doi.org/10.1088/1361-6579/ab8856
146. Pinheiro GDL, Cruz AF, Domingues DM, Genta PR, Drager LF, Strollo PJ, et al. Validation of an Overnight Wireless High-Resolution Oximeter plus Cloud-Based Algorithm for the Diagnosis of Obstructive Sleep Apnea. Clinics (Sao Paulo). 2020;75:e2414. https://doi.org/10.6061/clinics/2020/e2414
147. Rodrigues Filho JC, Neves DD, Velasque L, Maranhão AA, de Araujo-Melo MH. Diagnostic performance of nocturnal oximetry in the detection of obstructive sleep apnea syndrome: a Brazilian study. Sleep Breath. 2020;24(4):1487-1494. https://doi.org/10.1007/s11325-019-02000-4
148. Del Campo F, Crespo A, Cerezo-Hernández A, Gutiérrez-Tobal GC, Hornero R, Álvarez D. Oximetry use in obstructive sleep apnea. Expert Rev Respir Med. 2018;12(8):665-681. https://doi.org/10.1080/17476348.2018.1495563
149. Andrés-Blanco AM, Álvarez D, Crespo A, Arroyo CA, Cerezo-Hernández A, Gutiérrez-Tobal GC, et al. Assessment of automated analysis of portable oximetry as a screening test for moderate-to-severe sleep apnea in patients with chronic obstructive pulmonary disease. PLoS One. 2017;12(11):e0188094. https://doi.org/10.1371/journal.pone.0188094
150. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea with Positive Airway Pressure: An American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2019;15(2):335-343. https://doi.org/10.5664/jcsm.7640
151. Patil SP, Ayappa IA, Caples SM, Kimoff RJ, Patel SR, Harrod CG. Treatment of Adult Obstructive Sleep Apnea With Positive Airway Pressure: An American Academy of Sleep Medicine Systematic Review, Meta-Analysis, and GRADE Assessment. J Clin Sleep Med. 2019;15(2):301-334. https://doi.org/10.5664/jcsm.7638
152. Clinical guidelines for the manual titration of positive airway pressure in patients with obstructive sleep apnea. J Clin Sleep Med. 2008;4(2):157-171. https://doi.org/10.5664/jcsm.27133
153. Goh KJ, Soh RY, Leow LC, Toh ST, Song PR, Hao Y, et al. Choosing the right mask for your Asian patient with sleep apnoea: A randomized, crossover trial of CPAP interfaces. Respirology. 2019;24(3):278-285. https://doi.org/10.1111/resp.13396
154. Zonato AI, Rosa CFA, Oliveira L, Bittencourt LR. Efficacy of nasal masks versus nasal pillows masks during continuous positive airway pressure titration for patients with obstructive sleep apnea. Sleep Breath. 2021;25(3):1-8. https://doi.org/10.1007/s11325-020-02251-6
155. Duarte RLM, Mendes BA, Oliveira-E-Sá TS, Magalhães-da-Silveira FJ, Gozal D. Nasal versus oronasal mask in patients under auto-adjusting continuous positive airway pressure titration: a real-life study. Eur Arch Otorhinolaryngol. 2020;277(12):3507-3512. https://doi.org/10.1007/s00405-020-06242-x
156. Genta PR, Kaminska M, Edwards BA, Ebben MR, Krieger AC, Tamisier R, et al. The Importance of Mask Selection on Continuous Positive Airway Pressure Outcomes for Obstructive Sleep Apnea. An Official American Thoracic Society Workshop Report. Ann Am Thorac Soc. 2020;17(10):1177-1185. https://doi.org/10.1513/AnnalsATS.202007-864ST
157. Cassel W, Canisius S, Becker HF, Leistner S, Ploch T, Jerrentrup A, et al. A prospective polysomnographic study on the evolution of complex sleep apnoea. Eur Respir J. 2011;38(2):329-337. https://doi.org/10.1183/09031936.00162009
158. Zeineddine S, Badr MS. Treatment-Emergent Central Apnea: Physiologic Mechanisms Informing Clinical Practice. Chest. 2021;159(6):2449-2457. https://doi.org/10.1016/j.chest.2021.01.036
159. Khan MT, Franco RA. Complex sleep apnea syndrome. Sleep Disord. 2014;2014:798487. https://doi.org/10.1155/2014/798487
160. Veasey SC, Rosen IM. Obstructive Sleep Apnea in Adults. N Engl J Med. 2019;380(15):1442-1449. https://doi.org/10.1056/NEJMcp1816152
161. Masa JF, Jiménez A, Durán J, Capote F, Monasterio C, Mayos M, et al. Alternative methods of titrating continuous positive airway pressure: a large multicenter study. Am J Respir Crit Care Med. 2004;170(11):1218-1224. https://doi.org/10.1164/rccm.200312-1787OC
162. Kim H, Lee M, Hwangbo Y, Yang KI. Automatic Derivation of Continuous Positive Airway Pressure Settings: Comparison with In-Laboratory Titration. J Clin Neurol. 2020;16(2):314-320. https://doi.org/10.3988/jcn.2020.16.2.314
163. Gao W, Jin Y, Wang Y, Sun M, Chen B, Zhou N, et al. Is automatic CPAP titration as effective as manual CPAP titration in OSAHS patients? A meta-analysis. Sleep Breath. 2012;16(2):329-340. https://doi.org/10.1007/s11325-011-0495-z
164. Mulgrew AT, Fox N, Ayas NT, Ryan CF. Diagnosis and initial management of obstructive sleep apnea without polysomnography: a randomized validation study. Ann Intern Med. 2007;146(3):157-166. https://doi.org/10.7326/0003-4819-146-3-200702060-00004

165. Rotenberg BW, Murariu D, Pang KP. Trends in CPAP adherence over twenty years of data collection: a flattened curve. J Otolaryngol Head Neck Surg. 2016;45(1):43. https://doi.org/10.1186/s40463-016-0156-0

166. Mashaqi S, Gozal D. The impact of obstructive sleep apnea and PAP therapy on all-cause and cardiovascular mortality based on age and gender - a literature review. Respir Investig. 2020;58(1):7-20. https://doi.org/10.1016/j.resinv.2019.08.002

167. Weaver TE, Maislin G, Dinges DF, Bloxham T, George CF, Greenberg H, et al. Relationship between hours of CPAP use and achieving normal levels of sleepiness and daily functioning. Sleep. 2007;30(6):711-719. https://doi.org/10.1093/sleep/30.6.711

168. Martínez-García MA, Capote F, Campos-Rodríguez F, Lloberes P, Díaz de Atauri MJ, Somoza M, et al. Effect of CPAP on blood pressure in patients with obstructive sleep apnea and resistant hypertension: the HIPARCO randomized clinical trial. JAMA. 2013;310(22):2407-2415. https://doi.org/10.1001/jama.2013.281250

169. Lewis KE, Seale L, Bartle IE, Watkins AJ, Ebden P. Early predictors of CPAP use for the treatment of obstructive sleep apnea. Sleep. 2004;27(1):134-138. https://doi.org/10.1093/sleep/27.1.134

170. Pépin JL, Woehrle H, Liu D, Shao S, Armitstead JP, Cistulli PA, et al. Adherence to Positive Airway Therapy After Switching From CPAP to ASV: A Big Data Analysis. J Clin Sleep Med. 2018;14(1):57-63. https://doi.org/10.5664/jcsm.6880

171. Cistulli PA, Armitstead J, Pepin JL, Woehrle H, Nunez CM, Benjafield A, et al. Short-term CPAP adherence in obstructive sleep apnea: a big data analysis using real world data. Sleep Med. 2019;59:114-116. https://doi.org/10.1016/j.sleep.2019.01.004

172. Jacobsen AR, Eriksen F, Hansen RW, Erlandsen M, Thorup L, Damgård MB, et al. Determinants for adherence to continuous positive airway pressure therapy in obstructive sleep apnea. PLoS One. 2017;12(12):e0189614. https://doi.org/10.1371/journal.pone.0189614

173. Kohler M, Smith D, Tippett V, Stradling JR. Predictors of long-term compliance with continuous positive airway pressure. Thorax. 2010;65(9):829-832. https://doi.org/10.1136/thx.2010.135848

174. Genzor S, Prasko J, Vanek J, Asswad AG, Nadjarpour S, Sova M. Adherence of obstructive sleep apnoea syndrome patients to positive airway pressure therapy - 10-year follow-up [published online ahead of print, 2021 Jul 2]. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2021;10.5507/bp.2021.041. https://doi.org/10.5507/bp.2021.041

175. Richards D, Bartlett DJ, Wong K, Malouff J, Grunstein RR. Increased adherence to CPAP with a group cognitive behavioral treatment intervention: a randomized trial. Sleep. 2007;30(5):635-640. https://doi.org/10.1093/sleep/30.5.635

176. Lettieri CJ, Shah AA, Holley AB, Kelly WF, Chang AS, Roop SA, et al. Effects of a short course of eszopiclone on continuous positive airway pressure adherence: a randomized trial. Ann Intern Med. 2009;151(10):696-702. https://doi.org/10.7326/0003-4819-151-10-200911170-00006

177. Siccoli MM, Pepperell JC, Kohler M, Craig SE, Davies RJ, Stradling JR. Effects of continuous positive airway pressure on quality of life in patients with moderate to severe obstructive sleep apnea: data from a randomized controlled trial. Sleep. 2008;31(11):1551-1558. https://doi.org/10.1093/sleep/31.11.1551

178. Tomfohr LM, Ancoli-Israel S, Loredo JS, Dimsdale JE. Effects of continuous positive airway pressure on fatigue and sleepiness in patients with obstructive sleep apnea: data from a randomized controlled trial. Sleep. 2011;34(1):121-126. https://doi.org/10.1093/sleep/34.1.121

179. George CF. Reduction in motor vehicle collisions following treatment of sleep apnoea with nasal CPAP. Thorax. 2001;56(7):508-512. https://doi.org/10.1136/thx.56.7.508

180. Faccenda JF, Mackay TW, Boon NA, Douglas NJ. Randomized placebo-controlled trial of continuous positive airway pressure on blood pressure in the sleep apnea-hypopnea syndrome. Am J Respir Crit Care Med. 2001;163(2):344-348. https://doi.org/10.1164/ajrccm.163.2.2005037

181. Myhill PC, Davis WA, Peters KE, Chubb SA, Hillman D, Davis TM. Effect of continuous positive airway pressure therapy on cardiovascular risk factors in patients with type 2 diabetes and obstructive sleep apnea. J Clin Endocrinol Metab. 2012;97(11):4212-4218. https://doi.org/10.1210/jc.2012-2107

182. Barbé F, Durán-Cantolla J, Sánchez-de-la-Torre M, Martínez-Alonso M, Carmona C, Barceló A, et al. Effect of continuous positive airway pressure on the incidence of hypertension and cardiovascular events in nonsleepy patients with obstructive sleep apnea: a randomized controlled trial. JAMA. 2012;307(20):2161-2168. https://doi.org/10.1001/jama.2012.4366

183. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, et al. Prevention of Cardiovascular Events in Obstructive Sleep Apnea. N Engl J Med. 2016;375(10):919-931. https://doi.org/10.1056/NEJMoa1606599

184. Xie J, Sert Kuniyoshi FH, Covassin N, Singh P, Gami AS, Chahal CAA, et al. Excessive Daytime Sleepiness Independently Predicts Increased Cardiovascular Risk After Myocardial Infarction. J Am Heart Assoc. 2018;7(2):e007221. https://doi.org/10.1161/JAHA.117.007221

185. Sawyer AM, Gooneratne NS, Marcus CL, Ofer D, Richards KC, Weaver TE. A systematic review of CPAP adherence across age groups: clinical and empiric insights for developing CPAP adherence interventions. Sleep Med Rev. 2011;15(6):343-356. https://doi.org/10.1016/j.smrv.2011.01.003

186. Weaver TE, Grunstein RR. Adherence to continuous positive airway pressure therapy: the challenge to effective treatment. Proc Am Thorac Soc. 2008;5(2):173-178. https://doi.org/10.1513/pats.200708-119MG

187. Shamim-Uzzaman QA, Bae CJ, Ehsan Z, Setty AR, Devine M, Dhankikar S, et al. The use of telemedicine for the diagnosis and treatment of sleep disorders: an American Academy of Sleep Medicine update. J Clin Sleep Med. 2021;17(5):1103-1107. https://doi.org/10.5664/jcsm.9194

188. Bruyneel M. Telemedicine in the diagnosis and treatment of sleep apnoea. Eur Respir Rev. 2019;28(151):180093. https://doi.org/10.1183/16000617.0093-2018

189. Schutte-Rodin S. Telehealth, Telemedicine, and Obstructive Sleep Apnea. Sleep Med Clin. 2020;15(3):359-375. https://doi.org/10.1016/j.jsmc.2020.05.003

190. Pépin JL, Tamisier R, Hwang D, Mereddy S, Parthasarathy S. Does remote monitoring change OSA management and CPAP adherence?. Respirology. 2017;22(8):1508-1517. https://doi.org/10.1111/resp.13183

191. Hoet F, Libert W, Sanida C, Van den Broecke S, Bruyneel AV, Bruyneel M. Telemonitoring in continuous positive airway pressure-treated patients improves delay to first intervention and early compliance: a randomized trial. Sleep Med. 2017;39:77-83. https://doi.org/10.1016/j.sleep.2017.08.016

192. Budhiraja R, Parthasarathy S, Drake CL, Roth T, Sharief I, Budhiraja P, et al. Early CPAP use identifies subsequent adherence to CPAP therapy. Sleep. 2007;30(3):320-324. PMID: 17425228

193. Bros JS, Poulet C, Arnol N, Deschaux C, Gandit M, Charavel M. Acceptance of Telemonitoring Among Patients with Obstructive Sleep Apnea Syndrome: How is the Perceived Interest by and for Patients?. Telemed J E Health. 2018;24(5):351-359. https://doi.org/10.1089/tmj.2017.0134

194. Chen C, Wang J, Pang L, Wang Y, Ma G, Liao W. Telemonitor care helps CPAP compliance in patients with obstructive sleep apnea: a systemic review and meta-analysis of randomized controlled trials. Ther Adv Chronic Dis. 2020;11:2040622320901625. https://doi.org/10.1177/2040622320901625

195. Labarca G, Schmidt A, Dreyse J, Jorquera J, Barbe F. Telemedicine interventions for CPAP adherence in obstructive sleep apnea patients: Systematic review and meta-analysis. Sleep Med Rev. 2021;60:101543. https://doi.org/10.1016/j.smrv.2021.101543

196. Drager LF, Malhotra A, Yan Y, Pépin JL, Armitstead JP, Woehrle H, et al. Adherence with positive airway pressure therapy for obstructive sleep apnea in developing vs. developed countries: a big data study. J Clin Sleep Med. 2021;17(4):703-709. https://doi.org/10.5664/jcsm.9008

197. Srijithesh PR, Aghoram R, Goel A, Dhanya J. Positional therapy for obstructive sleep apnoea. Cochrane Database Syst Rev. 2019;5(5):CD010990. https://doi.org/10.1002/14651858.CD010990.pub2

198. Hudgel DW, Patel SR, Ahasic AM, Bartlett SJ, Bessesen DH, Coaker MA, et al. The Role of Weight Management in the Treatment of Adult Obstructive Sleep Apnea. An Official American Thoracic Society Clinical Practice Guideline. Am J Respir Crit Care Med. 2018;198(6):e70-e87. https://doi.org/10.1164/rccm.201807-1326ST

199. Peppard PE, Young T. Exercise and sleep-disordered breathing: an association independent of body habitus. Sleep. 2004;27(3):480-484. https://doi.org/10.1093/sleep/27.3.480

200. Ramar K, Dort LC, Katz SG, Lettieri CJ, Harrod CG, Thomas SM, et al. Clinical Practice Guideline for the Treatment of Obstructive Sleep Apnea and Snoring with Oral Appliance Therapy: An Update for 2015. J Clin Sleep Med. 2015;11(7):773-827. https://doi.org/10.5664/jcsm.4858

201. Lim J, Lasserson TJ, Fleetham J, Wright J. Oral appliances for obstructive sleep apnoea. Cochrane Database Syst Rev. 2006;2006(1):CD004435. https://doi.org/10.1002/14651858.CD004435.pub3

202. Phillips CL, Grunstein RR, Darendeliler MA, Mihailidou AS, Srinivasan VK, Yee BJ, et al. Health outcomes of continuous positive airway pressure versus oral appliance treatment for obstructive sleep apnea: a randomized controlled trial. Am J Respir Crit Care Med. 2013;187(8):879-887. https://doi.org/10.1164/rccm.201212-2223OC

203. Hoffstein V. Review of oral appliances for treatment of sleep-disordered breathing. Sleep Breath. 2007;11(1):1-22. https://doi.org/10.1007/s11325-006-0084-8

204. Brimioulle M, Chaidas K. Nasal function and CPAP use in patients with obstructive sleep apnoea: a systematic review. Sleep Breath. 2021;10.1007/s11325-021-02478-x. https://doi.org/10.1007/s11325-021-02478-x

205. Aurora RN, Casey KR, Kristo D, Auerbach S, Bista SR, Chowdhuri S, et al. Practice parameters for the surgical modifications of the upper airway for obstructive sleep apnea in adults. Sleep. 2010;33(10):1408-1413. https://doi.org/10.1093/sleep/33.10.1408

206. Zaghi S, Holty JE, Certal V, Abdullatif J, Guilleminault C, Powell NB, et al. Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea: A Meta-analysis. JAMA Otolaryngol Head Neck Surg. 2016;142(1):58-66. https://doi.org/10.1001/jamaoto.2015.2678

207. Strollo PJ Jr, Soose RJ, Maurer JT, de Vries N, Cornelius J, Froymovich O, et al. Upper-airway stimulation for obstructive sleep apnea. N Engl J Med. 2014;370(2):139-149. https://doi.org/10.1056/NEJMoa1308659

208. Costantino A, Rinaldi V, Moffa A, Luccarelli V, Bressi F, Cassano M, et al. Hypoglossal nerve stimulation long-term clinical outcomes: a systematic review and meta-analysis. Sleep Breath. 2020;24(2):399-411. https://doi.org/10.1007/s11325-019-01923-2

209. Fritscher LG, Canani S, Mottin CC, Fritscher CC, Berleze D, Chapman K, et al. Bariatric surgery in the treatment of obstructive sleep apnea in morbidly obese patients. Respiration. 2007;74(6):647-652. https://doi.org/10.1159/000107736

210. Zhang Y, Wang W, Yang C, Shen J, Shi M, Wang B. Improvement in Nocturnal Hypoxemia in Obese Patients with Obstructive Sleep Apnea after Bariatric Surgery: a Meta-Analysis. Obes Surg. 2019;29(2):601-608. https://doi.org/10.1007/s11695-018-3573-5

211. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, et al. Effects of bariatric surgery on mortality in Swedish obese subjects. N Engl J Med. 2007;357(8):741-752. https://doi.org/10.1056/NEJMoa066254

212. Kong WT, Chopra S, Kopf M, Morales C, Khan S, Zuccala K, et al. Perioperative Risks of Untreated Obstructive Sleep Apnea in the Bariatric Surgery Patient: a Retrospective Study. Obes Surg. 2016;26(12):2886-2890. https://doi.org/10.1007/s11695-016-2203-3

213. Carron M, Zarantonello F, Tellaroli P, Ori C. Perioperative noninvasive ventilation in obese patients: a qualitative review and meta-analysis. Surg Obes Relat Dis. 2016;12(3):681-691. https://doi.org/10.1016/j.soard.2015.12.013

214. Buchwald H, Avidor Y, Braunwald E, Jensen MD, Pories W, Fahrbach K, et al. Bariatric surgery: a systematic review and meta-analysis [published correction appears in JAMA. 2005 Apr 13;293(14):1728]. JAMA. 2004;292(14):1724-1737. https://doi.org/10.1001/jama.292.14.1724

215. Furlan SF, Drager LF, Santos RN, Damiani LP, Bersch-Ferreira AC, Miranda TA, et al. Three-year effects of bariatric surgery on obstructive sleep apnea in patients with obesity grade 1 and 2: a sub-analysis of the GATEWAY trial. Int J Obes (Lond). 2021;45(4):914-917. https://doi.org/10.1038/s41366-021-00752-2

216. Guimarães KC, Drager LF, Genta PR, Marcondes BF, Lorenzi-Filho G. Effects of oropharyngeal exercises on patients with moderate obstructive sleep apnea syndrome. Am J Respir Crit Care Med. 2009;179(10):962-966. https://doi.org/10.1164/rccm.200806-981OC

217. Hsu B, Emperumal CP, Grbach VX, Padilla M, Enciso R. Effects of respiratory muscle therapy on obstructive sleep apnea: a systematic review and meta-analysis. J Clin Sleep Med. 2020;16(5):785-801. https://doi.org/10.5664/jcsm.8318

218. Osman AM, Carter SG, Carberry JC, Eckert DJ. Obstructive sleep apnea: current perspectives. Nat Sci Sleep. 2018;10:21-34. https://doi.org/10.2147/NSS.S124657

219. Chebbo A, Tfaili A, Jones SF. Hypoventilation syndromes. Med Clin North Am. 2011;95(6):1189-1202. https://doi.org/10.1016/j.mcna.2011.09.002

220. Brown LK. Hypoventilation syndromes. Clin Chest Med. 2010;31(2):249-270. https://doi.org/10.1016/j.ccm.2010.03.002

221. Mokhlesi B, Tulaimat A, Faibussowitsch I, Wang Y, Evans AT. Obesity hypoventilation syndrome: prevalence and predictors in patients with obstructive sleep apnea. Sleep Breath. 2007;11(2):117-124. https://doi.org/10.1007/s11325-006-0092-8

222. Mokhlesi B, Masa JF, Brozek JL, Gurubhagavatula I, Murphy PB, Piper AJ, et al. Evaluation and Management of Obesity Hypoventilation Syndrome. An Official American Thoracic Society Clinical Practice Guideline [published correction appears in Am J Respir Crit Care Med. 2019 Nov 15;200(10):1326]. Am J Respir Crit Care Med. 2019;200(3):e6-e24. https://doi.org/10.1164/rccm.201905-1071ST

223. Athayde RAB, Oliveira Filho JRB, Lorenzi Filho G, Genta PR. Obesity hypoventilation syndrome: a current review. J Bras Pneumol. 2018;44(6):510-518. https://doi.org/10.1590/s1806-37562017000000332

224. Piper AJ, Grunstein RR. Obesity hypoventilation syndrome: mechanisms and management. Am J Respir Crit Care Med. 2011;183(3):292-298. https://doi.org/10.1164/rccm.201008-1280CI

225. Benditt JO, Boitano LJ. Pulmonary issues in patients with chronic neuromuscular disease. Am J Respir Crit Care Med. 2013;187(10):1046-1055. https://doi.org/10.1164/rccm.201210-1804CI

226. Baydur A, Layne E, Aral H, Krishnareddy N, Topacio R, Frederick G, et al. Long term non-invasive ventilation in the community for patients with musculoskeletal disorders: 46 year experience and review. Thorax. 2000;55(1):4-11. https://doi.org/10.1136/thorax.55.1.4

227. Buyse B, Meersseman W, Demedts M. Treatment of chronic respiratory failure in kyphoscoliosis: oxygen or ventilation?. Eur Respir J. 2003;22(3):525-528. https://doi.org/10.1183/09031936.03.00076103

228. Vanderlaan M, Holbrook CR, Wang M, Tuell A, Gozal D. Epidemiologic survey of 196 patients with congenital central hypoventilation syndrome. Pediatr Pulmonol. 2004;37(3):217-229. https://doi.org/10.1002/ppul.10438

229. Windisch W, Hennings E, Storre JH, Matthys H, Sorichter S. Long-term survival of a patient with congenital central hypoventilation syndrome despite the lack of continuous ventilatory support. Respiration. 2004;71(2):195-198. https://doi.org/10.1159/000076685

230. Weese-Mayer DE, Silvestri JM, Kenny AS, Ilbawi MN, Hauptman SA, Lipton JW, et al. Diaphragm pacing with a quadripolar phrenic nerve electrode: an international study. Pacing Clin Electrophysiol. 1996;19(9):1311-1319. https://doi.org/10.1111/j.1540-8159.1996.tb04209.x

231. Weitzenblum E, Chaouat A, Kessler R, Canuet M. Overlap syndrome: obstructive sleep apnea in patients with chronic obstructive pulmonary disease. Proc Am Thorac Soc. 2008;5(2):237-241. https://doi.org/10.1513/pats.200706-077MG

232. Owens RL, Malhotra A. Sleep-disordered breathing and COPD: the overlap syndrome. Respir Care. 2010;55(10):1333-1346.

233. Muza RT. Central sleep apnoea-a clinical review. J Thorac Dis. 2015;7(5):930-937. https://doi.org/10.3978/j.issn.2072-1439.2015.04.45

234. Ishikawa O, Oks M. Central Sleep Apnea. Clin Geriatr Med. 2021;37(3):469-481. https://doi.org/10.1016/j.cger.2021.04.009

235. Eckert DJ, Jordan AS, Merchia P, Malhotra A. Central sleep apnea: Pathophysiology and treatment. Chest. 2007;131(2):595-607. https://doi.org/10.1378/chest.06.2287

236. White DP. Pathogenesis of obstructive and central sleep apnea. Am J Respir Crit Care Med. 2005;172(11):1363-1370. https://doi.org/10.1164/rccm.200412-1631SO

237. Donovan LM, Kapur VK. Prevalence and Characteristics of Central Compared to Obstructive Sleep Apnea: Analyses from the Sleep Heart Health Study Cohort. Sleep. 2016;39(7):1353-1359. https://doi.org/10.5665/sleep.5962

238. Sin DD, Fitzgerald F, Parker JD, Newton G, Floras JS, Bradley TD. Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med. 1999;160(4):1101-1106. https://doi.org/10.1164/ajrccm.160.4.9903020

239. Oldenburg O, Lamp B, Faber L, Teschler H, Horstkotte D, Töpfer V. Sleep-disordered breathing in patients with symptomatic heart failure: a contemporary study of prevalence in and characteristics of 700 patients. Eur J Heart Fail. 2007;9(3):251-257. https://doi.org/10.1016/j.ejheart.2006.08.003

240. Küpper T, Schöffl V, Netzer N. Cheyne stokes breathing at high altitude: a helpful response or a troublemaker?. Sleep Breath. 2008;12(2):123-127. https://doi.org/10.1007/s11325-007-0155-5

241. Schütz SG, Lisabeth LD, Hsu CW, Kim S, Chervin RD, Brown DL. Central sleep apnea is uncommon after stroke. Sleep Med. 2021;77:304-306. https://doi.org/10.1016/j.sleep.2020.08.025

242. Seiler A, Camilo M, Korostovtseva L, Haynes AG, Brill AK, Horvath T, et al. Prevalence of sleep-disordered breathing after stroke and TIA: A meta-analysis. Neurology. 2019;92(7):e648-e654. https://doi.org/10.1212/WNL.0000000000006904

243. Pattinson KT. Opioids and the control of respiration. Br J Anaesth. 2008;100(6):747-758. https://doi.org/10.1093/bja/aen094

244. Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, et al. Central sleep apnea in stable methadone maintenance treatment patients. Chest. 2005;128(3):1348-1356. https://doi.org/10.1378/chest.128.3.1348

245. Randerath W, Verbraecken J, Andreas S, Arzt M, Bloch KE, Brack T, et al. Definition, discrimination, diagnosis and treatment of central breathing disturbances during sleep. Eur Respir J. 2017;49(1):1600959. https://doi.org/10.1183/13993003.00959-2016

246. Bradley TD, Logan AG, Kimoff RJ, Sériès F, Morrison D, Ferguson K, et al. Continuous positive airway pressure for central sleep apnea and heart failure. N Engl J Med. 2005;353(19):2025-2033. https://doi.org/10.1056/NEJMoa051001

247. Granton JT, Naughton MT, Benard DC, Liu PP, Goldstein RS, Bradley TD. CPAP improves inspiratory muscle strength in patients with heart failure and central sleep apnea. Am J Respir Crit Care Med. 1996;153(1):277-282. https://doi.org/10.1164/ajrccm.153.1.8542129

248. Cowie MR, Woehrle H, Wegscheider K, Angermann C, d'Ortho MP, Erdmann E, et al. Adaptive Servo-Ventilation for Central Sleep Apnea in Systolic Heart Failure. N Engl J Med. 2015;373(12):1095-1105. https://doi.org/10.1056/NEJMoa1506459

249. Potratz M, Sohns C, Dumitrescu D, Sommer P, Fox H. Phrenic Nerve Stimulation Improves Physical Performance and Hypoxemia in Heart Failure Patients with Central Sleep Apnea. J Clin Med. 2021;10(2):202. https://doi.org/10.3390/jcm10020202

250. Kaditis AG, Alonso Alvarez ML, Boudewyns A, Alexopoulos EI, Ersu R, Joosten K, et al. Obstructive sleep disordered breathing in 2- to 18-year-old children: diagnosis and management. Eur Respir J. 2016;47(1):69-94. https://doi.org/10.1183/13993003.00385-2015

251. Lumeng JC, Chervin RD. Epidemiology of pediatric obstructive sleep apnea. Proc Am Thorac Soc. 2008;5(2):242-252. https://doi.org/10.1513/pats.200708-135MG

252. Gipson K, Lu M, Kinane TB. Sleep-Disordered Breathing in Children [published correction appears in Pediatr Rev. 2019 May;40(5):261]. Pediatr Rev. 2019;40(1):3-13. https://doi.org/10.1542/pir.2018-0142

253. Schwengel DA, Dalesio NM, Stierer TL. Pediatric obstructive sleep apnea. Anesthesiol Clin. 2014;32(1):237-261. https://doi.org/10.1016/j.anclin.2013.10.012

254. Marcus CL, Brooks LJ, Draper KA, Gozal D, Halbower AC, Jones J, et al. Diagnosis and management of childhood obstructive sleep apnea syndrome. Pediatrics. 2012;130(3):576-584. https://doi.org/10.1542/peds.2012-1671

255. Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. The Report of an American Academy of Sleep Medicine Task Force. Sleep. 1999;22(5):667-689. https://doi.org/10.1093/sleep/22.5.667

Use of anticoagulants in patients with COVID-19: a living systematic review and meta-analysis

Diane R Batista[1], Idevaldo Floriano[2], Antonio Silvinato[3], Hélio A Bacha[4], Alexandre N Barbosa[5], Suzana E Tanni[1], Wanderley M Bernardo[6]

1. Divisão de Pneumologia, Faculdade de Medicina, Universidade Estadual Paulista, Botucatu (SP) Brasil.
2. Medicina Baseada em Evidências, Associação Médica Brasileira, São Paulo (SP) Brasil.
3. Medicina Baseada em Evidências, Cooperativa Baixa Mogiana, Mogi-Guaçu (SP) Brasil.
4. Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.
5. Departamento de Infectologia, Universidade Estadual Paulista, Botucatu (SP) Brasil.
6. Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Submitted: 28 January 2022.
Accepted: 7 April 2022.

Study carried out at the Faculdade de Medicina, Universidade Estadual Paulista, Botucatu (SP) Brasil.

ABSTRACT

Objective: To answer questions related to the use of anticoagulants in the treatment of COVID-19 patients. **Methods:** This was a systematic review and meta-analysis of phase 3 randomized controlled trials comparing the use of anticoagulants in non-hospitalized and hospitalized COVID-19 patients. We searched the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to January 22, 2022. The risk of bias was assessed by the Cochrane risk-of-bias tool, and the quality of evidence was assessed by the Grading of Recommendations Assessment, Development and Evaluation system. **Results:** A total of 401 studies were initially selected. Of those, 9 met the inclusion criteria and were therefore analyzed (a total of 6,004 patients being analyzed). In non-hospitalized COVID-19 patients, no significant difference was found between post-discharge prophylactic anticoagulation and no intervention regarding venous thromboembolism or bleeding at 30 days. In hospitalized COVID-19 patients, full anticoagulation resulted in a slight reduction in thrombotic events at 30 days (risk difference, −0.03; 95% CI, −0.06 to −0.00; p = 0.04; I^2 = 78%), the quality of evidence being moderate. However, no significant difference was found between full anticoagulation and no intervention regarding the risk of major bleeding, the quality of evidence being very low. No significant difference was found between intermediate- and standard-dose prophylactic anticoagulation (risk difference, −0.01; 95% CI, −0.07 to 0.06; p = 0.81; I^2 = 0%), the quality of evidence being very low. **Conclusions:** Therapeutic anticoagulation appears to have no effect on mortality in COVID-19 patients, resulting in a slight reduction in venous thromboembolism in hospitalized patients.

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

INTRODUCTION

Almost two years after the emergence of COVID-19, efforts have been made to control the severity of disease progression and reduce the risk of death. Reports from the World Health Organization confirm that nearly 269 million confirmed cases and nearly 5.3 million deaths had been reported globally as of December 12, 2021.[1]

Viral and host cell membrane fusion in pulmonary alveolar epithelial cells allows viral replication, with local and systemic inflammatory progression. The release of systemic cytokines characteristic of the cytokine storm can increase cyclic lung damage, including diffuse alveolar damage, and cause ARDS.[2] ARDS is associated with epithelial-endothelial barrier injury that increases the influx of inflammatory cells, as demonstrated by autopsy studies of patients with severe endothelial damage and intracellular viruses, rupture of cell membranes, infiltration of airspaces, interstitial edema, and pulmonary edema.[2] Concomitantly, the activation of coagulation and consumption of clotting factors increase the risk of coagulopathy and microthrombus formation, contributing to a high incidence of thrombotic events.[3] Therefore, in patients with severe COVID-19, the risk of death is high, and viral sepsis is life-threatening because of multiorgan failure.

COVID-19 is associated with an increased risk of venous thromboembolism (VTE); this can occur in 20% of patients and mainly affects those with very severe disease.[4] Therefore, most guidelines recommend assessing the risk of VTE by using stratification and prophylaxis models.[3] However, there is uncertainty regarding how to choose the best dose of chemoprophylaxis, or even if complete anticoagulation is capable of reducing VTE or arterial thromboembolism (ATE) in comparison with a prophylactic dose.

In a Cochrane systematic review published before the publication of a randomized controlled trial (RCT),[5] descriptive information was provided on the effects of anticoagulants on COVID-19. However, other systematic reviews have not considered the subgroups of COVID-19 severity or the doses of drugs administered, and most have included retrospective observational studies.[6-8] Therefore, our main objective was to evaluate the effect of anticoagulation on COVID-19 of varying severity, as

Correspondence to:
Diane R Batista. Divisão de Pneumologia, Faculdade de Medicina, Universidade Estadual Paulista, Distrito de Rubião Junior, s/n, CEP 18618-970, Botucatu, São Paulo, SP, Brasil.
Tel.: 55 14 3811-1171. E-mail: dianerezende@gmail.com
Financial support: None.

ISSN 1806-3756

well as to evaluate mortality, VTE, ATE, and major bleeding associated with anticoagulation interventions.

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[9]

Eligibility criteria

The study protocol followed the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. With the use of anticoagulants as the main study point, the PICO framework was as follows: patients—adult COVID-19 patients; intervention—use of anticoagulants; comparison—comparison between the standard of care (SOC) and placebo; and outcome—the 30-day all-cause mortality rate, bleeding or major bleeding, and ATE (ATE-myocardial infarction, non-hemorrhagic stroke, major adverse limb events, and cardiovascular death) or VTE at 30 days.

All phase 3 RCTs on the topic were included. No restrictions were imposed with regard to date of publication, language, or full-text availability. The study protocol was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42021289669).

Considering the living systematic review strategy, we will search for new RCTs every six months and add new information to this systematic review.

Information sources and search strategy

Two of the authors developed search strategies that were revised and approved by the research team; selected information sources; and systematically searched the following databases: MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Search strategies included the following: ("COVID-19" OR "COVID" OR "coronavirus" OR "SARS-CoV-2") AND ("anticoagulant" OR "anticoagulation" OR "agents anticoagulant") AND ("indirect thrombin inhibitors" OR "enoxaparin" OR "fondaparinux" OR "heparin" OR "warfarin") AND (therapy/narrow[filter] OR prognosis/narrow [filter] OR comparative study OR comparative studies); and (COVID-19 OR COVID OR CORONAVIRUS OR SARS-CoV-2) AND (anticoagulant).

Study selection

Two researchers independently selected and extracted data from the included studies. First, articles were selected by title and abstract. Then, the selected articles were read in their entirety to decide whether they should be included or excluded, with disagreements being resolved by consensus or following a discussion with a third researcher.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (anticoagulant use and SOC), absolute numbers of outcomes, and follow-up duration were independently extracted from the studies by two researchers, and the extracted values were compared.

Risk of bias and quality of evidence

The risk of bias for RCTs and other important data were assessed with the Cochrane risk-of-bias tool for randomized trials (RoB 2),[10,11] being expressed as very serious, serious, or non-serious. The risk of bias was assessed by two independent reviewers, disagreements being resolved through discussion with a third reviewer. The quality of evidence was extrapolated from the risk of bias and was described by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) terminology[12] as very low, low, or high; for meta-analyses, the GRADEpro Guideline Development Tool[13] describes the quality of evidence as very low, low, moderate, or high.

Synthesis of results and analysis

Categorical outcomes were expressed by group (anticoagulant use or SOC), number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference (RD) between the groups was significant, a 95% CI was expressed on the basis of the number needed to treat (NNT) or the number needed to harm. We analyzed separate RCTs assessing outpatients and hospitalized patients or full anticoagulation and intermediate prophylactic doses. We also analyzed the subgroups of patients with moderate COVID-19 (non-ICU patients) and severe COVID-19 (ICU patients).

We used fixed- or random-effects meta-analysis to evaluate the effect of anticoagulant use vs. SOC on the outcomes when these data were available in at least two RCTs. The effects were reported as RDs and corresponding 95% CIs; a 95% CI including 0 in its range indicated that there was no difference in the outcome effect between the anticoagulant and SOC arms. RDs show the absolute effect size in the meta-analysis when compared with the relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. Heterogeneity of effects across studies was quantified with the I^2 statistic, an $I^2 > 50\%$ indicating high heterogeneity. For the meta-analysis, we used the Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).

RESULTS

A total of 401 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, we selected 11 studies for full-text assessment. Of those, 2 were excluded (Figure 1). Therefore, 9 RCTs were included in the present systematic review and meta-analysis.[14-22] The study characteristics, risk of bias, and quality of evidence are presented in Tables 1 and 2, as well as in Tables S1-S3).

The study population included 6,004 patients with mild to severe COVID-19. Of those, 3,037 received anticoagulants and 2,967 received SOC or placebo. When the study population was stratified by COVID-19 hospitalization, post-discharge COVID-19 patients were represented in 1 RCT including 160 patients in the placebo group and 160 patients in the prophylactic group.[22] We included 8 RCTs of hospitalized patients with moderate to severe disease, stratified by type of anticoagulation: full anticoagulation vs. SOC and intermediate prophylactic dose vs. SOC.[14-21]

With regard to the risk of bias of RCTs,[14-22] 4 had randomization and blinded allocation with risk of bias.[15,17,20,22] Furthermore, only 1 RCT was double-blinded,[21] whereas the others (i.e., 8) were single-blinded, allowing the assessment of outcomes without being blinded .[14-20,22] Five RCTs used composite outcomes.[16-19,22] One study did not report baseline characteristics, thus precluding demonstration of similarity across groups for comparison.[21] One study did not describe the sample size calculation,[15] and one did not use intention-to-treat analysis[21]; all of these were considered a risk of bias (Table 2). Therefore, the global risk of bias was considered to be moderate.

Non-hospitalized COVID-19 patients

One RCT[22] was included in the analysis of non-hospitalized patients with COVID-19. The study in

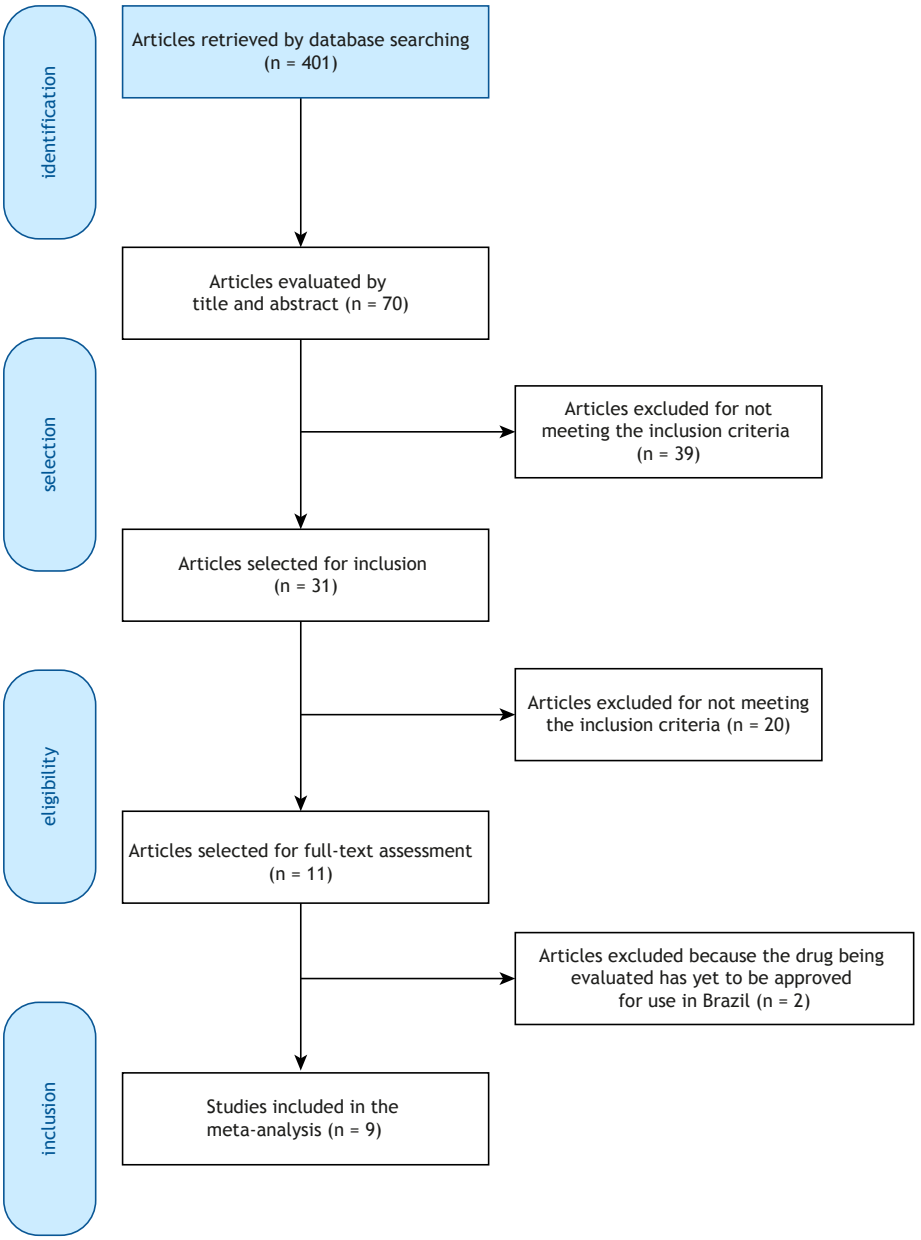


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of the process of including studies in our systematic review and meta-analysis.

Table 1. Description of the studies included in the meta-analysis.

Study	Design	Population	Intervention	Comparator	Outcome	Duration
Perepu et al.[20])	Open-label RCT	Adults hospitalized with COVID-19	N = 88 Intermediate dose of enoxaparin (of 1 mg/kg/day for a BMI of < 30 kg/m^2 or of 0.5 mg/kg 12/12 h for a BMI > 30 kg/m^2)	N = 88 Prophylactic enoxaparin 40 mg/day (for a BMI of < 30 kg/m^2) or 30-40 mg 12/12 h (for a BMI > 30 kg/m^2)	Mortality at 30 days Venous/arterial thromboembolism Bleeding	30 days
INSPIRATION Investigators et al.[21]	RCT with blinded outcome assessment	Adult ICU COVID-19 patients within 7 days of hospitalization	N = 280 Enoxaparin 1 mg/kg/day (120 kg) Changed to unfractionated heparin if kidney function < 30 ml/min	N = 286 Enoxaparin 40 mg/kg/day	Venous/arterial thromboembolism Need for ECMO No. of days free of mechanical ventilation ICU discharge Bleeding	30 days
REMAP-CAP Investigators et al.[16]	Open-label RCT	Adult ICU COVID-19 patients requiring respiratory or cardiac support	N = 534 Anticoagulation with unfractionated or low-molecular-weight heparin	N = 564 Low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis	Venous/arterial thromboembolism No. of organ support-free days Bleeding Survival to hospital discharge	21 days
ATTACC Investigators et al.[18]	Open-label RCT	Adult ward patients with COVID-19 not requiring respiratory or cardiac support	N = 1,190 Anticoagulation with unfractionated or low-molecular-weight heparin	N = 1,054 Low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis	Venous/arterial thromboembolism No. of organ support-free days Bleeding Survival to hospital discharge	21 days
Sholzberg et al.[17]	Open-label RCT	Adults hospitalized with COVID-19, a D-dimer above the upper limit of normal, and an SpO_2 of < 93% on room air	N = 228 Anticoagulation with unfractionated or low-molecular-weight heparin	N = 237 Low-dose thromboprophylaxis with unfractionated or low-molecular-weight heparin	Mortality Mechanical ventilation or death No. of days free of mechanical ventilation ICU admission or death Venous/arterial thromboembolism No. of organ support-free days Bleeding	28 days

Continue...▶

Table 1. Description of the studies included in the meta-analysis. (Continued...)

Study	Design	Population	Intervention	Comparator	Outcome	Duration
Lopes et al.[14]	Open-label RCT	Adults hospitalized with COVID-19 within 14 days of the onset of symptoms, a D-dimer above the upper limit of normal, and an SpO_2 of < 93% on room air	N = 310 Rivaroxaban 20 mg/day for stable patients or enoxaparin 1 mg/kg 12/12 h for unstable patients	N = 304 Low-dose thromboprophylaxis with unfractionated or low-molecular-weight heparin	Mortality Hospital length of stay Duration of oxygen use Venous/arterial thromboembolism Bleeding	30 days
Oliynyk et al.[15]	Open-label RCT	Adults hospitalized with COVID-19, a D-dimer > 3 mg/L, and a PaO_2 of < 60 mmHg on room air	N = 84 Anticoagulation with unfractionated or low-molecular-weight heparin	N = 42 Low-molecular-weight heparin	Mortality Mechanical ventilation or death	28 days
Spyropoulos et al.[19]	Open-label RCT	Adults hospitalized with COVID-19 and a D-dimer > 4 times the upper limit of normal, requiring supplemental oxygen	N = 130 Anticoagulation with enoxaparin 1 mg/kg 12/12 h or 0.5 mg/kg 12/12 h if CrCl = 15-39 mL/min/1.73 m^2	N = 127 Enoxaparin 30-40 mg/kg once or twice daily or unfractionated heparin 22,500 IU	Venous/arterial thromboembolism Mortality Bleeding Endotracheal intubation Rehospitalization	30 days
Ramacciotti et al.[22]	Open-label RCT	Discharged COVID-19 patients with an IMPROVE VTE risk score ≥ 4 or = 2-3 and a D-dimer > 1,000 ng/ml during hospitalization	N = 160 Rivaroxaban 10 mg/day for 35 days	N = 160 Standard of care	Mortality related to venous/arterial thromboembolism Bleeding	30 days

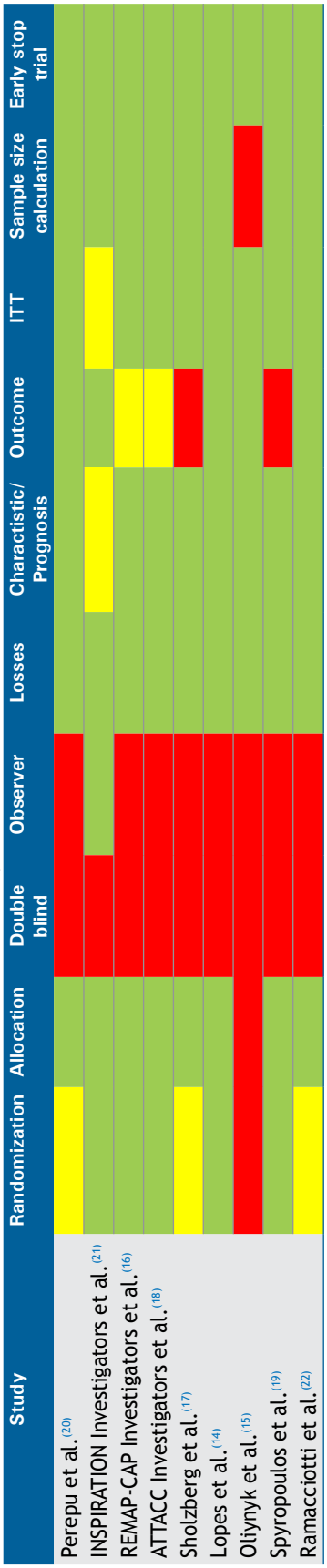
RCT: randomized controlled trial; IMPROVE: International Medical Prevention Registry on Venous Thromboembolism; VTE: venous thromboembolism; and ECMO: extracorporeal membrane oxygenation.

question randomized COVID-19 patients on the day of hospital discharge to receive rivaroxaban 10 mg (extended thromboprophylaxis) or no pharmacological intervention after 35 days. These patients presented with a high risk of VTE. To define this population, the authors used an International Medical Prevention Registry on Venous Thromboembolism VTE risk score > 4 or an International Medical Prevention Registry on Venous Thromboembolism VTE risk score of 2/3 with an elevated D-dimer (> 500 ng/mL or twice the baseline value). The primary outcome was a composite of the following: symptomatic VTE; VTE-related death; asymptomatic VTE detected by venous duplex ultrasound of the lower extremities and CT pulmonary angiography; symptomatic ATE; and cardiovascular death at day 35. The results of the study showed no significant difference in VTE between the intervention group and the SOC group (RD, −0.02; 95% CI, −0.04 to 0.01). There was also no significant difference in symptomatic pulmonary thromboembolism between the intervention group and the SOC group (RD, −0.01; 95% CI, −0.03 to 0.01). Finally, there was no significant difference in fatal pulmonary embolism between the intervention group and the SOC group (RD, −0.02; 95% CI, −0.04 to 0.01), the quality of evidence being very low (Table S1).[22]

Hospitalized COVID-19 patients

Six RCTs[14-19] were included in the analysis of hospitalized COVID-19 patients, with 2,491 patients in the therapeutic dose group (full anticoagulation) and 2,422 patients in the SOC group. As can be seen in Figure 2A, there was no significant reduction in the 30-day mortality rate in patients with moderate to severe disease (RD, −0.01; 95% CI, −0.04 to 0.02; p = 0.50; I^2 = 59%), the quality of evidence being

Table 2. Risk of bias of the randomized controlled trials included in the meta-analysis.[a]



ITT: intention to treat. [a]Red, risk of bias; yellow, not clear; and green, no risk of bias.

very low (Table S2). When patients with moderate COVID-19[14,15,17,18] or severe COVID-19[16] were analyzed separately, no significant difference was found between full anticoagulation and SOC in those with moderate COVID-19 (RD, −0.02; 95% CI, −0.06 to 0.03; p = 0.41; I^2 = 75%; Figure 2B), the quality of evidence being very low (Table S2). Only one study assessed severe COVID-19 patients, showing no significant difference in the mortality rate between the two groups (RD, 0.01; 95% CI, −0.04 to 0.07; p = 0.66), with a very low quality of evidence (Table S2).

Thrombotic events (VTE events, ATE events, or both) were assessed in 5 studies,[14,16-19] with a total of 2,449 patients in the therapeutic dose group and 2,338 patients in the SOC group. As can be seen in Figure 2C, there was a significant reduction (of 3%) in thrombotic events at 30 days in the therapeutic dose group in comparison with the SOC group (RD, −0.03; 95% CI, −0.06 to −0.00; p = 0.04; I^2 = 78%), the NNT being = 33. The quality of evidence was moderate (Table S2). This result was persistently significant when the severity of COVID-19 was evaluated. For patients with moderate COVID-19,[17,18] 2 studies demonstrated a reduction of 1% in RD (95% CI, −0.02 to −0.00; Figure 2D), the NNT being = 100 and the quality of evidence being low (Table S2). For severe COVID-19 patients,[16] 1 study demonstrated a significant reduction (of 4%) in VTE after 30 days (95% CI, −0.04 to −0.01; p = 0.02), the NNT being = 25 and the quality of evidence being low (Table S2).

Major bleeding within 30 days was described in 5 studies, with a total sample of 4,787 patients.[14,16-19] As can be seen in Figure 2E, there was no significant difference in major bleeding between full coagulation and SOC (RD, 0.02; 95% CI, −0.00 to 0.04; p = 0.13; I^2 = 71%), the quality of evidence being very low. When moderate COVID-19 patients were analyzed,[15,18-20] no significant difference was found between the two groups (RD, 0.01; 95% CI, −0.02 to 0.04; p = 0.40; I^2 = 72%), the quality of evidence being very low (Table S2). For patients with severe COVID-19, 2 RCTs showed no significant differences in major bleeding between the two groups (RD, 0.04; 95% CI, −0.03 to 0.11; p = 0.11; I^2 = 61%; Figure 2G),[16,19] the quality of evidence being very low (Table S2).

Intermediate prophylactic dose vs. prophylactic dose (SOC)

A total of 771 patients from 2 RCTs[21,22] were analyzed for an intermediate prophylactic dose in comparison with SOC. Both studies assessed interventions in patients with severe COVID-19. As can be seen in Figure 3A, no significant difference was found between the two groups regarding the 30-day mortality rate (RD, −0.01; 95% CI, −0.07 to 0.06; p = 0.81; I^2 = 0%), the quality of evidence being very low (Table S3).

As can be seen in Figure 3B, there was no significant difference between the two groups regarding VTE events (RD, −0.00; 95% CI, −0.03 to 0.03; p = 0.99; I^2 = 0%), the quality of evidence being low (Table S3). As

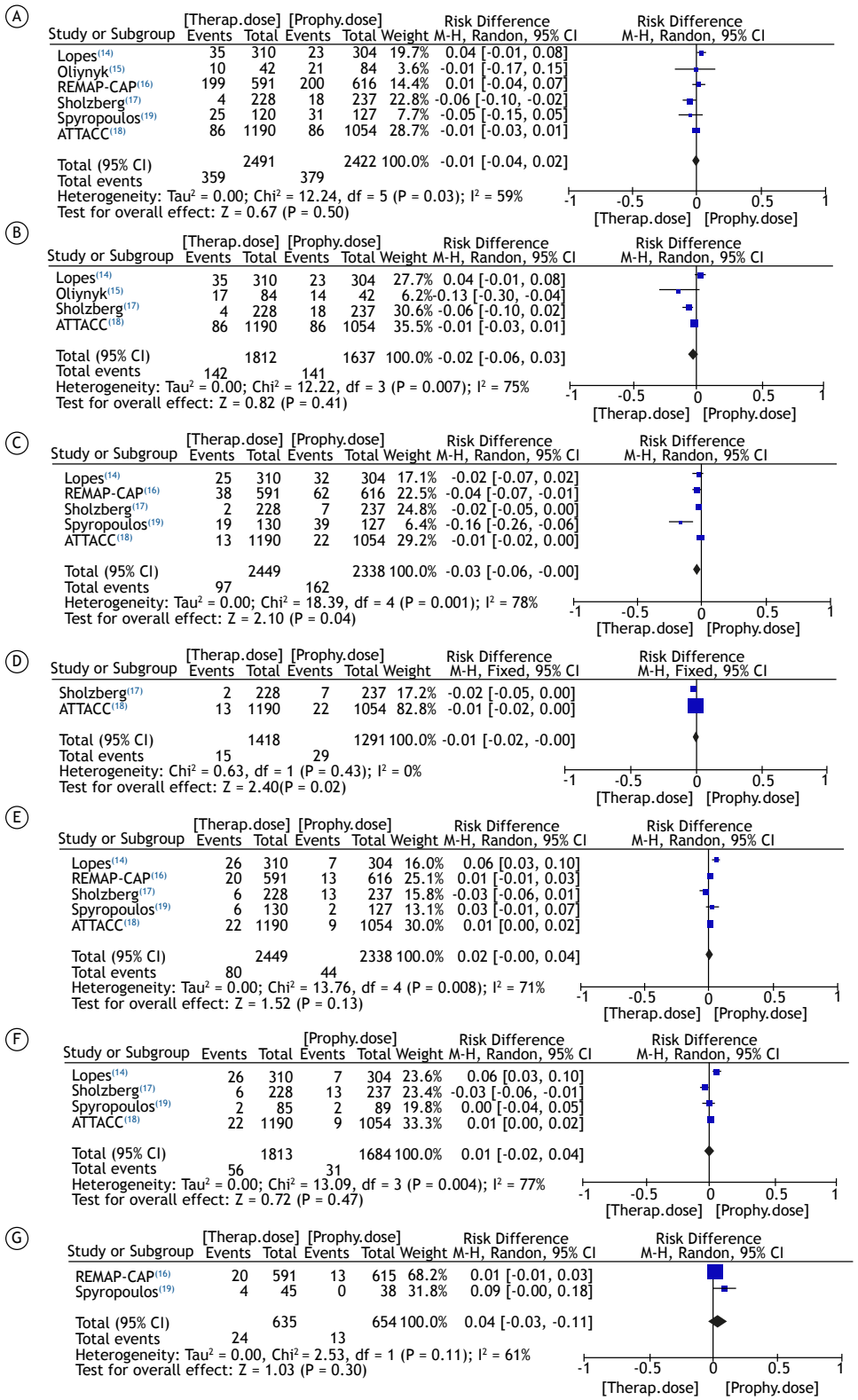


Figure 2. Forest plot of comparison: 1 Therapeutic anticoagulation vs. standard of care - randomized controlled trials, outcome: A: mortality at 30 days in all hospitalized COVID-19 patients, B: mortality at 30 days in patients with moderate COVID-19, C: venous thromboembolism at 30 days in all hospitalized COVID-19 patients, D: venous thromboembolism at 30 days in patients with moderate COVID-19, E: major bleeding at 30 days in all hospitalized COVID-19 patients, F: major bleeding at 30 days in patients with moderate COVID-19, G: major bleeding at 30 days in patients with severe COVID-19. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

can be seen in Figure 3C, the risk of ATE events was similar between the two groups (RD, 0.01; 95% CI, −0.04 to 0.05; p = 0.77; I^2 = 62%), the quality of evidence being very low (Table S3). As can be seen in Figure 3D, there was no significant difference between the two groups regarding major bleeding (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.44; I^2 = 0%), the quality of evidence being very low (Table S3).

DISCUSSION

The present systematic review and meta-analysis showed no effect of therapeutic anticoagulation on reducing mortality or increasing major bleeding events in patients with moderate to severe COVID-19. We observed a slight reduction in VTE events in hospitalized patients with moderate to severe COVID-19 at 30 days when therapeutic anticoagulation was used. The use of an intermediate prophylactic dose or post-discharge prophylactic intervention was not associated with reduced mortality, reduced VTE, reduced ATE, or increased bleeding.

With regard to the mortality outcome in hospitalized COVID-19 patients, our results are similar to those of other systematic reviews.[5,8] Therapeutic anticoagulation in these patients may not be directly associated with mortality, but it may be related to a reduction in VTE. VTE can be life-threatening in hospitalized patients and, if not recognized, can increase the risk of mortality. We observed a consistent effect of therapeutic anticoagulation on the reduction of VTE, even when moderate patients (ward patients) or severe patients (ICU patients) were analyzed as a subgroup. Moreover, therapeutic anticoagulation in this population did not increase major bleeding during treatment as a primary safety outcome. This finding is consistent with those of previous systematic reviews showing a reduction in VTE events in hospitalized patients.[23-25] However, the authors of the aforementioned reviews pooled all RCTs with different doses of anticoagulation as the intervention group. In our results, we were able to emphasize the reduction in VTE when therapeutic anticoagulation was used as an intervention. On the other hand, the reduction in VTE was small, a large NNT being required in order to reduce VTE by one. In addition, the quality of evidence was low, increasing the uncertainty. Further RCTs are needed in order to increase the certainty of the results.

The effect of intermediate anticoagulation was not related to the reduction in VTE in comparison with SOC. This finding is consistent with the literature.[24-26]

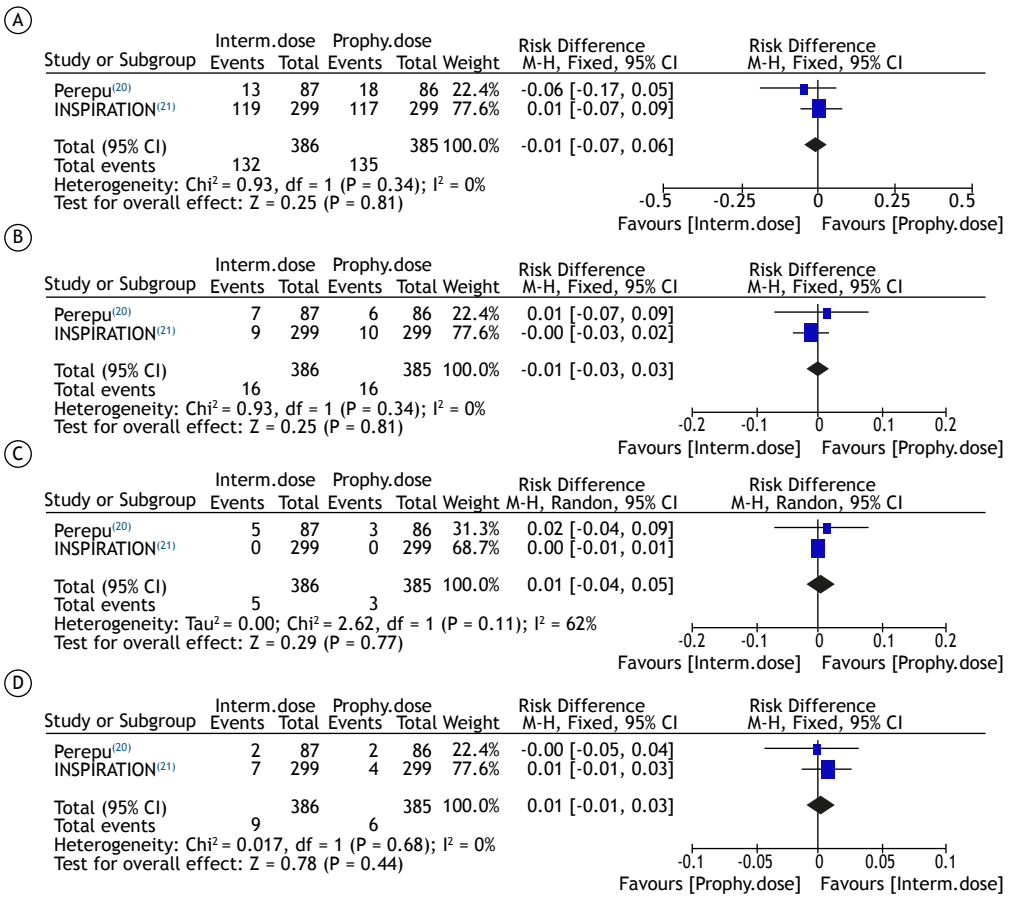


Figure 3. Forest plot of comparison: 1 Intermediate prophylactic anticoagulation vs. standard of care/placebo - randomized controlled trials, outcome: A: mortality at 30 days, B: venous thromboembolism at 30 days, C: major bleeding at 30 days. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

Most clinical COVID-19 guidelines recommend the use of prophylactic anticoagulation therapy during hospitalization. However, only 2 RCTs analyzed the effectiveness of this intervention. This important clinical recommendation needs to be evaluated on the basis of the clinical practice for patients whose characteristics are similar to those of patients included in the RCTs. We need to consider whether therapeutic intervention is recommended for all COVID-19 patients, even when they do not have elevated levels of systemic inflammatory markers. Some RCT protocols considered the need for an elevated level of systemic inflammation in the inclusion criteria. It is important to mention the NNT that is required in order to reduce the occurrence of VTE events by one. We identified a minimum of 100 patients who received therapeutic anticoagulation therapy to reduce VTE. Ongoing trials can determine whether therapeutic-dose anticoagulation provides an incremental effectiveness benefit in specific outcomes. Therefore, we need to evaluate the best balance to switch from prophylactic to therapeutic anticoagulation and attempt a VTE diagnosis.

In non-hospitalized COVID-19 patients, we observed no reduction in mortality, VTE, or ATE following the use of a prophylactic dose after hospital discharge. However, we need to consider the clinical condition of the patients when they are discharged. Most critically ill patients need to be rehabilitated for long periods of immobility, and we need to consider the risk of VTE events after hospital discharge. Unfortunately, only one of the RCTs included in the present study addressed this issue, and we do not have a robust answer to this question. Moreover, symptomatic COVID-19 outpatients need to be assessed in RCTs to evaluate the beneficial use of anticoagulants. To answer this question, RCTs are currently ongoing worldwide.

The present systematic review and meta-analysis has strengths and limitations. Because only phase 3 RCTs were included in the present study, we were able to demonstrate the real influence that the intervention used had on the selected outcomes. The certainty of the present results is dependent on novel RCTs and future analyses of larger populations. Other limitations include the characteristics of the study population, the outcomes evaluated at different time points, and the differences in interventions across studies, suggesting heterogeneity across studies. Moreover, one of the studies included in the present systematic review and meta-analysis included outpatients and had a small sample size, thus limiting the certainty of our results. Therefore, we cannot affirm whether the results presented herein will change in the future.

In conclusion, it appears that therapeutic anticoagulation does not reduce mortality in COVID-19 patients. In hospitalized patients, therapeutic anticoagulation appears to result in a slight reduction in VTE without an increased risk of major bleeding.

AUTHOR CONTRIBUTIONS

SET, HAB, IF, and WMB: study concept and design. WMB, SET, DRB, and IF: data collection, statistical analysis, and interpretation of data. WMB, DRB, and SET: drafting of the manuscript. SET, HAB, AN, AS, and WMB: critical revision of the manuscript for important intellectual content and approval of the final version.

CONFLICT OF INTEREST

None declared.

REFERENCES

1. World Health Organization [homepage on the Internet] Geneva: WHO; c2021 [cited 2021 Dec 21]. Situation reports. Coronavirus disease (COVID-19) Weekly Epidemiological Update and Weekly Operational Update. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
2. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. JAMA. 2020;324(8):782-793. https://doi.org/10.1001/jama.2020.12839
3. Schulman S, Hu Y, Konstantinides S. Venous Thromboembolism in COVID-19. Thromb Haemost. 2020;120(12):1642-1653. https://doi.org/10.1055/s-0040-1718532
4. Lu YF, Pan LY, Zhang WW, Cheng F, Hu SS, Zhang X, et al. A meta-analysis of the incidence of venous thromboembolic events and impact of anticoagulation on mortality in patients with COVID-19. Int J Infect Dis. 2020;100:34-41. https://doi.org/10.1016/j.ijid.2020.08.023
5. Flumignan RL, Tinôco JDS, Pascoal PI, Areias LL, Cossi MS, Fernandes MI, et al. Prophylactic anticoagulants for people hospitalised with COVID-19. Cochrane Database Syst Rev. 2020;10(10):CD013739. https://doi.org/10.1002/14651858.CD013739
6. Jiménez D, García-Sanchez A, Rali P, Muriel A, Bikdeli B, Ruiz-Artacho P, et al. Incidence of VTE and Bleeding Among Hospitalized Patients With Coronavirus Disease 2019: A Systematic Review and Meta-analysis. Chest. 2021;159(3):1182-1196. https://doi.org/10.1016/j.chest.2020.11.005
7. McBane RD 2nd, Torres Roldan VD, Niven AS, Pruthi RK, Franco PM, Linderbaum JA, et al. Anticoagulation in COVID-19: A Systematic Review, Meta-analysis, and Rapid Guidance From Mayo Clinic. Mayo Clin Proc. 2020;95(11):2467-2486. https://doi.org/10.1016/j.mayocp.2020.08.030
8. Abdel-Maboud M, Menshawy A, Elgebaly A, Bahbah EI, El Ashal G, Negida A. Should we consider heparin prophylaxis in COVID-19 patients? a systematic review and meta-analysis. J Thromb Thrombolysis. 2021;51(3):830-832. https://doi.org/10.1007/s11239-020-02253-x
9. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
10. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
11. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55-61. https://doi.org/10.1002/jrsm.1411
12. GRADE [homepage on the Internet]. The GRADE Working Group; c2004-2021 cited 2021 Aug 1]. Available from: https://gradeworkinggroup.org/
13. GRADEpro GDT [homepage on the Internet]. Hamilton, Canada: McMaster University and Evidence Prime; c2021. GRADEpro Guideline Development Tool [Software]. Available from: https://www.gradepro.org/
14. Lopes RD, de Barros E Silva PGM, Furtado RHM, Macedo AVS,

Bronhara B, Damiani LP, et al. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet. 2021;397(10291):2253-2263. https://doi.org/10.1016/S0140-6736(21)01203-4

15. Oliynyk O, Barg W, Slifirczyk A, Oliynyk Y, Dubrov S, Gurianov V, et al. Comparison of the Effect of Unfractionated Heparin and Enoxaparin Sodium at Different Doses on the Course of COVID-19-Associated Coagulopathy. Life (Basel). 2021;11(10):1032. https://doi.org/10.3390/life11101032
16. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, Goligher EC, Bradbury CA, McVerry BJ, et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021;385(9):777-789. https://doi.org/10.1056/NEJMoa2103417
17. Sholzberg M, Tang GH, Rahhal H, AlHamzah M, Kreuziger LB, Áinle FN, et al. Effectiveness of therapeutic heparin versus prophylactic heparin on death, mechanical ventilation, or intensive care unit admission in moderately ill patients with covid-19 admitted to hospital: RAPID randomised clinical trial. BMJ. 2021;375:n2400. https://doi.org/10.1136/bmj.n2400
18. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, et al. Therapeutic Anticoagulation with Heparin in Noncritically Ill Patients with Covid-19. N Engl J Med. 2021;385(9):790-802. https://doi.org/10.1056/NEJMoa2105911
19. Spyropoulos AC, Goldin M, Giannis D, Diab W, Wang J, Khanijo S, et al: HEP-COVID Investigators. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial [published correction appears in JAMA Intern Med. 2022 Feb 1;182(2):239]. JAMA Intern Med. 2021;181(12):1612-1620. https://doi.org/10.1001/jamainternmed.2021.6203
20. Perepu US, Chambers I, Wahab A, Ten Eyck P, Wu C, Dayal S, et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. J Thromb Haemost. 2021;19(9):2225-2234. https://doi.org/10.1111/jth.15450
21. INSPIRATION Investigators, Sadeghipour P, Talasaz AH, Rashidi F, Sharif-Kashani B, Beigmohammadi MT, et al. Effect of Intermediate-Dose vs Standard-Dose Prophylactic Anticoagulation on Thrombotic Events, Extracorporeal Membrane Oxygenation Treatment, or Mortality Among Patients With COVID-19 Admitted to the Intensive Care Unit: The INSPIRATION Randomized Clinical Trial. JAMA. 2021;325(16):1620-1630. https://doi.org/10.1001/jama.2021.4152
22. Ramacciotti E, Barile Agati L, Calderaro D, Aguiar VCR, Spyropoulos AC, de Oliveira CCC, et al. Rivaroxaban versus no anticoagulation for post-discharge thromboprophylaxis after hospitalisation for COVID-19 (MICHELLE): an open-label, multicentre, randomised, controlled trial. Lancet. 2022;399(10319):50-59. https://doi.org/10.1016/S0140-6736(21)02392-8
23. Wijaya I, Andhika R, Huang I. The Use of Therapeutic-Dose Anticoagulation and Its Effect on Mortality in Patients With COVID-19: A Systematic Review. Clin Appl Thromb Hemost. 2020;26:1076029620960797. https://doi.org/10.1177/1076029620960797
24. Ortega-Paz L, Galli M, Capodanno D, Franchi F, Rollini F, Bikdeli B, et al. Safety and efficacy of different prophylactic anticoagulation dosing regimens in critically and non-critically ill patients with COVID-19: A systematic review and meta-analysis of randomized controlled trials [published online ahead of print, 2021 Sep 14]. Eur Heart J Cardiovasc Pharmacother. 2021;pvab070. https://doi.org/10.1093/ehjcvp/pvab070
25. Jorda A, Siller-Matula JM, Zeitlinger M, Jilma B, Gelbenegger G. Anticoagulant Treatment Regimens in Patients With Covid-19: A Meta-Analysis. Clin Pharmacol Ther. 2022;111(3):614-623. https://doi.org/10.1002/cpt.2504
26. Zhang S, Li Y, Liu G, Su B. Intermediate-to-therapeutic versus prophylactic anticoagulation for coagulopathy in hospitalized COVID-19 patients: a systemic review and meta-analysis. Thromb J. 2021;19(1):91. https://doi.org/10.1186/s12959-021-00343-1

J Bras Pneumol. 2022;48(4):e20220002
https://dx.doi.org/10.36416/1806-3756/e20220002

Pulmonary diseases that cause abnormal lung parenchymal density: is this a problem in lung cancer screening?

Diana Penha[1], Erique Pinto[1], Edson Marchiori[2], Luís Taborda-Barata[1], Klaus Irion[3]

TO THE EDITOR:

This letter addresses recent research regarding how lung parenchymal attenuation influences pulmonary nodule volumetry. This topic is relevant to healthcare stakeholders and patients undergoing lung cancer screening (LCS) programs.

Low-dose chest CT in LCS has been proven to reduce lung cancer deaths by 20% compared with chest radiography.[1] The Hounsfield unit (HU) threshold between normal aerated lung and emphysema varies among authors, but a threshold of −950 HU has been commonly accepted.[2]

Healthcare systems worldwide are implementing LCS programs using low-dose CT and new software tools for lung nodule detection and segmentation, including software tools for automated and semi-automated pulmonary nodule volumetry. International societies recommend the use of such volumetry tools in the assessment of incidental pulmonary nodules and their follow-up if they are larger than 100 mm^3 (Fleischner Society) or 80 mm^3 (British Thoracic Society).[3,4]

From a technical point of view, these tools work by performing virtual extraction of the nodule from the adjacent lung parenchyma and other structures such as bronchial walls and vessels. The so-called "region-growing" segmentation algorithm can perform this extraction either in a semi-automated (i.e., the operator locates the nodule manually) or automated (i.e., the computer system automatically identifies and segments the pulmonary nodules) manner as in computer-aided detection.

Starting from the initial voxel selected, the algorithm tries to identify all the voxels that are contiguous to this point and that have a density value similar to that of the selected point. The process continues until the nodule margin is determined by the abrupt change in density values due to the presence of air in the lung adjacent to the nodule. There is high contrast between ventilated lung parenchymal airspaces close to −950 HU in attenuation and a solid pulmonary nodule (above −500 HU).[5]

A vast body of research has been dedicated to identifying the technical factors influencing volumetry tools. These factors may be related to the CT scanner, acquisition parameters (e.g., slice thickness, section overlap, kernel, reconstruction algorithm), and software used. Other factors are related to the patient or the nodule itself (e.g., acquisition in inspiration or expiration, size, location, shape, or density).[5]

Little has been researched on the influence of lung parenchymal density or lung parenchymal attenuation on these artificial intelligence tools, even though pulmonary diseases that cause abnormal lung parenchymal density are common in chest CT studies. Conditions that cause abnormal lung density can be grouped into two groups: diseases that cause increased parenchymal attenuation (e.g., infection, neoplasms, or interstitial lung disease); and diseases that cause decreased parenchymal attenuation (e.g., emphysema, cysts, bronchiectasis, or honeycombing).

It would be intuitive to consider that diseases that cause decreased lung attenuation, such as cysts and emphysema, would improve delineation of nodule margins when the decreased lung attenuation is adjacent to the nodule and would potentially improve the accuracy of the volumetry tool and reduce its variability (Figure 1A). However, several studies have investigated diseases that cause decreased lung attenuation, such as cysts and emphysema, as factors influencing lung nodule volumetry, and, so far, no consistent effect has been shown.[5,6]

A recent research paper based on a large LCS program showed that increased lung attenuation adjacent to a nodule is inversely related to the likelihood of good segmentation of that same nodule by volumetry tools (Figures 1B and 1C).[7] Therefore, we should exercise caution in using dedicated lung nodule volumetry tools in patients with diseases accompanied by increased lung density when nodules are located in affected areas.

Interstitial lung diseases (ILD) feature increased parenchymal density and are common in LCS patients. Studies concerning LCS programs report ILD in approximately 5% to 25% of the patients. The most common types of ILD found in LCS patients are smoking-related ILD, including smoking-related interstitial fibrosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, and respiratory bronchiolitis ILD.[8]

With this short letter, the authors aim to increase the awareness of radiologists and chest physicians regarding this recently identified limiting factor of volumetry tools. As we move towards early lung cancer detection and the worldwide implementation of LCS programs, we believe that recognizing the potential pitfalls of volumetry tools is essential to deriving the benefits of evidence-based healthcare.

1. Universidade da Beira Interior, Covilhã, Portugal.
2. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
3. Manchester University NHS Foundation Trust, Manchester, United Kingdom.

ISSN 1806-3756

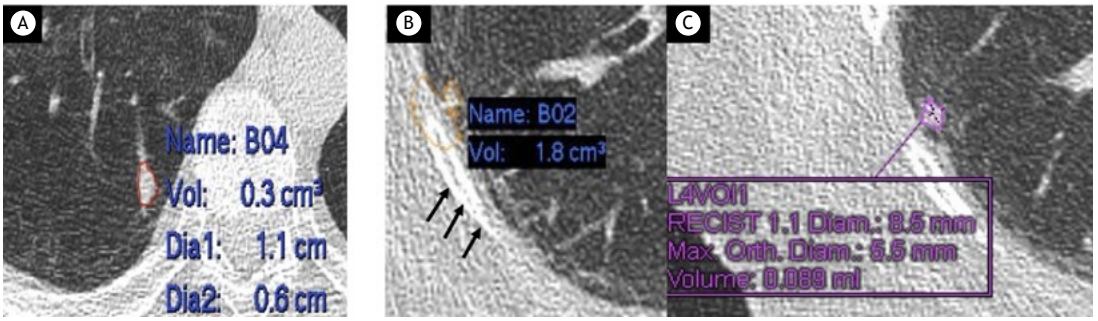


Figure 1. In A, application of a nodule volumetry tool to assess a lung nodule surrounded by pulmonary emphysema (red, "oval-shaped" circle). The segmentation and volume calculation are technically correct. In B, the application of the same nodule volumetry tool to assess a lung nodule surrounded by subpleural reticulation and fibrosis (arrows) in a patient with smoking-related interstitial lung disease under follow-up in a lung cancer screening program showed a significant nodule segmentation error. The incorrect segmentation included the subpleural fibrosis and also the chest wall. This error was influenced by the increased lung parenchymal density surrounding the nodule (reticulation and fibrosis), overestimating the volume of the nodule to be 1.8 cm^3, while, in C, the application of a different software tool to assess the same nodule correctly estimated its volume to be 0.089 cm^3. This corresponds to a 20-fold error in the volume calculation.

AUTHOR CONTRIBUTIONS

DP and EP: study conception and writing of the manuscript. EM: manuscript review and editing. LTB and KI: manuscript review. All authors: approval of the final version of the manuscript.

CONFLICT OF INTEREST

None.

REFERENCES

1. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. https://doi.org/10.1056/NEJMoa1102873
2. Lynch DA, Al-Qaisi MA. Quantitative computed tomography in chronic obstructive pulmonary disease. J Thorac Imaging. 2013;28(5):284-290. https://doi.org/10.1097/RTI.0b013e318298733c
3. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-243. https://doi.org/10.1148/radiol.2017161659
4. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British Thoracic Society guidelines for the investigation and management of pulmonary nodules [published correction appears in Thorax. 2015 Dec;70(12):1188]. Thorax. 2015;70 Suppl 2:ii1-ii54. https://doi.org/10.1136/thoraxjnl-2015-207168
5. Devaraj A, van Ginneken B, Nair A, Baldwin D. Use of Volumetry for Lung Nodule Management: Theory and Practice. Radiology. 2017;284(3):630-644. https://doi.org/10.1148/radiol.2017151022
6. Moser JB, Mak SM, McNulty WH, Padley S, Nair A, Shah PL, et al. The influence of inspiratory effort and emphysema on pulmonary nodule volumetry reproducibility. Clin Radiol. 2017;72(11):925-929. https://doi.org/10.1016/j.crad.2017.06.117
7. Penha D, Pinto E, Hochhegger B, Monaghan C, Marchiori E, Taborda-Barata L, et al. The impact of lung parenchyma attenuation on nodule volumetry in lung cancer screening. Insights Imaging. 2021;12(1):84. https://doi.org/10.1186/s13244-021-01027-0
8. Chung JH, Richards JC, Koelsch TL, MacMahon H, Lynch DA. Screening for Lung Cancer: Incidental Pulmonary Parenchymal Findings. AJR Am J Roentgenol. 2018;210(3):503-513. https://doi.org/10.2214/AJR.17.19003

Tell me where you went, I may tell who you infected

Sónia Silva Guerra[1], Eduarda Seixas[2], Ana Isabel Ribeiro[3,4,5], Raquel Duarte[3,6,7,8]

TO THE EDITOR,

The transmission of *Mycobacterium tuberculosis* depends on index-case characteristics, the type of exposure, and environmental factors.[1] Once a new case is identified, contact investigation is a key component of tuberculosis control. Screening contacts may become insufficient if we do not value person-to-person contact information in activity spaces (local areas where people go/travel to for their daily activities).[2] Spatial analysis using Geographic Information Systems (GIS) has promoted targeted tuberculosis surveillance; however, detailed data on individual mobility are generally not collected, a fact that explains the lack of studies on the micro-scale.[3,4]

Despite the overall decline in tuberculosis notification rates in Europe, the incidence of the disease in Portugal remains high (16.7/100,000 inhabitants), with northern coastal areas being the most concerning regions.[5,6] Tuberculosis outpatient centers are responsible for the management of active tuberculosis and screening of risk groups in the country. The reorganization of assistance response and screening optimization is a priority for the tuberculosis end strategy.[6]

This pilot study aimed to 1) characterize the spatial distribution of the activity spaces of tuberculosis patients from a tuberculosis outpatient center in an urban area in northern Portugal and 2) determine if the activity spaces identified during contact investigation were more clustered than expected and identify where those clusters were located.

We included all patients diagnosed with pulmonary tuberculosis between March 2019 and March 2021 who were 18 years old or older, contactable, and capable of providing information. The contagious period included three months prior to symptom development for those with a positive sputum smear or chest radiograph with lung cavitation; or the four weeks before sample collection in cases of diagnosis through positive culture (smear-negative, without cavitation). High-risk activity spaces were those where, during the contagious period, contacts had ≥8 cumulative hours of exposure to smear-positive patients or ≥40 cumulative hours if smear-negative.[2]

Patients answered a phone call inquiry by their medical doctors, after consenting to participate in the study. We asked them to describe their typical week during the contagious period and list the high-risk activity spaces they went/traveled to for their daily activities.

The activity spaces' addresses were geocoded using the QGIS software (Quantum GIS Development Team, 2013), the MMQGIS Python plugin, and Google Maps API. In order to depict the activity spaces' spatial distribution, we used the kernel density estimation (KDE) function, and the Nearest Neighbor Hierarchical Clustering (NNHC) method was applied using the CrimeStat 3.3 software to identify the clusters' areas.[7]

Among the 76 patients followed up for pulmonary tuberculosis, 19 were excluded (12 uncontactable, 6 deceased, and 1 minor of age). Most excluded patients were male (73.7%), with a mean age of 51 years (SD=26.7), and two-thirds were inactive/unemployed.

Thus, 57 patients were included in this study, most of whom were male (68.4%), with a mean age of 45.1 years (SD=16.4). Thirty-seven patients were active workers, and thirty were diagnosed before the COVID-19 pandemic and the implementation of containment measures.

The activity spaces (n=141) included mostly residencies (n=57) and public spaces, such as cafes and bakeries (n=41), companies/workplaces (n=15), schools (n=12), supermarkets (n=3), churches (n=2), and gyms (n=2). The median number of visited public spaces reported was 1 (IQR 1). More precisely, 57.9% reported 0 to 1 public spaces, while 42.1% reported ≥2. The number of visited public spaces was independent of gender (p=0.313), age (p=0.162), and the period (pre- or post-pandemic measures) (p=0.462).

The identified public spaces were located at a median distance of 1,483 meters (IQR 4,876) from the residential area. Figure 1A depicts the spatial distribution of the activity spaces' point locations and the resulting density map. Darker areas represent locations with a higher concentration of activity spaces, mostly located in the northwestern portion of the Espinho municipality and the parishes of Canidelo and Vilar de Andorinho, in the Vila Nova de Gaia (VNG) municipality.

Figure 1B, in turn, represents the three spatial clusters with higher concentrations of visited spaces, corresponding to parishes with higher population density, lower-income, poor living conditions, and higher youth unemployment rates.[8,9]

1. Serviço de Pneumologia, Centro Hospitalar Tondela-Viseu, Viseu, Portugal.
2. Serviço de Pneumologia, Centro Hospitalar Baixo-Vouga, Aveiro, Portugal.
3. EPIUnit - Instituto de Saúde Pública, Universidade do Porto, Porto, Portugal.
4. Laboratório para a Investigação Integrativa e Translacional em Saúde Populacional, Porto, Portugal.
5. Departamento de Ciências da Saúde Pública e Forenses e Educação Médica, Faculdade de Medicina, Universidade do Porto, Porto, Portugal.
6. ICBAS-UP - Instituto de Ciências Biomédicas de Abel Salazar, Universidade do Porto, Porto, Portugal.
7. Serviço de Pneumologia, Centro Hospitalar de Vila Nova de Gaia, Vila Nova de Gaia, Portugal.
8. Unidade de Investigação Clínica, Administração Regional de Saúde do Norte, Porto, Portugal.

ISSN 1806-3756

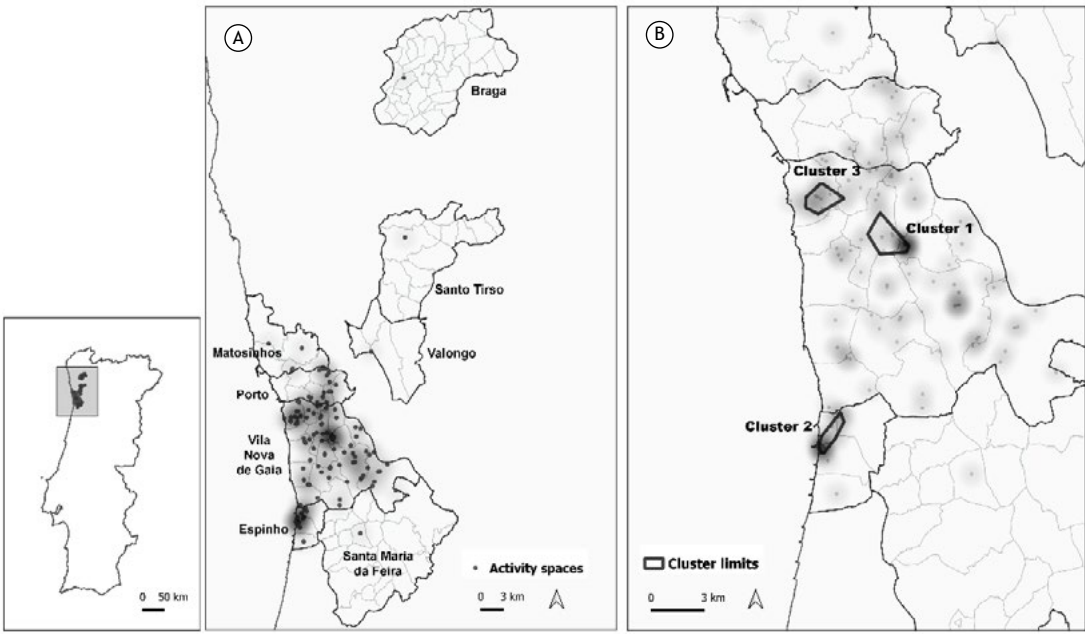


Figure 1. Spatial distribution of the activity spaces. A) Density surface and location of the tuberculosis patients' activity spaces. B) Clusters of activity spaces obtained using the Nearest Neighbor Hierarchical Clustering method.

Cluster 1 was in the intersection of Vilar de Andorinho, Mafamude, and Vilar do Paraíso (VNG municipality), with an area of 3.0 square kilometers (km^2), and encompassed 18 activity spaces, mainly composed of concentrated residential locations (large social housing complexes), cafes, bakeries, and supermarkets.

Meanwhile, cluster 2 was located mostly within the parish of Espinho (Espinho municipality), with a 2.1-km^2 area, and comprised 13 activity spaces, mainly residential locations (different social housing complexes), cafes, bakeries, restaurants, and schools.

Finally, cluster 3 was located mostly within Canidelo (VNG municipality), with a 1.3-km^2 area, and included 17 activity spaces, mainly residential locations, churches, companies, supermarkets, cafes, bakeries, gyms, and schools.

There is growing evidence that using spatial analysis in tuberculosis surveillance contributes to a better understanding of transmission dynamics.[1] We used a different approach by asking patients to describe their daily activities during the contagious period, in addition to the identification of close contacts. This method allowed the identification of several activity spaces that would remain unknown in a classic screening method, which usually focuses on close contacts rather than routine activities.

The georeferencing of activity spaces enabled us to identify three regions with a potentially higher risk of transmission. These clusters were mainly composed of social housing complexes and eating places, revealing the importance of sociability as a contributor to contagiousness. Additionally, correlating spatial analysis with sociodemographic data, such as immigrants' aggregation, socioeconomic deprivation, housing conditions, or poor healthcare accessibility, may help detect and improve tuberculosis diagnosis earlier and possibly break transmission links, especially in these vulnerable groups.[10]

This pilot study presented several limitations. Firstly, this is a retrospective study subject to recall bias, with a limited sample size. However, the included patients were more active/mobile than the excluded group, meaning we could identify a substantial number of public places. Secondly, the study period partially coincided with the COVID-19 pandemic and consequent mobility restrictions. Nevertheless, we did not observe significant differences in visited places pre- and post-pandemic measures.

In conclusion, using spatial analysis in tuberculosis screening can improve the understanding of tuberculosis local epidemiology at the micro-scale and allows for early interventions in tuberculosis control. Moreover, this methodology can be applied to other respiratory infections, namely influenza virus or SARS-CoV-2.

AUTHOR CONTRIBUTIONS

RD conceived the project idea and mentored the study. SSG and ES performed the inquiry, collected the data, and performed the statistical analysis. SSG and AIR performed the geocoding and spatial analysis and wrote the manuscript. RD and AIR revised the manuscript. All authors have read and approved the final version.

FUNDING

This study was funded by the ERDF through the Operational Program 'Competitiveness and

Internationalization' and received national funding from the Foundation for Science and Technology – FCT (Portuguese Ministry of Science, Technology, and Higher Education) under the Epidemiology Research Unit - Institute of Public Health of the University of Porto (EPIUnit) (UIDB/04750/2020) and the Laboratory for Integrative and Translational Research in Population Health (ITR) (LA/P/0064/2020). Ana Isabel Ribeiro was supported by National Funds through the FCT, under the 'Stimulus of Scientific Employment – Individual Support' program, within contract CEECIND/02386/2018.

REFERENCES

1. Shaweno D, Karmakar M, Alene KA, Ragonnet R, Clements A, Trauer JM, et al. Methods used in the spatial analysis of tuberculosis epidemiology: a systematic review. BMC Med. 2018;16:193. https://doi.org/10.1186/s12916-018-1178-4.
2. Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis; recommendations from the National Tuberculosis Controllers Association and CDC, and Guidelines for using the QuantiFERON®-TB Gold test for detecting Mycobacterium tuberculosis infection, United States. MMWR 2005;54:4-15.
3. Perez L, Dragicevic S. An agent-based approach for modeling dynamics of contagious disease spread. Int J Health Geogr. 2009;8:50. https://doi.org/10.1186/1476-072X-8-50.
4. Oliveira O, Ribeiro AI, Krainski ET, Rito T, Duarte R, Neves M. Using Bayesian spatial models to map and to identify geographical hotspots of multidrug-resistant tuberculosis in Portugal between 2000 and 2016. Sci Rep 2020;10:16646. https://doi.org/10.1038/s41598-020-73759-w.
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. Martins S, Carvalho I, Santos JV, Duarte R. Tuberculosis in undiagnosed children: What are the criteria to start treatment in Portugal? Rev Port Pneumol (2006). 2015;21(4):223-224. https://doi.org/10.1016/j.rppnen.2015.03.003.
7. CrimeStat: A Spatial Statistics Program for the Analysis of Crime Incident Locations (v 3.1). Ned Levine & Associates, Houston, TX, and the National Institute of Justice, Washington, DC, March 2007.
8. Divisão de Ação Social, Voluntariado e Saúde da Câmara Municipal de Gaia. Plano de Desenvolvimento Social Vila Nova de Gaia 2017-2021. Vila Nova de Gaia, 2021.
9. Rede Social de Espinho da Câmara Municipal de Espinho. Diagnóstico Social do Concelho de Espinho. Espinho, 2021.
10. Zão I, Ribeiro AI, Apolinário D, Duarte R. Why does it take so long? The reasons behind tuberculosis treatment delay in Portugal. Pulmonology. 2019;25(4):215-222. https://doi.org/10.1016/j.pulmoe.2019.02.005.

Unilateral proximal interruption of a pulmonary artery

Marcos A. Mestas Nuñez[1], Ernestina M.J. Gentile[1]

A previously healthy, 43-year-old woman presented to the emergency department with dry cough and hypoventilation at the right lung base. A chest X-ray showed a small right lung with an inconspicuous hilum and mediastinal shift (Figure 1A). Chest CT angiography allowed the diagnosis of proximal interruption of a pulmonary artery (PIPA) on the right side, with multiple collateral vessels supplying the ipsilateral lung (Figure 1B-D). Her echocardiogram was unremarkable, and no other abnormality was found.

PIPA is a rare vascular anomaly with an estimated prevalence of 1 in 200,000 people.[1] The term interruption is preferred to the term absence because the intrapulmonary arteries remain intact despite the blind end of the ipsilateral pulmonary artery at the hilum.[2] Right-sided PIPA tends to be an isolated finding and is more common than left-sided PIPA, which is usually associated with other congenital cardiovascular anomalies.[1]

Oxygenated blood is supplied to the lung through collateral systemic vessels, such as bronchial arteries and transpleural branches of the internal mammary, intercostal, subclavian, and innominate arteries,[3] or directly from the aorta.

Clinical presentation can be asymptomatic or include dyspnea, chest pain, recurrent infections, and

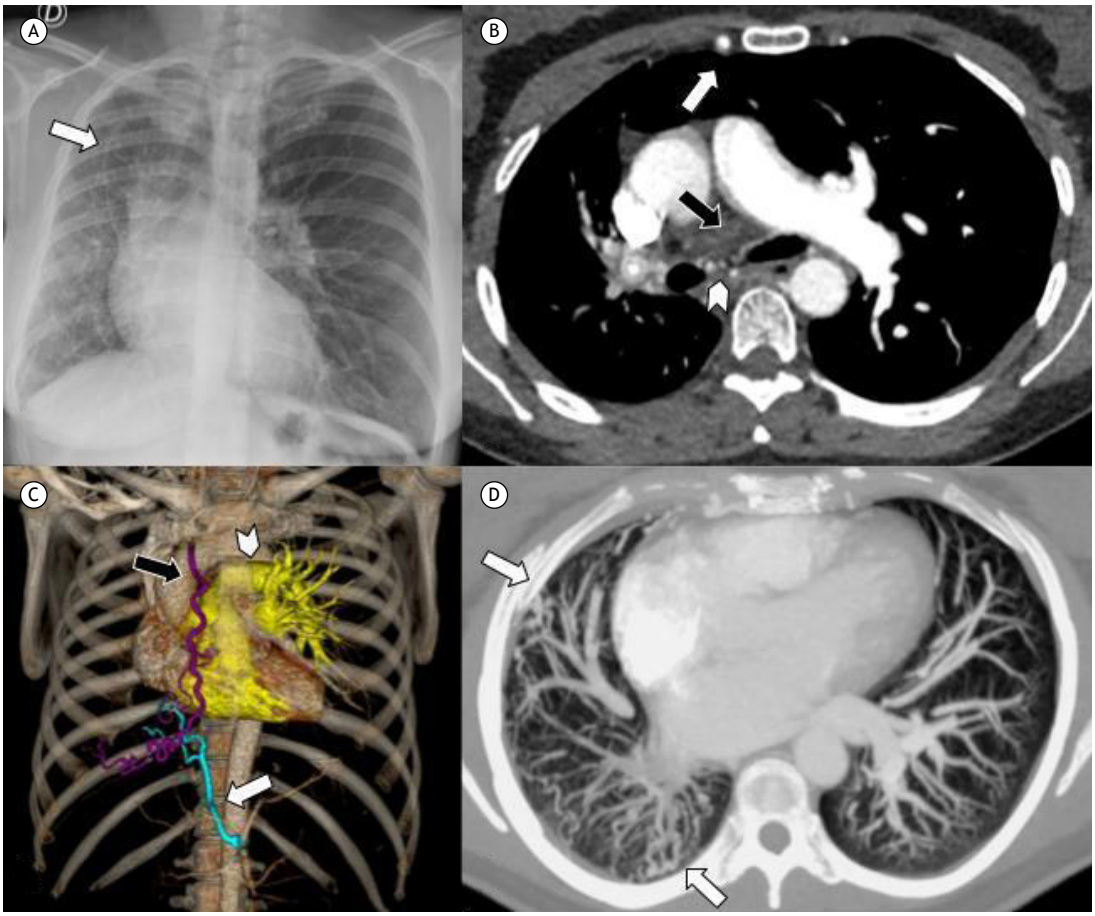


Figure 1. In A, chest X-ray showing an inconspicuous right hilum, a small right lung with reticular opacities, mediastinal shift, and a hyperinflated left lung with herniation to the right hemithorax, represented by a displaced anterior junction line (arrow). In B, axial CT angiographic image showing interruption of the right pulmonary artery (black arrow), as well as hypertrophied bronchial arteries (arrowhead) and right internal mammary artery (white arrow). In C, three-dimensional reconstruction showing the dilated right internal mammary artery (in purple; black arrow), a branch of the celiac artery (in light blue; white arrow), and a normal left pulmonary artery (in yellow; arrowhead). In D, maximum intensity projection showing multiple tortuous transpleural vessels (arrows) throughout the right lung.

1. Servicio de Diagnóstico por Imágenes, Hospital Italiano de Buenos Aires, Ciudad Autónoma de Buenos Aires, Argentina.

hemoptysis.[1,3] Pulmonary hypertension is the most feared complication.

Chest X-ray and CT findings can lead to the correct diagnosis. Awareness of this anomaly is important in order to rule out alternative diagnoses and allow appropriate management.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Williams EA, Cox C, Chung JH, Grage RA, Rojas CA. Proximal Interruption of the Pulmonary Artery. J Thorac Imaging. 2019;34(1):56-64. https://doi.org/10.1097/RTI.0000000000000373
2. Kieffer SA, Amplatz K, Anderson RC, Lillehei CW. Proximal interruption of a pulmonary artery. Am J Roentgenol Radium Ther Nucl Med. 1965;95(3):592-597. https://doi.org/10.2214/ajr.95.3.592
3. Castañer E, Gallardo X, Rimola J, Pallardó Y, Mata JM, Perendreu J, et al. Congenital and acquired pulmonary artery anomalies in the adult: radiologic overview. Radiographics. 2006;26(2):349-371. https://doi.org/10.1148/rg.262055092

Variation in lung function and clinical aspects in adults with cystic fibrosis

Elias Aguiar da Silva[1], Camila Durante[2], Daniele Rossato[3,4], Paulo de Tarso Roth Dalcin[5], Bruna Ziegler[2]

TO THE EDITOR:

An important marker for monitoring disease progression is FEV_1, which is considered the single most important predictor of life expectancy in individuals with cystic fibrosis (CF).[1,2] The coefficient of variation (CoV) for FEV_1 has been studied in individuals with CF to investigate its relationship with treatment adherence, clinical outcomes, exacerbations, and hospitalizations, as well as a predictor of future decline in FEV_1 and of future reduction of functional capacity.[3-5] One study[5] reported that patients who had a variation in $FEV_1 \geq 10\%$ in one year had a worse rate of decline in FEV_1 in the next two years.

The present study aimed to assess the relationship between CoV for FEV_1 and the number of days of hospitalization for adult individuals with CF. Secondarily, the relationship of CoV for FEV_1 with the number of pulmonary exacerbations and performance in the six-minute walk test (6MWT) was also assessed.

This was a retrospective cohort study, conducted under the auspices of the Adult CF Program at the *Hospital de Clínicas de Porto Alegre* (HCPA), in the city of Porto Alegre, Brazil, over a period of one year (from January to December of 2019). Inclusion criteria were individuals ≥ 18 years of age with a confirmed diagnosis of CF, being regularly monitored at the adult CF outpatient clinic at least three times a year and having undergone at least three spirometry tests at three-month intervals.

Clinical and demographic data were extracted from electronic medical records from HCPA. Data on the following variables were recorded at the entry date in the study: BMI, sputum bacteriology, number of exacerbations in the last year, number of hospitalizations in the last year, length of hospital stay (days), 6MWT results, and spirometric parameters. The number of respiratory exacerbations was recorded by determining the number of hospital admissions due to exacerbations and the frequency of oral antibiotic use.

Spirometry was performed in accordance with Brazilian guidelines.[6] The variables compiled were FEV_1, FVC and FEV_1/FVC expressed in liters and percentages of predicted values.[6] The highest and lowest FEV_1 values obtained within the study period were extracted, and CoV was calculated as the ratio of standard deviation to the mean for each subject individually and expressed as a proportion.

The 6MWT was performed at the HCPA Pulmonary Physiology Unit in accordance with international guidelines.[7] The distance walked on the 6MWT (6MWD) was expressed in meters and in percentage of predicted values.[8] The presence of chronic infection with *Staphylococcus aureus*, *Pseudomonas aeruginosa*, or *Burkholderia cepacia* was recorded. Chronic bacterial infection was defined as three or more positive bacterial isolates during the previous 12 months.

For analysis purposes, subjects were classified into two groups according to CoV for FEV_1: CoV for $FEV_1 < 10\%$ and CoV for $FEV_1 \geq 10\%$. The correlations between CoV for FEV_1 and other variables were analyzed using Spearman's correlation coefficient. Categorical variables were compared between the groups using the chi-square test, and data were expressed as number of cases.

The electronic medical records of 58 patients who attended the HCPA Adult CF Program during the study period were evaluated, and 47 were considered eligible and included in the study. The remaining 11 patients were excluded because of incomplete records. In the final sample, 20 and 27 patients were male and female, respectively, with a median age of 27 years and a mean BMI of 21.3 kg/m^2. Mean FEV_1 was 47% of the predicted value, and mean 6MWD was 81% of the predicted value. The median numbers for exacerbations and hospitalizations within a year were 2 and 1, respectively. Regarding the CoV groups, 28 (59.5%) and 19 (40.5%) of the subjects were allocated to the $FEV_1 \geq 10\%$ and $FEV_1 < 10\%$ groups, respectively. The comparisons between the two groups are shown in Table 1.

There were no statistically significant correlations of CoV for FEV_1 with age at diagnosis and sputum bacteriology. There were statistically significant correlations of CoV for FEV_1 with age ($\rho = -0.358$; $p = 0.013$); BMI ($\rho = -0.423$; $p = 0.003$); total number of exacerbations within a year ($\rho = 0.345$; $p = 0.018$); number of days of oral antibiotic use within a year ($\rho = 0.356$; $p = 0.014$); length of hospital stay in days within a year ($\rho = 0.386$; $p = 0.007$); 6MWD in % of the predicted value ($\rho = -0.359$; $p = 0.013$); and SpO_2 at the end of the 6MWT ($\rho = -0.330$; $p = 0.024$).

In this study, CoV for $FEV_1 \geq 10\%$, in comparison with CoV for $FEV_1 < 10\%$, was related to a greater number of hospitalizations; that is, a greater number of pulmonary exacerbations and a greater number of

1. Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Ciências Pneumológicas, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
3. Faculdade de Fisioterapia e Psicologia, Universidade do Vale do Rio dos Sinos – UNISINOS – São Leopoldo (RS) Brasil.
4. Serviço de Fisioterapia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
5. Serviço de Pneumologia, Hospital de Clínicas de Porto Alegre, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

Table 1. General characteristics of adult subjects with cystic fibrosis according to the coefficient of variation for FEV_1.[a,b]

Variable	Overall sample (n = 47)	Group		p
		CoV for FEV_1 ≥ 10% (n = 28)	CoV for FEV_1 < 10% (n = 19)	
Sex, n (%)				0.514
Male	20 (42,5)	13 (46.4)	7 (36.8)	
Female	27 (57.5)	15 (53.5)	12 (63.1)	
Age, years	27 (10)	25 (10)	27.5 (12)	0.185
Age at diagnosis, years	3 (10.8)	3 (8.5)	2 (10.8)	0.752
BMI, kg/m^2	21.3 ± 3	20.4 ± 2.7	22.0 ± 3.1	0.068
Exacerbations/year	2 (3)	4 (3)	2 (3)	0.007
Oral antibiotics, cycles/year	2 (3)	4 (4)	2 (3)	0.003
Oral antibiotics, days/year	35 (37)	42 (51)	21 (28)	0.026
Hospitalizations/year	1 (2)	2 (2)	0 (2)	0.003
Hospitalizations, days/year	15 (38)	27 (30)	0 (24)	0.002
6MWD, m	525 (111)	475 (83)	536 (87)	0.009
6MWD, % predicted	81.2 (15.1)	76.4 (15.3)	84.1 (14.2)	0.018
SpO_2 at the end of the 6MWT, %	94 (4)	93 (10)	95 (5)	0.031
Best spirometric results within a year				
FEV_1, L	1.78 (1.0)	1.47 (0.9)	1.91 (1.5)	0.135
FEV_1, % predicted	46.90 (2.9)	45 (30.2)	48 (33.6)	0.274
FVC, L	2.69 (1.84)	2.05 (1.6)	2.97 (1.7)	0.031
FVC, % predicted	68.6 ± 24.7	63.7 ± 29.6	72.8 ± 20.4	0.220
FEV_1/FVC	68.3 + 12.2	68.7+ 10.6	65.1 + 13.1	0.220
FEV_1/FVC, % predicted	78 ± 14.6	80.3 ± 11.8	75.5 ± 16.2	0.256
Bacteriology, n (%)				
MSSA	32 (68)	13 (46.4)	19 (100)	0.968
MRSA	7 (14.9)	3 (10.7)	4 (21)	0.887
Pseudomonas aeruginosa	32 (68)	15 (53.7)	17 (89.5)	0.188
Burkholderia cepacia	12 (25.5)	5 (17.8)	7 (36.8)	0.919

CoV: coefficient of variation; 6MWD: six-minute walk distance; 6MWT: six-minute walk test; MSSA: methicillin-sensitive *Staphylococcus aureus*; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Values expressed as mean ± SD (normal distribution) or median (IQR) for non-normal distribution, except where otherwise indicated. [b]Only the best spirometric results were used in the calculations.

days of oral or intravenous antibiotic use throughout the year. The findings are in agreement with those of Heinzmman-Filho et al.,[5] who identified a significant relationship between variations in pulmonary function and the number of hospitalizations. Also, there was a relationship between that variation in one year and a higher number of hospitalizations in the two subsequent years.

In general, regular monitoring of pulmonary function in individuals with CF during outpatient visits is essential for establishing early and aggressive treatment of pulmonary exacerbations, seeking to avoid huge variations over time and ensuring greater disease stability.[9] In this context, CoV for FEV_1 presents itself as a valid tool for monitoring the abrupt decline of lung function and progression of the disease in individuals with CF.

The retrospective nature of the present study, the small number of participants, the lack of assessment of adherence to treatment, and the unavailability of other, more sophisticated, tests, such as imaging tests and the lung clearance index, are some of the limitations of the study. Another important limitation is that only FEV_1 was used for the prognostic evaluation of hospitalizations and pulmonary exacerbations.

In conclusion, our findings suggest that a CoV for FEV_1 ≥ 10% over a year is associated with a greater number of exacerbations and hospitalizations in adult individuals with CF. The use of CoV for FEV_1 can benefit the screening and monitoring of disease progression in this population.

FINANCIAL SUPPORT

This study received financial support from the *Fundo de Incentivo à Pesquisa* (FIPE, Research Incentive Fund) of the HCPA (Protocol no. 2018-0459).

AUTHOR CONTRIBUTIONS

EAS: data collection. DR: study design. PTRD: study design, data analysis, and review of the manuscript. BZ: data collection, study design, data analysis, and review of the manuscript. All authors participated in the literature search, drafting of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Breuer O, Caudri D, Stick S, Turkovic L. Predicting disease progression in cystic fibrosis. Expert Rev Respir Med. 2018;12(11):905-917. https://doi.org/10.1080/17476348.2018.1519400
2. Taylor-Robinson D, Whitehead M, Diderichsen F, Olesen HV, Pressler T, Smyth RL, et al. Understanding the natural progression in %FEV1 decline in patients with cystic fibrosis: a longitudinal study. Thorax. 2012;67(10):860-866. https://doi.org/10.1136/thoraxjnl-2011-200953
3. White H, Shaw N, Denman S, Pollard K, Wynne S, Peckham DG. Variation in lung function as a marker of adherence to oral and inhaled medication in cystic fibrosis. Eur Respir J. 2017;49(3):1600987. https://doi.org/10.1183/13993003.00987-2016
4. Morgan WJ, VanDevanter DR, Pasta DJ, Foreman AJ, Wagener JS, Konstan MW; et al. Forced Expiratory Volume in 1 Second Variability Helps Identify Patients with Cystic Fibrosis at Risk of Greater Loss of Lung Function [published correction appears in J Pediatr. 2018 Jun;197:322]. J Pediatr. 2016;169:116-21.e2. https://doi.org/10.1016/j.jpeds.2015.08.042
5. Heinzmann-Filho JP, Pinto LA, Marostica PJ, Donadio MV. Variation in lung function is associated with worse clinical outcomes in cystic fibrosis. J Bras Pneumol. 2015;41(6):509-515. https://doi.org/10.1590/s1806-37562015000000006
6. Sociedade Brasileira de Pneumologia e Tisiologia (SBPT). Diretrizes para testes de função pulmonar. J Bras Pneumol. 2002;28(Suppl 3):S1 S238.
7. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446. https://doi.org/10.1183/09031936.00150314
8. Soares MR, Pereira CA. Six-minute walk test: reference values for healthy adults in Brazil. J Bras Pneumol. 2011;37(5):576-583. https://doi.org/10.1590/S1806-37132011000500003
9. Eakin MN, Riekert KA. The impact of medication adherence on lung health outcomes in cystic fibrosis. Curr Opin Pulm Med. 2013;19(6):687-691. https://doi.org/10.1097/MCP.0b013e3283659f45

Pulmonary embolism: an underdiagnosed and underreported entity in Brazil

Carlos Henrique Miranda[1]

TO THE EDITOR,

A recent investigation[1] published in this journal revealed a significant increase in hospitalizations due to pulmonary embolism (PE) over the past decade in Brazil, from 2.57/100,000 inhabitants in 2008 to 4.4/100,000 inhab. in 2019, with an average annual percentage change (AAPC) in the period of 5.6%; $p < 0.001$ (Figure 1A).

Several registries in different countries have also shown an increase in PE hospitalizations in recent decades.[2] An American registry recorded a significant increase in hospitalizations due to PE after the introduction of computed tomographic pulmonary angiography (CTPA) for the diagnosis of this condition (62.1/100,000 inhab. *vs*. 112.3/100,000 inhab.; $p < 0.0001$) comparing the periods before and after 1998, when multi-detector computed tomography was introduced.[3] A Spanish registry also showed an increase in PE hospitalizations, from 20.44/100,000 inhab. in 2002 to 32.69/100,000 inhab. in 2011; $p < 0.05$.[4] Similar findings were observed in registries in Italy and Australia.[5,6]

It is noteworthy that the PE hospitalization rates in Brazil have been much lower than those reported in developed countries worldwide (Figure 1B). According to Figure 1A, the highest annual PE hospitalization rate in Brazil was recorded in 2019, with 4.7 hospitalizations/100,000 inhab. Meanwhile, in Figure 1B, an American registry showed a PE hospitalization rate of 112.3/100,000 inhab. between 1998-2006;[3] a Spanish registry recorded an annual PE hospitalization rate of 32.69/100,000 inhab. in 2011,[4] and an Italian registry showed yearly PE hospitalization rates of 55.5 and 40.6/100,000 inhab. for women and men, respectively, from 2002 to 2012.[5]

Based on these data, it is possible that PE is underdiagnosed in Brazil; therefore, it is likely that many patients do not receive the correct diagnosis of this condition. Since the symptoms of PE are non-specific, its clinical presentation can be confused with several other diseases, such as pneumonia, heart failure, and chronic obstructive pulmonary disease, among others. The definitive diagnosis is only possible using imaging tests such as CTPA or planar ventilation/perfusion lung scintigraphy. These diagnostic tests are expensive, and their availability is still restricted to large centers in Brazil, especially in the public health system. Moreover, rational measures for diagnosis and treatment based on algorithms proposed by international guidelines that include, for example, pre-test probability, d-dimer, and direct oral anticoagulants (DOACs), need to be more widely adopted in the country.

On the other hand, this study also showed a significant reduction in PE fatality rates over the past decade, decreasing from 21.21% to 17.11% (AAPC: -1.9%; $p < 0.001$).[1] This finding corroborates those reported by other major international registries, which also showed a substantial reduction in PE fatality rates in recent years.[2] In an American registry, for example, the PE fatality rates for the first episode were 5.9%, 4.2%, 3.8%, and 2.4%, respectively, in the 2001-2002, 2003-2004, 2005-2006, and 2007-2008 periods.[7] Another American registry showed a decrease in PE fatality rates for males and females between 2003-2011.[8] In a Chinese registry, a decrease in PE fatality rates was observed from 25.1% (95% confidence interval (CI) 16.2-36.9) in 1997 to 8.7% (95%CI 3.5-15.8) in 2008.[9] In an Italian registry, the PE fatality rates decreased between 2002 and 2012 in women (15.6% to 10.2%) and men (17.6% to 10.1%) ($p < 0.0001$).[5] In addition, a World Health Organization (WHO) database showed a decrease in age-adjusted PE fatality rates between the years 2000 and 2015 in European countries from 12.8% (95%CI 11.4-14.2) to 6.5% (95%CI 5.3-7.7).[10]

Despite the significant decline in PE fatality rates in the past decade in Brazil, the rates registered in the country are still higher than those documented in other countries around the world (Figure 1C). The higher fatality rates in Brazil could be directly related to PE underdiagnosis. In this scenario, only the diagnosis of more severe conditions, which account for the highest in-hospital mortality rates, is carried out, whereas PE with little clinical significance may remain undiagnosed in most cases in Brazil. On the other hand, we cannot rule out the possibility that the lower PE fatality rates in developed countries could be influenced by overdiagnosis, given that the number of PE diagnoses could have been inflated with clinically less significant cases that were only detectable through highly sensitive imaging tests and experienced radiologists.

PE underreporting in Brazil may also be another significant issue. According to Gomes et al. (2022),[1] hospitalization data extracted from the Hospital Information System (SIH) of the Brazilian Unified Health System (SUS) Information Technology Department comprises approximately 70% of public hospital admissions. Another possibility would be the high number of outpatient PE diagnoses. However, even though the home treatment of low-risk PE is feasible, we know this approach is still not widespread in Brazil; most physicians still hospitalize their patients for anticoagulant treatment initiation. Another problem could be the underreporting of in-hospital PE, since the diagnosis of PE may not be included within the primary

1. Divisão de Medicina de Emergência, Departamento de Clínica Médica, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Ribeirão Preto (SP), Brasil.

ISSN 1806-3756

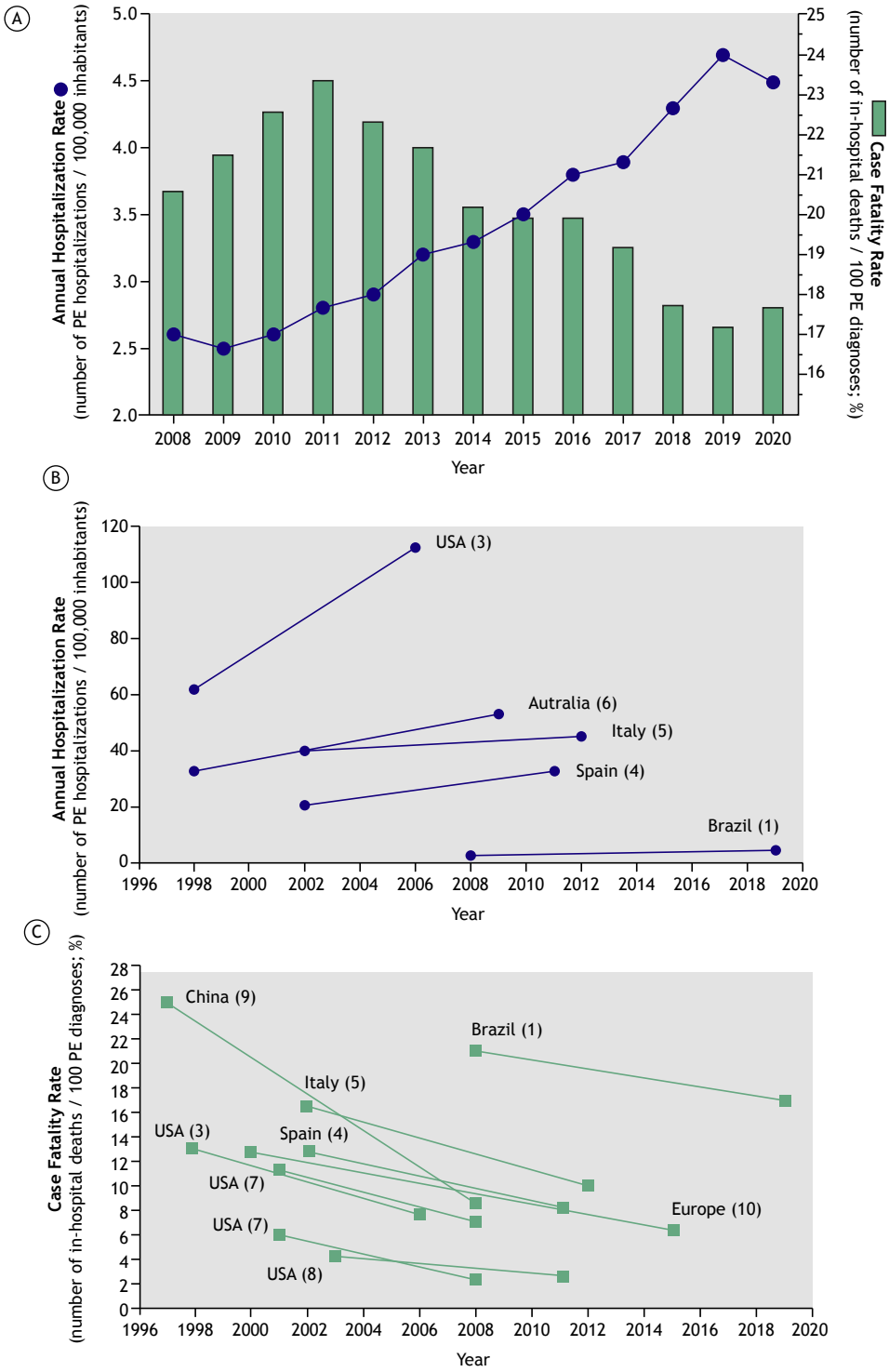


Figure 1. (A) Line graph showing the annual pulmonary embolism (PE) hospitalization rates per 100,000 inhabitants over time (left y-axis) and bar graph showing the change in the yearly PE fatality rates (right y-axis) in the period from January 2008 through December 2020 in Brazil. Source: Hospital Information System (SIH) of the Brazilian Unified Health System (SUS) Information Technology Department. (B) Comparison of Brazil's annual PE hospitalization rates with other countries in the world. (C) Comparison of Brazil's annual PE fatality rates with other countries in the world. PE: pulmonary embolism; USA: United States of America. Numbers in parentheses indicate the reference number from which the data was retrieved.

hospitalization diagnoses in patients hospitalized due to other medical conditions, such as femur fracture, etc. Nevertheless, even underreporting alone would not explain these lower PE hospitalization rates in Brazil.

In conclusion, as in other countries around the globe, Brazil recorded increased PE hospitalization rates and decreased PE fatality rates over the past decade. However, it is essential to emphasize that the PE hospitalization rates are lower and the PE fatality rates are higher in Brazil than in any other developed country. A significant percentage of PE is probably not diagnosed in Brazil. In addition, this condition may be underreported. Undiagnosed and inadequately treated PE can have numerous future consequences for these patients, such as the development of chronic thromboembolic pulmonary hypertension.

PE is a neglected disease in Brazil. The Brazilian Unified Health System (SUS) needs to incorporate new strategies to improve the diagnosis and promote adequate treatment of this disease in the country. The use of clinical scores (Wells and modified Geneva), rational flowcharts for diagnosis, and risk stratification should be encouraged, allowing for more adequate management and better outcomes. In addition, when indicated, these patients should have access to DOACs since, aside from their more predictable effects, these drugs can be administered at home. In this way, we can increase the diagnosis rate, decrease the fatality rate, and cut down on hospital costs.

REFERENCES

1. Gomes JA, Barros JEB, Nascimento ALOD, Rocha CAO, Almeida JPO, Santana GBA, et al. Hospitalizations for pulmonary embolism in Brazil (2008-2019): an ecological and time series study. J Bras Pneumol. 2022;48(3):e20210434. https://doi.org/10.36416/1806-3756/e20210434.
2. Konstantinides SV, Barco S, Lankeit M, Meyer G. Management of Pulmonary Embolism: An Update. J Am Coll Cardiol. 2016;67(8):976-90. https://doi.org/10.1016/j.jacc.2015.11.061.
3. Wiener RS, Schwartz LM, Woloshin S. Time trends in pulmonary embolism in the United States: evidence of overdiagnosis. Arch Intern Med. 2011;171(9):831-7. https://doi.org/10.1001/archinternmed.2011.178.
4. de Miguel-Díez J, Jiménez-García R, Jiménez D, Monreal M, Guijarro R, Otero R, et al. Trends in hospital admissions for pulmonary embolism in Spain from 2002 to 2011. Eur Respir J. 2014;44(4):942-50. https://doi.org/10.1183/09031936.00194213.
5. Dentali F, Ageno W, Pomero F, Fenoglio L, Squizzato A, Bonzini M. Time trends and case fatality rate of in-hospital treated pulmonary embolism during 11 years of observation in Northwestern Italy. Thromb Haemost. 2016;115(2):399-405. https://doi.org/10.1160/TH15-02-0172.
6. Shiraev TP, Omari A, Rushworth RL. Trends in pulmonary embolism morbidity and mortality in Australia. Thromb Res. 2013;132(1):19-25. https://doi.org/10.1016/j.thromres.2013.04.032.
7. Tsai J, Grosse SD, Grant AM, Hooper WC, Atrash HK. Trends in in-hospital deaths among hospitalizations with pulmonary embolism. Arch Intern Med. 2012;172(12):960-1. https://doi.org/10.1001/archinternmed.2012.198.
8. Agarwal S, Clark D 3rd, Sud K, Jaber WA, Cho L, Menon V. Gender Disparities in Outcomes and Resource Utilization for Acute Pulmonary Embolism Hospitalizations in the United States. Am J Cardiol. 2015;116(8):1270-6. https://doi.org/10.1016/j.amjcard.2015.07.048.
9. Yang Y, Liang L, Zhai Z, He H, Xie W, Peng X, et al. Pulmonary embolism incidence and fatality trends in chinese hospitals from 1997 to 2008: a multicenter registration study. PLoS One. 2011;6(11):e26861. https://doi.org/10.1371/journal.pone.0026861.
10. Barco S, Mahmoudpour SH, Valerio L, Klok FA, Munzel T, Middeldorp S, et al. Trends in mortality related to pulmonary embolism in the European Region, 2000-15: analysis of vital registration data from the WHO Mortality Database. Lancet Respir Med. 2020;8(3):277-287. https://doi.org/10.1016/S2213-2600(19)30354-6.

J Bras Pneumol. 2022;48(4):e20220074
https://dx.doi.org/10.36416/1806-3756/e20220074

Evaluation of thoracic surgery as a treatment approach in patients with rifampin-resistant chronic tuberculous empyema

Xiaogang Zeng[1], Wuyang Yue[2], Sikuan Ye[1], Long Zhang[1], Song Yang[2]

TO THE EDITOR,

Rifampin-resistant chronic tuberculous empyema (RR-CTE) is caused by tuberculous bacilli infection in the pleural space and purulent exudate accumulation. It always develops from the untimely or inappropriate treatment of tuberculous pleurisy. Unfortunately, thick and calcified pleural walls limit the penetration of anti-tuberculosis drugs into the infected empyema space, contributing to the prevalence of drug resistance.[1,2]

When traditional treatment of RR-CTE is ineffective, intensified chemotherapy and surgical intervention should be considered. Surgical interventions assist in disease diagnosis, reduce infection, re-expand the lung, and prevent subsequent chronic respiratory impairments.[2-4] The present study aimed to explore the outcomes and complications of pleural fiberboard decortication.

Preoperative RR-CTE patients were considered eligible if they presented with chronic empyema for > 6 weeks, tolerated surgery, and complied with the anti-tuberculosis program for more than 2 months. Meanwhile, postoperative histopathological examinations from patients who were not eligible were excluded. The postoperative cure standards were as follows: abscess cavity closure, no active lesions in chest computed tomography (CT) scans, lung reexpansion > 80%, and negative etiological examination.

The evaluations included analysis of medical records, surgical treatment, complications, and recurrence rate.

All analyses were conducted using the SPSS 22.0 software. Normally distributed data were analyzed using the T-test. Non-normally distributed data were analyzed using the non-parametric Rank Sum Test (Mann-Whitney Test). Differences and correlations were considered statistically significant when p-values were < 0.05.

In this retrospective observational study, the convenience sample was obtained from the electronic database at the Department of Thoracic Surgery in Chongqing. Given that the medical information of inpatients was recorded necessarily and anonymously by case history, our data analysis could not cause any breach of privacy or present any undue personal risk to the participants. The Ethics Committee of the Chongqing Public Health Medical Center approved this study and waivered informed consent from the patients involved.

A total of 47 patients (male: 33, female: 14), with a median age of 23 years (range 13-55), received surgical treatment from May 1, 2015 to March 31, 2019.

Surgical anesthesia was performed using double-lumen intubation and the intravenous route. In short, the basic operation method consists of open surgery and VATS. If the focus invaded other tissues, they were also resected. After the operation, sufficient drainage (including closed thoracic drainage and negative pressure drainage) and corresponding anti-infection symptomatic treatment were necessary.

Based on the drug sensitivity results, the duration of the anti-tuberculosis regimen was adjusted for 2-14 months before surgery in 9 patients; meanwhile, the duration of the anti-tuberculosis regimen of 38 patients was adjusted for 1-4 months after surgery. Thirty-two patients accepted simple pleural fiberboard stripping, while 15 accepted pleural fiberboard stripping combined with another form of surgery (7 cases of chest wall tuberculosis resection, 4 cases of wedge resection, 2 cases of chest wall tuberculosis resection + lobectomy, 1 case of chest wall tuberculosis resection + partial pneumonectomy + wedge resection, and 1 case of bronchial fistula repair).

All patients were followed up for more than 1 year. Forty-six patients (97.87%) healed with the stage I wound and had negative sputum etiological examination for *Mycobacterium tuberculosis* (Mtb). The symptoms of 45 patients were obviously relieved, with pus cavities completely closed and the lungs reopened. CT examination showed that there was no active pulmonary focus in the postoperative evaluation.

The mean operative time was 220.81 ± 78.32 minutes (range 75-420), with a blood loss of 322.34 ± 261.85 mL (range 50-1000) during surgery. Five patients received blood transfusion during the operation (10.64%), and the transfusion volume was 0.21 ± 0.62 U of red blood cell suspension (range 0-2). The drainage duration was 13.22 ± 7.94 days (range 5-38). Two patients underwent long-term thoracic closed tube drainage (median 17 days, range 10-38) (Table 1).

Five patients had postoperative complications (10.64%): 1 case of atelectasis, 1 case of delayed wound healing, 1 case of continuous air leakage after the operation,

1. Departamento de Cirurgia Torácica, Centro Médico de Saúde Pública de Chongqing, Hospital de Saúde Pública, Universidade do Sudoeste, Chongqing, China.
2. Departamento de Pesquisa em Tuberculose, Centro Médico de Saúde Pública de Chongqing, Hospital de Saúde Pública, Universidade do Sudoeste, Chongqing, China.

Table 1. Short-term postoperative data.

	Median	Range
Operation time (min)	220.81 ± 78.32	75-420
Intraoperative blood loss (mL)	322.34 ± 261.85	50-1000
Transfusion volume (U)	0.21 ± 0.62	0-2
Closed thoracic cavity drainage time (days)	13.22 ± 7.94	5-38
Length of hospitalization (days)	17.99 ± 7.02	10-38

which was finally cured by a second operation after 6 months, and 2 cases of hepatic impairment.

The closed drainage time of empyema complicated with pulmonary tuberculosis (n = 30) was 13.17 days (range 5-37), and the median length of hospitalization was 17.74 days (range 10-38). The closed thoracic cavity drainage time of the extrapulmonary tuberculosis group (n = 17) was 13.31 days (range 6-38), and the length of stay at the hospital was 18.44 days (range 11-38). This group included chest wall TB, spinal TB, ankle TB, and chest wall TB complicated with mammary gland TB. No significant differences were found between the two groups regarding early recurrence (p = 0.06; p = 0.51).

Anti-tuberculosis medication in RR-CTE has not been favorable yet, inducing condition relapse, long courses of treatment, obvious pleural thickening, and complications with other forms of extrapulmonary tuberculosis.[5] Fortunately, surgery for tuberculosis sequelae and the complications had a significant effect. Nowadays, the combination of anti-infective drug treatment and tube thoracostomy/intermittent thoracentesis always shows therapeutic effect in patients with pulmonary, pleural, mediastinal, or thoracic wall involvement, which may promote complete resolution of the thickened visceral parietal pleura and retain the functional capacity of the lung to a great extent.[6-8] In the present study, RR-CTE was common at all ages, a fact that was corroborated by Somenath Kundu and Acharya et al.[9,10]

Surgery would clear the intrathoracic lesion and enable fiberboard excision. Moreover, the normal elasticity of the chest would be restored, lung function would be improved, and the treatment duration shortened. Herein, based on the effective anti-tuberculosis treatment program, the total curative effect was 45 cases, and the cure rate was 95.74%.

In our study, we combined available surgery information on drug-resistant tuberculous pleurisy to estimate its clinical characteristics and therapeutic effect. We found that once the pleural cavity is infected with tuberculosis and develops into chronic empyema, forming irreversible tuberculosis, early surgical intervention should be performed to maximize the possibility of recovery. The advantages of surgery include: the quick obtainment of specimens and enhanced cure rates, clinical symptom relief, and quality of life improvement, facts that should be worthy of widespread clinical application.

Being a retrospective observational study, the reached conclusion may be affected by some selective bias. Prospective randomized controlled trials should be encouraged to further evaluate the long-term efficacy and safety of surgical treatment in RR-CTE.

AUTHOR CONTRIBUTIONS

Sikuan Ye: software and design. LZ: materials or referral of patients. WY and XZ: analysis and writing-review. Song Yang: study conception and design. All authors: drafting and revision of the manuscript and approval of the final version.

CORRESPONDING AUTHOR

Song Yang. Department of Tuberculosis Research, Chongqing Public Health Medical Center, Public Health Hospital, Southwest University, Chongqing, China. Phone: +86-023-65057243. E-mail: yangsong5@aliyun.com.

FINANCIAL SUPPORT

Joint Medical Research Project of Chongqing Science & Technology Commission and Health Commission in 2019 (2019ZDXM035).

REFERENCES

1. Nakajima Y. Surgical Treatment of Pulmonary Tuberculosis [J]. Nihon Geka Gakkai Zasshi, 2004, 105(12):745-50. PMID: 15651475.
2. Iseman MD, Madsen LA. Chronic tuberculous empyema with bronchopleural fistula resulting in treatment failure and progressive drug resistance. Chest. 1991;100(1):124-127. https://doi.org/10.1378/chest.100.1.124.
3. Vencevicius V, Serpytis J, Grazelis E, Gineitis A, Venslovas V, Rudys D. Surgical Approach to Lung Tuberculosis [J]. Medicina (Kaunas). 2004;40 Suppl 1:142-4. Lithuanian. PMID: 15079124.
4. Chen B, Zhang J, Ye Z, Ye M, Ma D, Wang C, et al. Outcomes of Video-Assisted Thoracic Surgical Decortication in 274 Patients with Tuberculous Empyema. Ann Thorac Cardiovasc Surg. 2015;21(3):223-228. https://doi.org/10.5761/atcs.oa.14-00185.
5. Long R, Barrie J, Peloquin CA. Therapeutic drug monitoring and the conservative management of chronic tuberculous empyema: case report and review of the literature. BMC Infect Dis. 2015;15:327. https://doi.org/10.1186/s12879-015-1093-7.
6. Kilani T, Boudaya MS, Zribi H, Ouerghi S, Marghli A, Mestiri T, et al. La chirurgie dans la tuberculose thoracique [Surgery for thoracic tuberculosis]. Rev Pneumol Clin. 2015;71(2-3):140-158. https://doi.org/10.1016/j.pneumo.2014.03.005.

7. Xia Z, Qiao K, Wang H, Ning X, He J. Outcomes after implementing the enhanced recovery after surgery protocol for patients undergoing tuberculous empyema operations. J Thorac Dis. 2017;9(7):2048-2053. https://doi.org/10.21037/jtd.2017.06.90.
8. Elliott AM, Berning SE, Iseman MD, Peloquin CA. Failure of drug penetration and acquisition of drug resistance in chronic tuberculous empyema. Tuber Lung Dis. 1995;76(5):463-467. https://doi.org/10.1016/0962-8479(95)90016-0.
9. Kundu S, Mitra S, Mukherjee S, Das S. Adult thoracic empyema: A comparative analysis of tuberculous and nontuberculous etiology in 75 patients. Lung India. 2010;27(4):196-201. https://doi.org/10.4103/0970-2113.71939.
10. Acharya PR, Shah KV. Empyema thoracis: a clinical study. Ann Thorac Med. 2007;2(1):14-17. https://doi.org/10.4103/1817-1737.30356.

Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression

Anna Kempisty[1], Maria Korzeniewska-Kosela[2]

We read with great interest the article by Dias et al.[1] on the prevalence of latent tuberculosis infection (LTBI) among patients with interstitial lung diseases (ILDs) requiring immunosuppression. We would like to share some comments on using the tuberculin skin test (TST) as the only screening strategy.

There is no gold standard for LTBI detection, and both TST and interferon-gamma release assays (IGRAs) are approved for use in all settings.[2] Dias et al.[1] reported positive TST reactions in only 9.1% of patients, while the estimated prevalence of LTBI for Brazil (a country with intermediate tuberculosis incidence) is 19-20%.[1,3] Possibly, the low infection rate reflects the fact that the participants did not belong to high-risk groups for tuberculosis or that tuberculin reaction may have waned over time. It remains unclear if IGRAs would be a better option. Although IGRAs yield fewer false-negative results than does TST in immunosuppressed and elderly patients, they are less sensitive in detecting remote infections.[4] It is also possible that the disease itself may have suppressed the reaction. In a country with high tuberculosis incidence, most patients with sarcoidosis showed negative TST response, but most patients and controls also tested positive on IGRAs.[5]

Interestingly, a large diameter of tuberculin reaction was noted in TST-positive patients, suggesting recent infection (the main risk factor for active tuberculosis). However, the authors did not include information on risk factors for tuberculosis in the study group.[1] Perhaps tuberculosis preventive treatment (TPT) was required because of a recent contact with a patient with pulmonary tuberculosis. It would be interesting to know IGRA results of TST-positive patients. None of the current diagnostic tests for LTBI have a sufficient predictive value for progression to active tuberculosis, although IGRAs might better identify candidates for TPT among BCG vaccine recipients. Thus, IGRAs might have provided additional data on the actual LTBI prevalence among ILD patients. Moreover, 63 patients were excluded because they either failed to schedule the test or did not return for the reading. This might have been avoided with IGRAs, which require only one visit.[4]

Another important question is whether all ILD patients with LTBI need TPT. Identifying target groups is essential. Glucocorticoids and other immunosuppressants may increase the risk of progression to active tuberculosis. However, screening for LTBI is recommended by the WHO only before anti-TNF therapy.[2] The risk-benefit ratio must be carefully considered.[4] Additional research is needed to evaluate whether patients on specific immunosuppressive drugs would benefit more from TPT than from watchful waiting.

Before TPT, it may be insufficient to exclude active tuberculosis solely based on clinical and radiological signs in patients with ILDs due to abnormalities such as fibrosis or nodules. Histopathologic features may mimic tuberculosis in sarcoidosis and hypersensitivity pneumonia. Thus, microbiological analysis should be performed in all candidates for TPT to avoid misdiagnosis.

Finally, screening for LTBI (preferably with TST) in treatment-naïve ILD patients might provide valuable information. In conclusion, further studies are needed to assess the actual prevalence of LTBI in ILD patients and to identify candidates for TPT.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

AK: conceptualization and drafting of the manuscript. MKK: drafting, editing, and reviewing of the manuscript. Both authors approved the final version of the manuscript.

REFERENCES

1. Dias VL, Storrer KM. Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression. J Bras Pneumol. 2022;48(2):e20210382. https://doi.org/10.36416/1806-3756/e20210382
2. World Health Organization. WHO consolidated guidelines on tuberculosis: tuberculosis preventive treatment: Module 1: prevention. [monograph on the Internet]. Geneva: World Health Organization; 2020 [cited 2022 Apr 28]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK554956/
3. Cohen A, Mathiasen VD, Schön T, Wejse C. The global prevalence of latent tuberculosis: a systematic review and meta-analysis. Eur Respir J. 2019;54(3):1900655. https://doi.org/10.1183/13993003.00655-2019
4. Haas MK, Belknap RW. Diagnostic Tests for Latent Tuberculosis Infection. Clin Chest Med. 2019;40(4):829-837. https://doi.org/10.1016/j.ccm.2019.07.007
5. Gupta D, Kumar S, Aggarwal AN, Verma I, Agarwal R. Interferon gamma release assay (QuantiFERON-TB Gold In Tube) in patients of sarcoidosis from a population with high prevalence of tuberculosis infection. Sarcoidosis Vasc Diffuse Lung Dis. 2011;28(2):95-101.

1. First Department of Lung Diseases, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland.
2. Department of Tuberculosis Epidemiology and Surveillance, National Tuberculosis and Lung Diseases Research Institute, Warsaw, Poland.

ISSN 1806-3756

Authors' reply

Vitor Loureiro Dias[1], Karin Mueller Storrer[1]

We would like to address some questions that were raised about our recently published study on the prevalence of latent tuberculosis infection (LTBI) in patients with interstitial lung diseases (ILDs) requiring immunosuppression.[1]

The prevalence of LTBI in our sample (9.1%) was indeed lower than that estimated for the world population (about 25%). It should be noted, though, that Kussen et al.[2] reported a similar prevalence (9.0%) in people living with HIV, a known high-risk group, in a study that also took place in the state of Paraná, Brazil, where our center is located, which might reflect a different scenario of infection by *Mycobacterium tuberculosis* in our region.

As for the use of tuberculin skin test (TST) as a screening method, we considered it a plausible choice, given that there is no consensus on a preferred method for immunocompromised patients.[3] Interferon-gamma release assays could be a reasonable choice for these patients, especially when the TST is negative; however, despite having recently been incorporated into the Brazilian public health care system, they are not available for patients with ILDs requiring immunosuppression.

Regarding risk factors for tuberculosis, we excluded patients with high-risk factors, such as those living with HIV, and we found that the frequency of positive TST results was not significantly higher in those with a history of smoking or diabetes. Nevertheless, we acknowledge that other variables associated with a higher risk of tuberculosis, such as recent contact with someone with the disease, were not addressed in our study. Moreover, we reinforce that patients with a positive TST result underwent not only clinical and radiological evaluation for active tuberculosis, but also microbiological evaluation whenever possible.

Finally, the lack of consensus on the need to treat LTBI in patients on immunosuppressants other than TNF inhibitors could be justified by the fact that the literature on the subject is scarce.

In conclusion, we agree that more studies are needed to determine the prevalence of LTBI in patients with ILDs effectively and to decide whether these patients should be prescribed preventive treatment. However, our study definitely marks a starting point to answering these important questions.

REFERENCES

1. Dias VL, Storrer KM. Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression. J Bras Pneumol. 2022;48(2):e20210382. https://doi.org/10.36416/1806-3756/e20210382
2. Kussen GM, Dalla-Costa LM, Rossoni A, Raboni SM. Interferon-gamma release assay versus tuberculin skin test for latent tuberculosis infection among HIV patients in Brazil. Braz J Infect Dis. 2016;20(1):69-75. https://doi.org/10.1016/j.bjid.2015.10.007
3. Hasan T, Au E, Chen S, Tong A, Wong G. Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines. BMJ Open. 2018;8(9):e022445. https://doi.org/10.1136/bmjopen-2018-022445

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

Manuscript: Understanding diagnostic tests. Part 1.

Publication: J Bras Pneumol. 2022;43(5):330

DOI: http://dx.doi.org/10.1590/S1806-37562017000000330

On page 330 of the original publication, in Table 1, last line of the text, where is written
Specificity (dark grey column) = b/(b + d)

Should be read
Specificity (dark grey column) = d/(b + d)

ISSN 1806-3756

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

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