ISSN (ON-LINE): 1806-3756

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 48, Number 1
January | February
2022

Volume 48, Number 1 January | February 2022

HIGHLIGHT

Use of remdesivir in COVID-19

Incidental findings during screening for lung cancer

Prognostic factors of sarcoidosis in Brazil

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.

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ISSN (ON-LINE): 1806-3756

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 1, January/February 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:
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ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 1, January/February 2022

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ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 48, n. 1, January/February 2022

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J Bras Pneumol. 2022;48(1):e20220023
https://dx.doi.org/10.36416/1806-3756/e20220023

Towards a new definition of non-cystic fibrosis bronchiectasis

Miguel Ángel Martinez-Garcia[1,2], Grace Oscullo[1], Alberto Garcia-Ortega[1]

One of the most obvious peculiarities of bronchiectasis is that it is an enormously heterogeneous disease in its presentation and evolution,[1] as well as being complex in nature in terms of both phenotype[2] and endotype.[3] This is probably due, at least in part, to the fact that dozens of different pulmonary and extra-pulmonary etiologies[4] are capable of causing irreversible damage to the bronchial wall and the variable pulmonary and systemic clinical picture,[5,6] including exacerbations,[7,8] that characterizes this disease.

Since the 1990s, High-resolution CT (HRCT) scan has been the gold standard in the diagnosis of bronchiectasis and a series of radiological diagnostic criteria have been established. These criteria have been used to this day, in both clinical practice and trials, and basically include the following: an increase in the diameter of the bronchial lumen relative to that of the adjacent vessel—this is the most widely used criterion (a broncho-arterial ratio > 1); lack of bronchial tapering; and the presence of dilated bronchi adjacent to the pleura.[9] However, the increasing use of HRCT and improved interpretation of HRCT images have also revealed several additional problems. First, dilated bronchi with a broncho-arterial ratio ≥ 1 may be found in up to 20% of individuals older than 70 years of age with no comorbidities or respiratory symptoms,[10] and something similar seems to be found in individuals living at high altitude. Second, some interstitial or post-infectious diseases (probably including bronchiectasis following COVID-19 pneumonia) as well as diseases with an emphysematous component may also be associated with areas of traction bronchiectasis and little or no clinical component.[11] Third, as a consequence of the variation in the diameter of the vessels adjacent to the bronchus in patients with chronic pulmonary diseases, bronchiectasis may be either underdiagnosed (due to an increase in vessel diameter in patients with pulmonary hypertension) or overdiagnosed (in patients with hypoxic vasoconstriction).[12] Fourth, the visualization and quantification of the thickening of the bronchial wall (a reflection of the underlying inflammatory process of the airways), with a subsequent increase in the diameter of the bronchus, has been constantly improving. Finally, on top of all that, there have been disparities in the radiological interpretation of images, depending on the readers and the specialist skills available at a given centre.

Obviously, the aforementioned issues undoubtedly have an impact on both the daily clinical management of such individuals and the homogeneity of their inclusion in clinical trials, the results of which, to a great extent, will be included in guidelines for clinical practice.

Accordingly, a large group of experts (including both clinicians and radiologists) from all over the world have recently come together to agree on a definition of bronchiectasis that is based on a combined radiological and clinical perspective. Although this definition may vary over time, it does ensure homogeneity of diagnosis for both clinical and research purposes.[13]

Perhaps the key point of this agreed definition is the assertion that the diagnosis of bronchiectasis must include both radiological and clinical factors. This reflects the fact that the so-called "asymptomatic radiological bronchiectasis", which usually includes the bronchiectasis observed in healthy individuals or in fibrotic lung diseases, does not have any clear meaning and does not require, for the moment, any type of therapeutic approach.[13]

The criteria established from a radiological perspective are similar to those that are already well known, with the most relevant change probably being the addition of the thickness of the bronchial wall to the diameter measurement. Accordingly, a broncho-arterial ratio of the inner diameter (only the diameter of the bronchial lumen) and the outer diameter (the diameter of the bronchial lumen plus the thickness of the bronchial wall) ≥ 1 can be considered bronchiectasis if it is accompanied by related symptoms. In any case, from a purely radiological point of view, the greatest diagnostic certainty has been set at a broncho-arterial ratio ≥ 1.5, in an attempt to avoid as much as possible small bronchial dilatations in healthy subjects (although, from a clinical point of view, those are not usually active). From a scientific perspective, centralized reading of the images is recommended.[13]

There are greater discrepancies in clinical criteria, since there are no characteristic, easily recognizable symptoms attributable to bronchiectasis. Assuming this limitation, the presence of at least two of the following symptoms or signs has been established as a criterion: a cough most days of the week, sputum production most days of the week, and a history of exacerbations. In any case, a series of considerations are necessary in this regard. First, the aforementioned agreed definition has a fundamentally scientific purpose, i.e., its application is recommended above all for the homogenization of the type of patient who is suitable for inclusion in a clinical trial. Although the parameters can be used in a clinical setting, cases need to be individualized, since patients may present with other symptoms or signs related to radiologically relevant bronchiectasis, and these symptoms or signs may be modified by treatment. Second, the symptoms described must be attributable to bronchiectasis, so it is important to make every effort to identify both the

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possible etiologies of bronchiectasis and the lung diseases frequently associated with it, such as COPD and asthma. Third, with time and increasing knowledge of bronchiectasis, changes may occur in the clinical interpretation of this disease and the relative impact of each symptom on the patient.[13]

In short, it is very important to be able to find homogeneity in heterogeneity, and few lung diseases are more heterogeneous than bronchiectasis. This point is absolutely essential when comparing the results of clinical trials that will be the basis for guidelines that will inform diagnostic and therapeutic actions for most of our patients in clinical practice. However, we must not lose the perspective of common sense and of our own experience, and we must be aware that each patient has a unique clinical phenotype and should be treated on an individualized basis.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20220012
https://dx.doi.org/10.36416/1806-3756/e20220012

The ability to predict the clinical course of pulmonary sarcoidosis from data that is right in front of us

Marc A. Judson[1]

The natural course of sarcoidosis is highly variable. It is a disease that may never lead to symptoms or functional impairment. However, sarcoidosis may cause distressing symptoms that greatly impair quality of life. Sarcoidosis may also lead to significant organ dysfunction that may incapacitate patients and lead to death. The majority of poor outcomes from sarcoidosis relate to the development of pulmonary fibrosis[1] and specific organ involvement (heart and central nervous system).[2] In addition, even chronic, well-controlled disease is often debilitating because of the need for chronic corticosteroid therapy and its resultant complications.[3]

This wide variation in sarcoidosis outcomes creates problems for the caregiver treating patients newly diagnosed with the disease. The clinician wants to avoid overaggressive treatment of inconsequential cases as well as adequately treat cases destined for a poor outcome. Clearly, sarcoidosis patient care could be improved by the construction of reliable prognostic tools. However, at the present time, such tools are lacking including reliable screening algorithms for cardiac sarcoidosis[4] and reliable biomarkers for the development of pulmonary fibrosis.[5] Proposed prognostic biomarkers for sarcoidosis include imaging studies and technical genetic, proteomic, or immunologic tests, as well as gene transcription tests, that are all unproven and unavailable in most parts of the world.[5,6]

In this issue of the Brazilian Journal of Pulmonology, Castro et al.[7] performed a longitudinal retrospective analysis of the clinical presentation and the results of routine medical tests in 200 pulmonary sarcoidosis patients treated at three Brazilian medical centers. These authors recorded patient demographics, symptom onset, date of diagnosis, routine chest imaging results, and sarcoidosis organ involvement. All these clinical data are standard, and a clinician should obtain them in the routine management of a sarcoidosis patient. These authors[7] then analyzed the association of these clinical data with the sarcoidosis outcome of self-limited disease versus persistent disease at two years. The authors performed this analysis on the 160 non-fibrotic patients, as those with fibrotic disease would be expected to have chronic pulmonary symptoms and frequently require treatment, although this is not always the case. In a multivariate analysis, the following clinical features were statistically associated with persistent disease in non-fibrotic pulmonary sarcoidosis patients: reduced FVC, the presence of dyspnea, parenchymal lung involvement on radiographic imaging, involvement of ≥ 2 non-thoracic organs with sarcoidosis, and a delay in the diagnosis of sarcoidosis of > 12 months after symptom onset. The authors went on to construct a scoring system based on weighing these factors that was able to discriminate the likelihood of persistent disease at two years after diagnosis between 13% (low score) and 82% (high score).

This analysis has several problems and limitations. First, many of the factors that were found to be associated with poor sarcoidosis outcomes were not novel and had been identified in previous studies. These include symptoms versus no symptoms,[8] parenchymal disease versus no parenchymal disease,[9] extrapulmonary disease,[9] and reduced FVC.[10] Second, the results may not be generalizable to other populations living where there is a low prevalence of tuberculosis. Tuberculosis is not only a very common granulomatous lung disease in Brazil, but a misdiagnosis of tuberculosis as sarcoidosis may result in inappropriate corticosteroid treatment with disastrous consequences. Therefore, despite the association of a delayed diagnosis of sarcoidosis and persistent disease at two years, it may be prudent to delay the diagnosis and treatment of sarcoidosis in areas of high tuberculosis prevalence to ensure that the latter disease is clearly excluded. In other words, a rapid diagnosis of sarcoidosis may improve sarcoidosis outcomes, but it is unclear what consequences may result from the misdiagnosis of tuberculosis as sarcoidosis, especially in areas with a high frequency of tuberculosis. Finally, a rapid diagnosis of sarcoidosis may have been associated with a good prognosis simply because physicians who are knowledgeable in the management of sarcoidosis may establish the diagnosis more rapidly.

Despite these issues, these researchers[7] should be commended for performing this analysis. Even though many of the factors that these authors identified as associated with the prognosis of pulmonary sarcoidosis have been known, they are often not appreciated by the clinician. In addition, these prognostic factors involve routine clinical tests that should be available. We await accurate and more reliable biomarkers to clearly distinguish the clinical course of pulmonary sarcoidosis. However, in the meantime, the clinician should use all the tools that are currently available. The prognostic utility of this scoring system is accurate enough to give the pulmonary sarcoidosis patient a reasonable estimate of a long-term outcome and give the physician a framework of how aggressively to monitor and treat these patients.

CONFLICT OF INTEREST

MAJ has received grant support from Mallinckrodt, Foundation for Sarcoidosis Research. He is a consultant for Star Therapeutics, Xentria, and Riovant.

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J Bras Pneumol. 2022;48(1):e20220046
https://dx.doi.org/10.36416/1806-3756/e20220046

Something not so new for lymphangioleiomyomatosis: is VEGF-D a glass half empty or half full?

Alexandre Franco Amaral[1], Carlos Roberto Ribeiro Carvalho[1], Bruno Guedes Baldi[1,2,3]

An isolated lung cyst on an HRCT scan of the chest is usually just an incidental finding with no relevant clinical significance[1]; however, one only needs to find a few more cysts for it to become a real diagnostic puzzle. HRCT, alongside a thorough clinical assessment, is actually an essential first-step tool for trying to narrow down the broad range of differential diagnoses, but in several patients with diffuse cystic lung disease (DCLD) a definitive diagnosis still cannot be achieved without further investigation.[2]

Lymphangioleiomyomatosis (LAM) is a rare low-grade neoplastic disease that mainly affects women of reproductive age in its sporadic form or associated with tuberous sclerosis complex. LAM is characterized by diffuse small regular well-defined thin lung cysts on HRCT, and imaging has become an essential modality in the diagnosis of the disease. Nonetheless, the diagnosis of LAM can only be established in the presence of extrathoracic accompanying features, otherwise it may require histopathological confirmation.[3] Even when a "typical" tomographic presentation of LAM could be considered, alternative and less common diagnoses, such as bronchiolitis, have been proven to be possible.[4]

Serum VEGF-D quantification has emerged as a potential diagnostic tool with great specificity and reasonable sensitivity to differentiate LAM from other DCLD and from healthy controls.[5-7] Additionally, since the first prospective assessment of VEGF-D, it has been shown to carry prognostic information and to be useful as a biomarker of disease severity and treatment response.[7-9] An important implication of elevated VEGF-D concentrations in the approach of DCLD is to obviate the need for lung biopsy, which has led the American Thoracic Society/Japanese Respiratory Society in their clinical practice guidelines,[10] despite their moderate confidence, to strongly recommend the use of this biomarker as a diagnostic tool in suspected LAM before tissue sampling. Well, the matter seems to be settled then—but it is not all roses.

First, the optimal threshold of serum VEGF-D level is yet to be determined. Currently, a cutoff value ≥ 800 pg/mL has high specificity and is recommended as a diagnostic parameter for LAM, but median values are extremely variable, and using this threshold to discriminate LAM patients from non-LAM patients lacks sensitivity: it might leave almost half of truly LAM patients with a false-negative result.[6] Our group[7] has also described a cohort of Brazilian patients with LAM with serum VEGF-D concentrations somewhat lower than those in previous reports.[5,6] Although such variations in VEGF-D levels might be attributable to true differences in intrinsic population characteristics, they may also be partially explained by discrepancies in laboratory analysis, such as sample collection, storage, and processing; time from diagnosis; and other individual patient features, such as lymphatic involvement, which is associated with higher VEGF-D levels.[7] Greater disease severity and faster disease progression associated with elevated baseline VEGF-D levels have been shown in some studies, but these findings could not be replicated in others.[3] Furthermore, treatment with sirolimus may lead to a decrease in serum VEGF-D levels,[8] but the magnitude of decline is not well correlated with functional improvement.[11]

In this issue of the *Jornal Brasileiro de Pneumologia*, Li et al.[12] shed additional light on the matter. The authors have conducted a rigorous systematic review and meta-analysis of VEGF-D diagnostic performance for LAM. Ten studies conducted between 2009 and 2019 were included in the meta-analysis, yielding a total of almost one thousand individuals, a number probably unachievable otherwise in the setting of a rare disease. The findings might sound expected, but are yet somehow reassuring. The study showed an excellent diagnostic performance of VEGF-D with great overall accuracy, including an AUC of 0.98. No effect on the adopted threshold, control group composition, or site location was observed, inferring reasonable generalizability of the findings. However, the quality of the results was considered low based on the GRADE system, mainly due to a high risk of bias and heterogeneity among the studies. Also, although specificity barely reached unity, sensitivity was lower and showed greater variability, with a wider confidence interval.

Such news might not be new, since VEGF-D has already been recommended as a standard diagnostic tool, but by revisiting established concepts with the addition of fresh evidence, especially in the setting of conflicting findings, doubts regarding optimal values and the extent of the conclusions drawn from previous work are definitely very welcome.

The study by Li et al.[12] confirmed the utility of VEGF-D as a biomarker to avoid an invasive procedure in several patients with LAM and ratified an albeit conservative cutoff value of 800 pg/mL as the greatest possible accuracy within variability. The direct clinical implication of such a safe intervention justifies the fact that the authors[12]

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have strongly recommended the use of serum VEGF-D quantification in the suspicion of LAM. On the other hand, the study reinforces that, even with the determination of serum VEGF-D levels, a number of patients will still need to undergo lung biopsy to confirm the diagnosis of LAM. The incorporation of VEGF-D in clinical practice is also far from feasible for most health care professionals, since wide availability and access to standardized testing with controlled quality are yet to be within reach, even in referral centers.[3]

Finally, the role of serum VEGF-D in the diagnosis of LAM seems to be well established, with its strengths and weaknesses corroborated by that study.[12] After all, is VEGF-D still the best diagnostic method for the approach of patients with suspected LAM without other confirmatory clinical and tomographic features? The answer is yes, but there are relevant limitations and issues that still need to be addressed. That is, the glass remains half full or half empty. Therefore, the assessment of emerging biomarkers in serum or in BAL fluid, perhaps in combination with VEGF-D, is warranted and should be further explored in the approach of LAM and other DCLD as an aid to diagnosis, prognosis, and treatment response.

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J Bras Pneumol. 2022;48(1):e20220005
https://dx.doi.org/10.36416/1806-3756/e20220005

ELMO: an innovative interface for noninvasive ventilation

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During the COVID-19 pandemic, many patients were admitted to ICUs due to acute hypoxemic respiratory failure (AHRF) and required either noninvasive or invasive ventilatory support. The mortality rate of those patients was high in many regions.[1,2] Patients with severe disease, ICU overburden, and lack of equipment, including ventilators capable of offering safe and efficient mechanical ventilation, might have contributed to excessive mortality.[3]

In this scenario, a multidisciplinary task force in the state of Ceará, Brazil, developed a new interface for applying noninvasive ventilation (NIV). It has been designated ELMO. The results of a preliminary study that assessed feasibility, acute response, and adverse effects of the use of ELMO are published in this issue of the Brazilian Journal of Pulmonology.[4]

ELMO is a helmet-type interface that allows the application of CPAP = 8-15 cmH_2O, with a FIO_2 up to 100%. Positive pressure is generated by two compressed air flow meters (up to 30 L/min each) and a PEEP valve coupled to an air outlet. A total gas flow higher than 40 L/min is sufficient to avoid CO_2 rebreathing.[4] ELMO allows applying NIV without a ventilator, which is a significant advantage, especially during the COVID-19 pandemic, when the number of available ventilators was not nearly enough in some regions.[5]

The results of this preliminary study showed that applying CPAP with ELMO (ELMOcpap) is feasible. Only one patient out of ten (10%) did not tolerate ELMOcpap and used it for less than 40 min. The median number of days using ELMOcpap was 2 (IQR: 1-5 days), with a median of 310 min of daily use (IQR: 60-1,230 min). During ELMOcpap use, patients remained comfortable, and neither sedatives nor analgesics were needed. ELMOcpap was associated with increases in PaO_2, SaO_2, and PaO_2/FiO_2, as well as with Borg dyspnea score reduction. CO_2 rebreathing was not detected. Only mild side effects were observed: cough, dry mouth, eye irritation, regurgitation, and cervical/armpit discomfort.[4] The success rate of ELMOcpap was 60%, a result that is similar to those found in other studies that applied NIV in patients with AHRF due to COVID-19.[6] Four patients failed: one did not tolerate the interface and received conventional oxygen therapy, and three had their respiratory condition worsened and were intubated. Among these three patients, two died.[4]

The efficacy of helmet NIV in AHRF has previously been demonstrated in a network meta-analysis that included randomized clinical trials that compared high-flow nasal oxygen (HFNO), face mask NIV, helmet NIV, and standard oxygen therapy.[7] Those authors showed that NIV applied with helmet was associated with a lower risk of tracheal intubation and death when compared with the other three options. The following factors might explain the better results with helmet NIV: 1. better tolerance for helmet interface minimizes interruptions in therapy and may increase its effectiveness; and 2. helmet interface decreases leaks and may be more effective in delivering higher levels of PEEP, increasing alveolar recruitment and oxygenation.[8] The ELMO interface was well tolerated and allowed the application of PEEP levels from 8 to 12 cmH_2O, showing that it can be effective in treating AHRF.[4] However, those results are preliminary, and further studies are necessary to determine the actual role of ELMOcpap in treating AHRF.

In patients with AHRF due to COVID-19 in particular, the effectiveness of treatment with helmet NIV has been demonstrated. A randomized clinical trial[9] that included patients with COVID-19 with moderate to severe AHRF (PaO_2/FIO_2 < 200 mmHg) showed that treatment with helmet NIV, when compared with HFNO, improved oxygenation, reduced dyspnea, reduced the rate of endotracheal intubation (OR = 0.41; 95% CI: 0.18-0.89; p = 0.03), and increased the number of days free from invasive mechanical ventilation at 28 days: median = 28 days (IQR: 13-28 days) vs. 25 days (IQR: 4-28 days); p = 0.04. Despite these better outcomes, helmet NIV neither reduced ICU mortality nor hospital mortality when compared with HFNO.[9]

An important limitation of NIV in patients with AHRF is the mortality rate among those who failed and were intubated, which is usually higher than those who are intubated without previously receiving NIV.[8,10] In line with those findings, in that study,[4] among the four patients who failed NIV treatment, two died (50%). The main hypothesis to explain the higher mortality in patients who are intubated after receiving NIV first is the delay in intubation. This delay might be associated with cardiac ischemic events, respiratory muscle fatigue, and complications of emergency intubation, which are factors that can worsen patient outcomes.[8,10] To reduce NIV failure rates, studies to identify high risk patients and to establish objective parameters to indicate intubation are needed.

Innovative initiatives capable of effectively and safely increasing the treatment of critically ill patients are extremely important and, in Brazil, are still few and far between. Therefore, the remarkable development of ELMOcpap should be regarded as an example of how to face an adverse and catastrophic event, the COVID-19 pandemic, in a creative and ingenious way.

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AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20220058
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Prescription is not enough: the importance of adherence to pharmacological treatment of COPD

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COPD is a chronic and progressive disease characterized by persistent respiratory symptoms and reduction in airflow, secondary to an abnormal inflammatory response of the lungs to the inhalation of noxious particles or toxic gases, and influenced by host factors including abnormal lung development and genetic susceptibility. In addition to affecting the lungs, COPD is also accompanied by systemic manifestations that have a serious impact on the quality of life and survival of patients.[1]

Data on COPD prevalence vary widely due to differences in survey methods and diagnostic criteria. Despite the complexities, data are emerging that enable more accurate estimates of COPD prevalence. The Latin American Project for the Investigation of Obstructive Lung Disease (PLATINO)[2] investigated the prevalence of post-bronchodilator airflow limitation among individuals > 40 years of age living in five Latin American countries. The prevalences ranged from 7.8% in Mexico City (Mexico) to 19.7% in Montevideo (Uruguay).[2]

According to the WHO,[3] COPD is the third leading cause of death in the world, and 80% of these deaths occur in low- and middle-income countries. COPD represents a considerable human burden due to its high prevalence, morbidity, and mortality, creating a formidable challenge for health care systems.[3,4]

Patients with COPD usually present with respiratory symptoms, comorbidities, decline in lung function, and episodes of acute exacerbation. The severity and frequency of exacerbations are strongly correlated with patient prognosis. Patients with a higher frequency of exacerbations have an accelerated decline in lung function, poor health-related quality of life, and increased mortality. The management of the disease requires early diagnosis, removal of risk factors, as well as pharmacological and nonpharmacological treatments.[1,4]

Pharmacological therapy for stable COPD includes inhaled long-acting bronchodilators (long-acting muscarinic antagonists and long-acting β_2 agonists) that can be used individually or in combination with inhaled corticosteroids as dual or triple therapy. Increasing evidence from randomized controlled trials suggests that pharmacological treatments may have meaningful benefits on a range of endpoints including dyspnea, health-related quality of life, frequency of exacerbations, and mortality.[5-7]

In this issue of the Brazilian Journal of Pulmonology, Moreira et al.[8] have reported an association between nonadherence to pharmacological treatment and overall mortality among patients with COPD monitored at a public disease management program from the Brazilian public health care system. They observed, among moderate-to-severe COPD patients, an overall adherence rate of 87.2%. Using an adjusted Cox regression model, the investigators observed that the chance of mortality was almost two times greater in nonadherent patients.

The authors recognize that they used an indirect method to assess treatment adherence. However, it is important to note that there is no gold standard method to assess adherence to inhaled medications.[9] One of the most accurate method is directly observed administration, but this is largely impractical in the setting of clinical practice and research protocols.

The increasing advances in medicine result in benefits for human health, although the costs are also increasing and often reach an economically unsustainable point. Therefore, it is important that resources are used efficiently to benefit as many patients as possible.

Guidelines for the treatment of COPD and other diseases are primarily based on evidence gathered from randomized controlled trials that assess the efficacy of drugs.[1] However, evidence gathered from real-life observational studies that assess effectiveness is also important. Nonadherence is pointed out as an important contributor to reduce effectiveness.

Nonadherence to COPD treatment can be primary, when the patient does not follow the prescription, or secondary, when the medication is not used in the recommended dose or the inhalation device is used incorrectly. Both primary and secondary types of nonadherence contribute to reducing the effectiveness of treatment.[9,10]

Several factors are identified as modifiers of the level of adherence, including those related to the drugs and those related to the patient. The quality of communication between prescribers and patients influences the level of adherence to treatment. Good quality communication with information about the disease, drugs, and device use techniques can improve primary and secondary adherence.[9,10]

The route of administration can also influence adherence. Overall, oral drugs have higher adherence rates than do inhaled drugs of the same class. This is particularly a problem for patients with asthma or COPD, since the use of inhaled medications is desirable because of the lower incidence of side effects. Errors in the inhalation technique are common and interfere with the proper administration of the drug.[9,10]

The Brazilian public health care system provides access to inhaled medications, free of charge, for COPD patients in order to reduce the heavy social and economic burden of the disease.

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We consider that the results in the study by Moreira et al.[8] are highly important to alert physicians and health care managers to the need of assessing the level of primary and secondary adherence and to implement actions aimed at increasing the effectiveness of treatment and efficiency of health care.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICT OF INTEREST

None declared.

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Peribronchovascular thickening

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A 48-year-old male was admitted with a five-month history of dry cough, followed by dyspnea on exertion and a 4-kg weight loss. A CT scan of the chest showed diffuse peribronchovascular thickening (Figure 1).

Predominant peribronchovascular distribution represents an identifiable pattern on CT, having as causes disorders related to the airways, pulmonary arteries, and lymphatic vessels in central or axial interstitium.

The bronchi and pulmonary arteries are surrounded and enclosed by a connective tissue sheath called peribronchovascular interstitium (PBVI) that extends from the pulmonary hila to the lung periphery. PBVI thickening can be found in a wide variety of diseases. Its appearance on CT may be smooth, nodular, or irregular, depending on the underlying cause. Many of the diseases that affect PBVI are conditions that have a predilection for lymphatic pathways, such as sarcoidosis, carcinomatous lymphangitis, and lymphoproliferative diseases, especially lymphomas. There are other conditions that mainly affect the PBVI without a predominant perilymphatic distribution, such as hydrostatic pulmonary edema, Wegener's granulomatosis, and organizing pneumonia, among others. In immunodeficient patients, Kaposi's sarcoma should be remembered.[1,2]

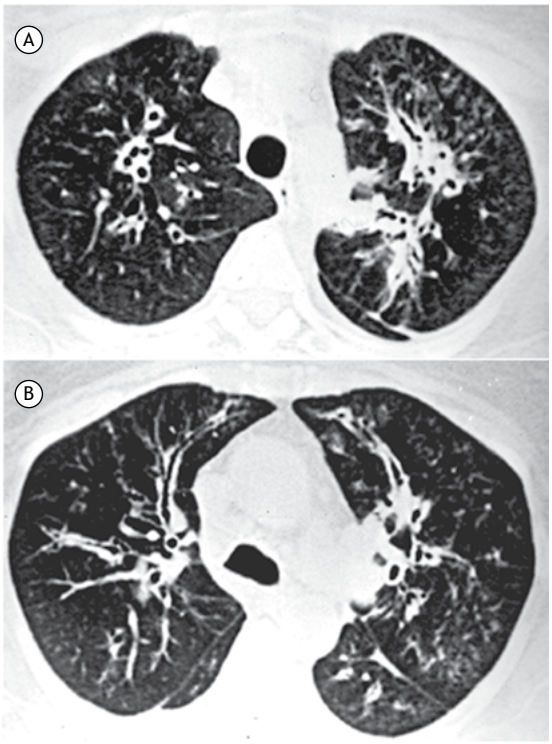

Figure 1. Axial CT scans at the level of the upper lobes showing marked thickening of the peribronchovascular interstitium bilaterally.

The correlation of imaging findings with clinical and laboratory aspects is essential for the correct diagnosis. When peribronchovascular involvement is identified on CT, specific clinical information and associated imaging findings can help narrow down the differential diagnosis. It should be noted that the peribronchovascular distribution of the lesions results in a high proportion of positive results in transbronchial biopsy.

In sarcoidosis, PBVI thickening usually takes on a nodular aspect, determined by the presence of granulomas. It is often accompanied by nodules in other perilymphatic regions, such as pleural surfaces. In carcinomatous lymphangitis, which also has perilymphatic distribution, in addition to subpleural nodules, nodular thickening of interlobular septa is common. The presence of a known primary tumor may help with diagnostic suspicion. In lymphomas, other associated findings, such as consolidations, nodules/masses, or lymph node enlargement, may guide the diagnosis. Organizing pneumonia can be primary or secondary. When secondary, knowledge of previous processes (e.g., infections) can help the diagnosis. In Wegener's granulomatosis, laboratory tests, especially positive antineutrophil cytoplasmic antibody results, guide the diagnosis.[1,2]

Our patient had lymph node enlargement in different chains. A transbronchial biopsy was performed, and the final diagnosis was pulmonary lymphoma.

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Why should noninferiority clinical trials be performed?

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PRACTICAL SCENARIO

A double-blind, randomized, placebo-controlled, noninferiority clinical trial assessed the efficacy of adding five extra days of β-lactam treatment (amoxicillin plus clavulanate) versus placebo after three days of that therapy on clinical cure among clinically stable, moderately severe, community-acquired pneumonia adult patients admitted to 16 hospitals in France.[1] Results showed that 77% of the participants in the placebo group and 68% of the participants in the β-lactam group were considered clinically cured—the between-group difference was 9.4% (95% CI: −0.38 to 20.04). The authors concluded that treatment for three days was noninferior to treatment for eight days, and that these results could lead to important reductions in antibiotic consumption and decrease hospital costs.

NONINFERIORITY TRIALS

Among the types of randomized controlled trials, superiority trials are the most common. However, sometimes it is important to evaluate whether a new intervention is noninferior (equal or not worse) than an existing treatment in terms of efficacy, but exhibits other additional benefits, such as lower costs, fewer side/adverse effects, easier administration, or improved adherence.[2]

In our example, the authors chose a noninferiority clinical trial because their goal was to assess whether a shorter antibiotic regimen was not worse than the standard therapy, within a predefined noninferiority margin (NIM). The NIM is defined as an acceptable clinically difference in efficacy that is a trade-off for other advantages of the new treatment, such as shorter duration in our example. As long as the new treatment is not worse than the standard of care by this margin, the new treatment is considered noninferior.

The NIM is the largest reduction in efficacy of the new treatment compared with the standard of care that is acceptable to the expert community, and can be challenging to establish. If the width of the NIM is too narrow, a clinically acceptable alternative intervention might be considered inferior, and if it is too wide, an inferior intervention might be considered noninferior. Choosing the NIM requires both statistical and clinical consideration, and it is defined a priori and reported in the study protocol. Guidelines recommend defining the NIM based on a comprehensive review of the historical evidence of the efficacy of the current standard of care, which must also be the comparator.

Once the NIM is set (< 10% in our example),[1] the study hypothesis is described. The null hypothesis (H0) states that the between-group difference is larger than

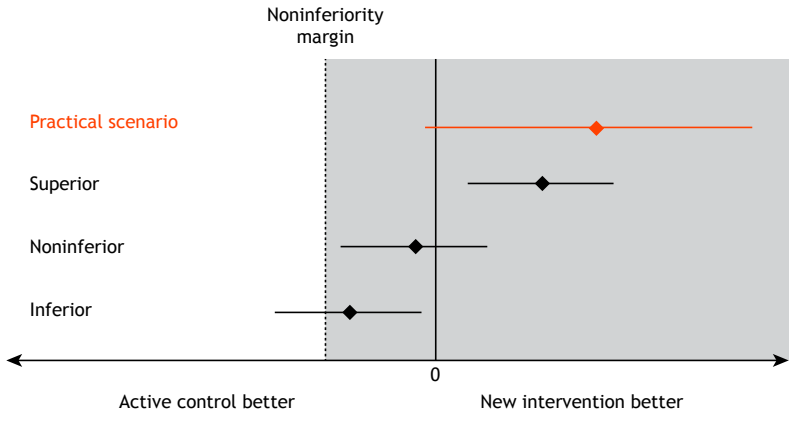

Figure 1. The figure shows possible result scenarios of a noninferiority clinical trial. The mean between-group differences (black circles) and respective 95% CIs (black error bars) for three potential scenarios comparing the new intervention with the active control are shown. The null hypothesis is that the difference between the new intervention and the active control is beyond the noninferiority margin, shown in the shadowed area. In our example (in red)[1], the lower bound of the 95% CI is within the noninferiority margin; therefore, the null hypothesis is rejected and noninferiority can be claimed.

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ISSN 1806-3756

the noninferiority margin (i.e., the new intervention is inferior) and the alternative hypothesis (H1) is that the between-group difference is smaller than the noninferiority margin (i.e., the new intervention is at least not worse). The statistical approach involves calculating the 95% CI of the mean difference (in our example)[1] in efficacy between the groups and evaluating if the lower bound of the 95% CI is greater than the noninferiority margin (Figure 1). The null hypothesis is rejected, and noninferiority can be claimed, when the lower bound of the 95% CI is smaller than this margin.

KEY POINTS

1) A noninferiority trial is the appropriate design to answer a research question when a new intervention is not expected to be superior to the standard of care in terms of efficacy, but it is not unacceptably inferior either, and offers additional advantages.

2) The noninferiority margin is the largest reduction in efficacy of the new treatment compared with the standard of care that is acceptable, so that the new treatment is not "unacceptably worse." This predefined margin should be based on clinical and statistical considerations.

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Breathing too much! Ventilatory inefficiency and exertional dyspnea in pulmonary hypertension

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BACKGROUND

Dyspnea and exercise intolerance are hallmarks of pulmonary hypertension (PH). Extant knowledge in the field has mostly accrued from studies involving patients with pulmonary arterial hypertension.[1] Less is known on the determinants of exertional dyspnea in chronic thromboembolic PH,[2] a much more frequent cause of PH in clinical practice.

OVERVIEW

A non-smoking 29-year-old woman complained of progressive dyspnea — modified Medical Research Council (mMRC) scale score = 4 — after pulmonary thromboembolism with a high clot burden two years earlier. Unremarkable spirometry coexisted with a moderate reduction in DL_{CO} (Figure 1A). Echocardiography unveiled PH, and right heart catheterization confirmed precapillary PH. After a pulmonary CT angiogram demonstrating residual filling defects in the pulmonary arteries to the lower lobes, the patient underwent pulmonary endarterectomy (PEN). Improvement in dyspnea during activities of daily living (mMRC = 1) after surgery was accompanied by a significant increase in DL_{CO} (Figure 1A) and O_2 uptake ($\dot{V}O_2$) at a given work rate (WR) and at peak exercise (Figure 1B). A decrease in ventilation ($\dot{V}E$) requirements for a given CO_2 output ($\dot{V}CO_2$) from the start of exercise, together with a delayed respiratory compensation point (RCP) to lactic acidosis were associated with lower dyspnea scores throughout exercise (Figure 1C).

In healthy subjects, pulmonary gas exchange efficiency improves during exercise since a lower fraction of VT is wasted in the physiological (anatomical plus alveolar) dead space ($V_{D_{phys}}$). Thus, less $\dot{V}E$ is needed to clear a given amount of CO_2, that is, $\dot{V}E/\dot{V}CO_2$ decreases down to a low minimum (nadir; Figure 1C, Graph 2). If $V_{D_{phys}}$ does not improve as expected (or even increases) (a) and/or the subject hyperventilates dropping $PaCO_2$ (b), $\dot{V}E/\dot{V}CO_2$ increases, bringing shortness of breath.[3] The relative importance of (a) or (b) to increase $\dot{V}E/\dot{V}CO_2$ seems to vary, depending on the location of the occluding clots: whereas proximal, larger-vessel disease markedly increases $V_{D_{phys}}$ since blood flow is reduced over a large portion of the vascular tree (a), increased neurochemical stimulation leading to hyperventilation (b) has a greater contributory role in distal, smaller-vessel disease.[4]

A	Pre PEN	% pred	Post PEN	% pred
FVC, L	3.50	91	3.42	89
FEV_1, L	3.02	94	2.85	88
FEV_1, FVC	0.86		0.83	
DLco, mmol/min/kPa	4.71	51	8.04	88

B	Pre PEN	% pred	Post PEN	% pred
Peak $\dot{V}O_2$, L/min	0.706	42	1.230	74
Peak WR, W	44	29	96	65
$\Delta\dot{V}O_2/\Delta$WR, mL/min/W	5.7	57	9.3	93
Peak SpO_2, %	95		94	

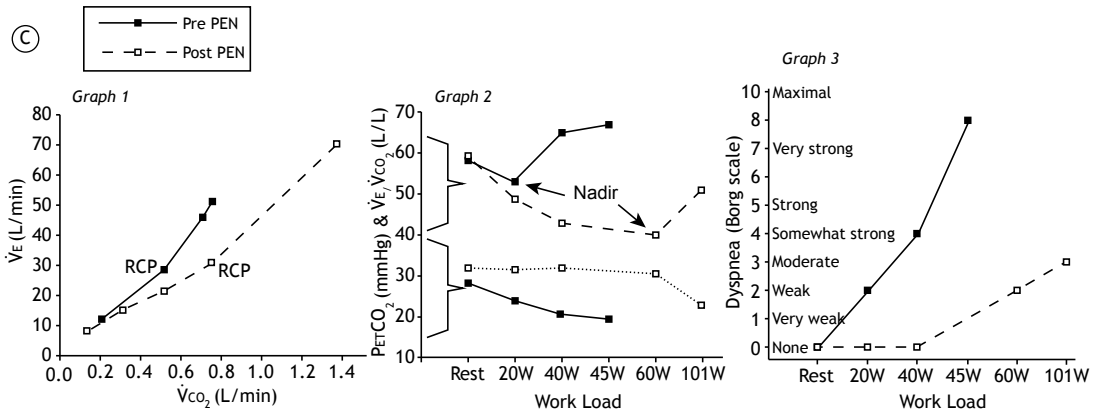

Figure 1. Resting pulmonary function (in A), tabular exercise data (in B), and selected physiologic (and sensory) responses (in C) as a function of exercise intensity before and after pulmonary endarterectomy (PEN) in a 29-year-old woman with chronic thromboembolic pulmonary hypertension. $\dot{V}O_2$: oxygen output; $P_{ET}CO_2$: end-tidal carbon dioxide pressure; $\dot{V}E$: ventilation; RCP: respiratory compensation point; and $\dot{V}CO_2$: carbon dioxide output.

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ISSN 1806-3756

End-tidal P_{CO_2} is characteristically reduced in chronic thromboembolic PH (Figure 1C, Graph 2, bottom) secondary to impaired perfusion of ventilated alveoli decreasing the rate of CO_2 "unloading" from mixed venous blood to alveoli (a) and/or due to alveolar hyperventilation (b).[5] In the current patient, PEN led to a dramatic decrease in the ventilatory requirements during exercise (Figure 1C, Graphs 1 and 2) and enhanced central hemodynamics, leading to higher O_2 delivery to the contracting muscles (higher $\dot{V}O_2$/WR), which delayed the onset of metabolic acidosis (RCP). These factors, together with lower pulmonary vascular pressures, likely contributed to decreased neural drive to breathe. Jointly, these mechanisms explain why the patient required 25 L/min less $\dot{V}E$ to clear 1 L/min $\dot{V}CO_2$ at 45 W ($\dot{V}E/\dot{V}CO_2$ declined from 67 L/L to 42 L/L); consequently, dyspnea intensity decreased from "very intense" to "light" (Figure 1C, Graph 3).

CLINICAL MESSAGE

Lessening the ventilatory requirements for exercise has major beneficial effects on dyspnea in patients with PH. Therapeutic approaches that improve pulmonary gas exchange efficiency and cardiocirculatory function (peripheral O_2 delivery) are poised to reduce breathing discomfort, enhancing exercise tolerance of patients.

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J Bras Pneumol. 2022;48(1):e20210349
https://dx.doi.org/10.36416/1806-3756/e20210349

ELMO, a new helmet interface for CPAP to treat COVID-19-related acute hypoxemic respiratory failure outside the ICU: a feasibility study

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Submitted: 1 September 2021.
Accepted: 28 October 2021.

Study carried out at the Universidade Federal do Ceará, and at Hospital Estadual Leonardo da Vinci, Fortaleza (CE) Brasil.

ABSTRACT

Objective: To assess the feasibility of using a new helmet interface for CPAP, designated ELMO, to treat COVID-19-related acute hypoxemic respiratory failure (AHRF) outside the ICU. **Methods:** This was a proof-of-concept study involving patients with moderate to severe AHRF secondary to COVID-19 admitted to the general ward of a public hospital. The intervention consisted of applying CPAP via the ELMO interface integrated with oxygen and compressed air flow meters (30 L/min each) and a PEEP valve (CPAP levels = 8-10 cmH_2O), forming the ELMOcpap system. The patients were monitored for cardiorespiratory parameters, adverse events, and comfort. **Results:** Ten patients completed the study protocol. The ELMOcpap system was well tolerated, with no relevant adverse effects. Its use was feasible outside the ICU for a prolonged amount of time and was shown to be successful in 60% of the patients. A CPAP of 10 cmH_2O with a total gas flow of 56-60 L/min improved oxygenation after 30-to 60-min ELMOcpap sessions, allowing a significant decrease in estimated FIO_2 ($p = 0.014$) and an increase in estimated PaO_2/FIO_2 ratio ($p = 0.008$) within the first hour without CO_2 rebreathing. **Conclusions:** The use of ELMOcpap has proven to be feasible and effective in delivering high-flow CPAP to patients with COVID-19-related AHRF outside the ICU. There were no major adverse effects, and ELMO was considered comfortable. ELMOcpap sessions significantly improved oxygenation, reducing FIO_2 without CO_2 rebreathing. The overall success rate was 60% in this pilot study, and further clinical trials should be carried out in the future.

(ClinicalTrials.gov identifier: NCT04470258 [http://www.clinicaltrials.gov/])

Keywords: Pneumonia; SARS-CoV-2; COVID-19; Respiratory protective devices; Continuous positive airway pressure; Noninvasive ventilation.

INTRODUCTION

Approximately 15-20% of COVID-19 patients develop severe forms of the disease, including acute hypoxemic respiratory failure (AHRF) and ARDS. These patients need oxygen therapy and ventilatory support, which leads to an increase in the number of admissions to ICUs.[1] The mortality rate for intubated patients has remained very high, reaching up to 80% in those submitted to invasive mechanical ventilation (MV) in Brazil.[2] The increased need to use a mechanical ventilator and to be admitted to an ICU bed puts a strain on health care systems. Regions of the world with scarce resources are at a greater risk of facing a collapse in health care systems due to the high number of patients.[2,3] Brazil currently ranks third in the number of cases, and, until April 18, 2021, the country recorded 371,678 deaths from the disease.[4] Therefore, noninvasive strategies have become increasingly important to avoid intubation in these patients. On the other hand, insistence on noninvasive ventilation (NIV) may delay orotracheal intubation. This fact may worsen the outcomes of patients.[2]

The administration of CPAP through a helmet is safe and ensures minimal contamination of the environment.[5] Furthermore, it improves patient comfort[6] and oxygenation,[7,8] preventing intubation in up to 55.4% of the patients.[9,10]

In the state of Ceará, Brazil, a multidisciplinary task force developed a new helmet-type interface with complete sealing and respiratory isolation of the patient's head, which allows the application of CPAP at 8-15 cmH_2O in association

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Financial support: This study received financial support from the *Escola de Saúde Pública do Ceará, Federação das Indústrias do Estado do Ceará/Serviço Nacional de Aprendizagem Industrial* (FIEC/SENAI), and *Fundação Cearense de Apoio ao Desenvolvimento Científico e Tecnológico* (FUNCAP; Grant no. 03883368/2020). Betina Santos Tomaz is the recipient of a grant from the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Funding Code 001).

ISSN 1806-3756

with the supply of a gas mixture flow containing oxygen and compressed air (CA), designated ELMO (Patent no. BR 20 2020 014212 2; ANVISA 82072609001).[11] As ELMO does not require a mechanical ventilator, it can be used outside ICUs, for instance, in general wards. When tested on volunteers, the device proved to be comfortable and safe, as well as to have good usability by health care professionals. Moreover, it avoided CO_2 rebreathing as long as adequate gas flow (≥ 40L/min) was offered,[11] since this adverse effect is one of the limitations of this type of interface.[12] Figure 1 shows the components of the whole system (ELMOcpap system).

The present study aimed to assess the feasibility of and the acute cardiorespiratory response to (as well as gas exchange parameters, comfort, and adverse effects) using this new helmet device, by offering CPAP and O_2 to patients with COVID-19-related AHRF outside the ICU. The main hypothesis was that the use of ELMO is feasible in a general ward and able to improve hypoxemia with comfort and no relevant adverse effects, thereby being suitable for treating these patients outside the ICU.

METHODS

This prospective cohort study was conducted from June to November of 2020 in the general ward of the Leonardo Da Vinci Hospital, a tertiary hospital with 230 beds that has been a referral center for treating COVID-19 cases during the pandemic in the city of Fortaleza, Brazil. This study was performed in accordance with the Declaration of Helsinki. The study was approved by the Brazilian National Research Ethics Commission and registered at https://clinicaltrials.gov/ (NCT04470258). Written informed consent and authorization for use of images were obtained from all of the patients.

The study protocol and statistical analyses are described in the supplementary material.

RESULTS

Ten patients diagnosed with COVID-19-related AHRF completed the proposed study protocol (Figure 2).

Demographic, anthropometric, and clinical characteristics at baseline (i.e., at hospital admission) are shown in Table 1. Eight participants were men, and the sample was predominantly elderly—median [IQR] = 65 [42-75] years. Four participants presented with normal weight, and six were classified as overweight (n = 3) or class II obesity (n = 3). Severity scores at admission were determined using SOFA and APACHE II (medians of 2 [2-2] and 9 [5-11], respectively; Table 1).

Seven of the participants presented with at least one comorbidity, the most frequent ones being systemic arterial hypertension (in 60%) and diabetes mellitus (in 40%). The most commonly reported initial symptoms were dry cough, dyspnea, and fever (Table 1).

The median day of initiation of ELMOcpap use was day 12 [10-13] after the onset of symptoms. Half of the patients presented with a 75% lung involvement on chest CT performed within 24 h before ELMOcpap initiation (Figure S1).

Arterial blood gas and cardiorespiratory parameters

During the first hour of an ELMOcpap session, eight patients were evaluated regarding arterial blood gas and cardiorespiratory parameters. Patients 7 and 8 were not included in this analysis, because the device had to be removed. Patient 7 reported feeling dyspneic 40 min after starting therapy, and patient 8 presented a worsening of cardiorespiratory parameters, leading to the removal of the device.

Figure 3 shows the acute effects of the ELMOcpap use on arterial blood gas parameters. There was a significant improvement, defined as an increase in all oxygenation parameters (PaO_2, SaO_2, and estimated PaO_2/FIO_2) 30-60 min after starting the ELMOcpap session. This improvement made it possible to reduce

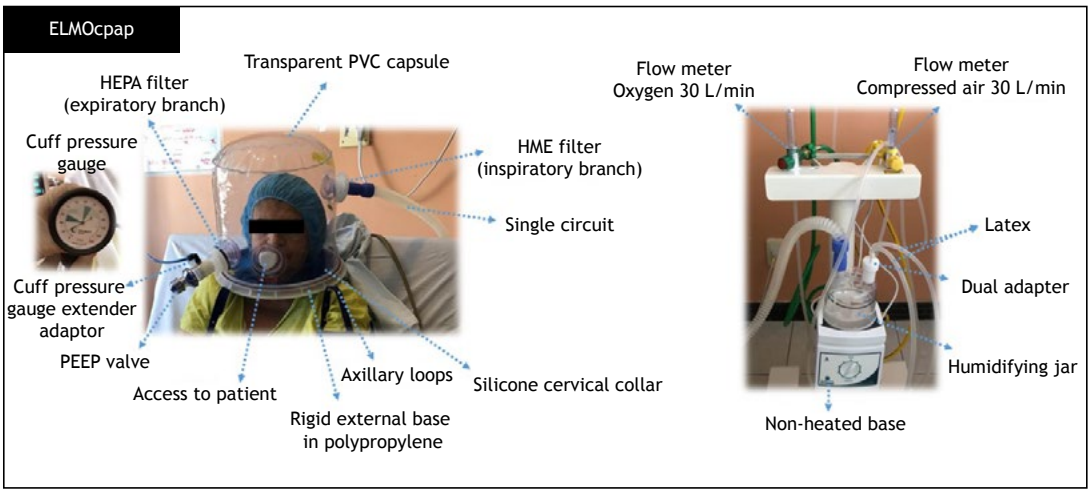

Figure 1. Images showing the components of the ELMOcpap system. HEPA: high-efficiency particulate air; and HME: heat and moisture exchanger.

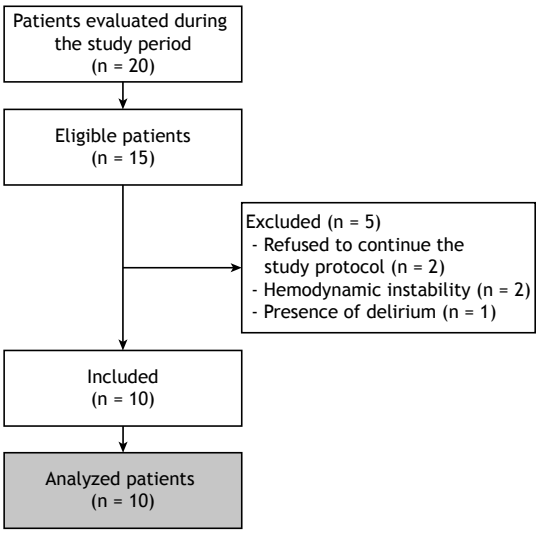

Figure 2. Flow chart of the patient selection process.

the median estimated FIO_2 (0.77 [0.65-0.89] vs. 0.60 [0.49-0.61]; p = 0.014). There was an increment of 72 [50-136] units in estimated PaO_2/FIO_2. In addition, there was a tendency toward a decrease in respiratory alkalosis, which was reflected in arterial blood pH (7.49 [7.49-7.50] vs. 7.47 [7.47-7.49]; p = 0.056; Figure 3).

As for cardiorespiratory parameters prior to and during the ELMOcpap session (30-60 min), there were significant improvements in median SpO_2/FIO_2 ratio (126.0 [105.0-147.5] vs. 164.0 [157.0-204.0]; p = 0.008) and Borg dyspnea score (4.0 [1.5-6.5] vs. 2.0 [0.5-3.5]; p = 0.054), whereas the other parameters remained stable: HR (89.0 [82.5-98.0] vs. 88.0 [76.0-97.5] bpm; p = 0.233); mean arterial pressure (97.0 [86.0-108.0] vs. 93.0 [87.5-107.0] mmHg; p = 0.641); RR (28.5 [24.5-34.0] vs. 26.5 [23.5-32.5] breaths/min; p = 0.866); end-tidal carbon dioxide ($ETCO_2$; 33 [29-37] vs. 31 [26-36] mmHg; p = 0.750); and $PaCO_2$ minus $ETCO_2$ (7 [3-8] vs. 9 [5-11] mmHg; p = 0.175). It should be noted that none of the patients experienced CO_2 rebreathing since inspired CO_2 (iCO_2) remained zero throughout the ELMOcpap session.

The absolute values for cardiorespiratory parameters before the ELMOcpap session (T0), as well as 2 min (T2) and 20 min (T20) after session initiation are shown in Figure S2. There was an improvement in oxygenation (an increase in SpO_2 and SpO_2/FIO_2 ratio and a decrease in HR [from 92 bpm to 87 bpm]; p = 0.006).

ELMOcpap utilization

All patients underwent ELMOcpap sessions, initial settings being as follows: total flow = 60 L/min (O_2 = 30 L/min and CA = 30 L/min); CPAP = 8 cmH_2O; and estimated FIO_2 = 0.60. At the end of the first session, the settings were as follows: total flow = 56 L/min (O_2 = 26 L/min and CA = 30 L/min); CPAP = 10 cmH_2O; and estimated FIO_2 = 0.58.

The rate of success rate—herein defined as either weaning from off oxygen supplementation delivered via ELMOcpap to that via nasal cannula at a flow ≤ 3 L/min via a nasal cannula or complete discontinuation of oxygen support—was 60%. Of the four patients who failed, one did not tolerate the therapy 40 min after the initiation of the first session, and three underwent orotracheal intubation in less than 24 h after the first session. Of these, two presented with delirium and refused the second session, and one showed no improvement in oxygenation during the session (PaO_2 and SpO_2 decreased by 8% and 12%, respectively, when compared with baseline values, as well as presented with worsening of dyspnea, resulting in its discontinuation after 20 min.

The median number of sessions with ELMOcpap sessions was 3.5 [1.0-11.0] for a median of 2 [1-5] days. The median daily duration of the sessions was 310 [60-1,230] min. Throughout that period, there was a gradual decrease in oxygen supplementation until complete weaning off in seven of the ten patients. The respiratory rate-oxygenation (ROX) index at the end of the first session was 6.8 [5.2-8.1]; however, this index has yet to be validated for use with the device.

The median scores assigned to the comfort provided by the interface, measured at the end of each session using a visual analog scale was 7.5 [5.0-8.8]. This score suggested that the use of ELMO was classified as moderately comfortable or very comfortable. None of the patients used any sedatives or analgesics continuously while using the interface.

The adverse effects observed with the use of ELMO are described in Table 2, all of them being considered mild by the patients. It should be noted that there were no air leaks during the sessions.

Of the ten patients, three underwent orotracheal intubation, none of which having been recommended during ELMOcpap sessions. Of these, two died, and one underwent tracheostomy and decannulation and was then discharged after being able to sustain spontaneous breathing after nearly two months of hospitalization. The median length of hospital stay for intubated patients was 24 [7-58] days, and the median number of days on and off MV was 19 [4-22] and 5 [3-36], respectively. The median length of hospital stay for patients whose therapy was considered successful was 13 [13-14] days. Eight patients were discharged after 13 [7-19] days of hospitalization.

None of the research team members or hospital staff acquired COVID-19 during the study, and all of them made rigorous use of personal protective equipment.

DISCUSSION

The present proof-of-concept study showed that the use of a new helmet device called ELMO was able to offer CPAP through a continuous flow of oxygen and CA to patients with COVID-19-related AHRF who needed oxygen supplementation outside the ICU. The use of ELMOcpap system resulted in improved oxygenation,

Table 1. Baseline demographic and clinical characteristics of the patients.

Characteristic	Patient									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Age, years	76	70	71	77	42	75	37	54	60	39
Sex	F	F	M	M	M	M	M	M	M	M
Weight, kg	72	58	63	66	110	64	93	65	75	105.2
Height, cm	154	158	164	156	170	159	182	163	174	172
BMI, kg/m^2	30.2	23.2	23.4	27.1	38.0	25.7	28.0	24.9	24.7	35.6
SOFA score at study entry	2	2	2	2	2	4	2	2	2	2
APACHE II score at study entry	11	11	15	10	5	12	4	8	4	5
Smoking history	Yes	Yes	No	Yes	No	Yes	No	No	Yes	No
Comorbidities	Diabetes Obesity	Hypertension Diabetes	Hypertension Diabetes	Hypertension	Obesity	Hypertension	-	Hypertension	Hypertension Diabetes	-
Symptoms before hospital admission	Cough Dyspnea Loss of appetite Adynamia	Cough Dyspnea Fever	Dyspnea Fever	Cough Fever Loss of appetite Headache	Cough Dyspnea Fever Nausea Vomiting	Cough Dyspnea Fever Odynophagia Coryza	Cough Fever	Cough Dyspnea	Cough Dyspnea Fever Loss of appetite Myalgia	Fever Adynamia
Extension of pulmonary impairment on CT	-	> 75%	> 75%	50-75%	> 75%	50-75%	-	50-75%	> 75%	> 75%
1st arterial blood gas analysis after hospital admission										
pH	7.51	7.50	7.50	7.52	7.51	7.48	7.46	7.52	7.49	7.49
PaO_2, mmHg	51	68	68	75	167	91	60	89	74	79
$PaCO_2$, mmHg	35	33	41	35	37	34	41	34	41	39
HCO_3, mEq/L	28.5	28.5	28.5	28.5	28.5	28.5	29.2	27.8	28.5	29.7
BE, mEq/L	4.9	2.5	8.8	2.8	6.2	1.8	4.9	2.0	7.2	5.9
SaO_2, %	89	95	95	96	100	98	92	98	96	97
Lactate, mmol/L	1.4	2.0	1.3	1.5	1.1	1.8	1.3	2.0	2.0	1.4
Oxygen therapy at hospital admission	RV 8 L/min	NC 5 L/min	RV 8 L/min	RV 8 L/min	RV 10 L/min	RV 9 L/min	NC 4 L/min	RV 15 L/min	NC 6 L/min	RV 10 L/min
Laboratory findings at hospital admission										
White blood cell count/mm^3	10,780	8,351	19,340	14,630	10,730	13,610	10,870	14,950	7,931	12,900
Lymphocyte count/mm^3	757	1,338	1,355	586	537	681	1,088	1,346	795	1,419
Hemoglobin level, g/dL	11.6	13.3	12.3	13.5	13.8	14.7	13.4	13.5	14.4	13.9

Continue...▶

Table 1. Baseline demographic and clinical characteristics of the patients. (Continued...)

Characteristic	Patient									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Hematocrit, %	36.6	40.9	36.8	41.4	41.2	41.5	39.0	39.3	45.5	41.9
Band cell count/mm^3	107	83	580	0	0	136	0	149	0	0
Segmented cell count/mm^3	9,809	6,513	16,825	13,313	9,764	12,249	9,130	12,857	6,582	10,707
Platelet count/mm^3	211,500	168,200	187,000	283,000	237,800	128,500	287,500	301,900	232,500	190,000
CRP, mg/dL	27.2	3.8	20.4	7.9	11.4	3.4	14.3	5.4	4.5	5.35
Urea, mg/dL	24	29	64	43	37	44	41	63	44	35
Creatinine, mg/dL	0.3	0.5	1.4	0.9	0.7	0.7	0.6	1.1	0.7	0.7
D-dimer, µg/mL	> 20	0.42	1.38	0.7	1.28	1.32	0.74	0.73	1	1.69
Fibrinogen, mg/dL	221	-	687	-	-	-	-	-	-	-
AST, U/L	64	33	54	55	37	109	24	34	40	98
ALT, U/L	99	30	47	26	47	29	26	45	75	216
CPK, U/L	42	52	185	28	18	1,393	35	173	198	37
LDH, U/L	548	247	386	373	401	1,503	405	312	371	545
Ferritin, ng/mL	> 1,500	280	> 1,500	> 1,500	> 1,500	> 1,500	1,307	-	1,091	766
Days of symptoms preceding ELMOcpap use, n	7	13	4	13	13	10	15	17	11	11

F: female; M: male; HCO_3: bicarbonate; BE: base excess; RV: nonrebreathing reservoir mask; NC: nasal cannula; CRP: C-reactive protein (1-5 mg/dL: slight inflammation; 5-10 mg/dL: severe inflammation; > 10 mg/dL: probable bacterial infection); and CPK: creatine phosphokinase.

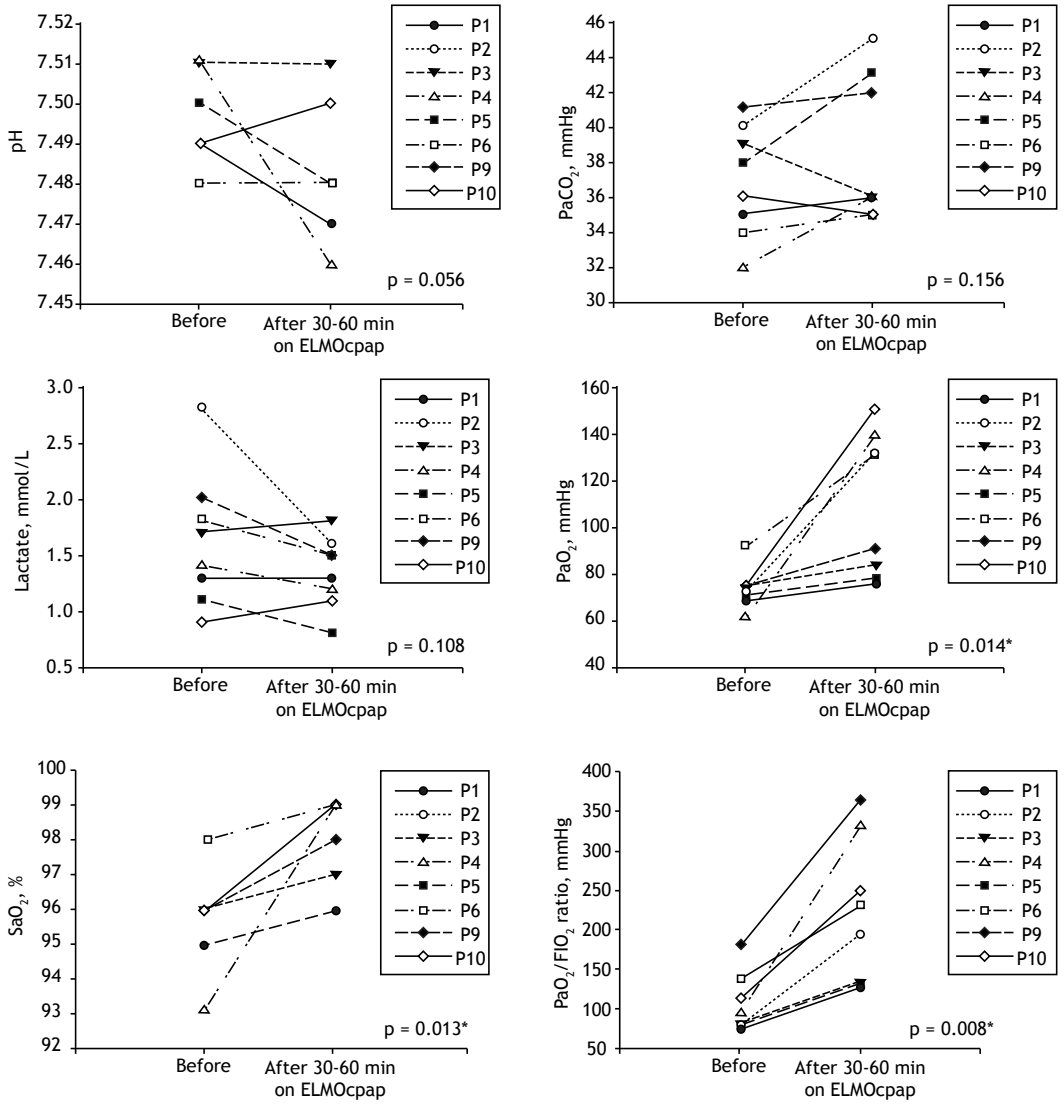

Figure 3. Arterial blood gas parameters before the first ELMOcpap session and after 30-60 min of use (CPAP = 10 cmH_2O and total gas flow = 56-60 L/min) in individual patients (P1-P6,P9,10). There were significant improvements in PaO_2, SaO_2, and estimated PaO_2/FIO_2 30-60 min after starting ELMOcpap use. These improvements made it possible to reduce median estimated FIO_2 (from 0.77 [0.65-0.89] to 0.60 [0.49-0.61]; p = 0.014). *p < 0.05.

making it possible to decrease FIO_2 without causing CO_2 rebreathing or hypercapnia. The device was well tolerated, and no relevant adverse effects were observed; its use was feasible outside the ICU for a prolonged time and was shown to be successful in 60% of the patients.

The feasibility, safety, and clinical impact of noninvasive ventilatory support in patients with COVID-19 outside the ICU were described in a prospective multicenter observational study[13] that analyzed data from 670 patients. In that study, a total of 330 patients received CPAP either via a helmet or a face mask, the helmet being used with a mean CPAP of 10.2 cmH_2O in most patients.[13] This setting is similar to the one in the present study. The researchers concluded that the use of NIV outside the ICU was feasible when performed by experienced staff and was associated with favorable outcomes, such as lower rates of endotracheal intubation and mortality. On the other hand, that use was associated with a risk of staff contamination, which was minimized when the helmet interface was used.[13] None of our research team members was infected with SARS-CoV-2 during the study period while the patients were on ELMOcpap.

The patients considered the use of the ELMOcpap system to be moderately to very comfortable. This allowed one of the patients to remain on ELMOcpap for 15 uninterrupted hours with no adverse effects. The main adverse effects reported in the literature are helmet deflation and pressure ulcers on the neck.[10]

Table 2. ELMOcpap use and patient outcomes.[a]

Variable	Patient									
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10
Total number of sessions	2	5	11	7	17	1	1	1	2	14
CPAP level, cmH_2O	10 [10-12]	8 [8-10]	10 [8-10]	10 [10-10]	10 [8-10]	8 [8-8]	10 [8-10]	8 [8-8]	8 [8-8]	10 [10-10]
Total therapy time, min	100	440	1,230	880	1,980	60	40	20	180	2,640
ROX index within 2 h after the 1st session	6.2	5.2	5.2	7.7	8.2	5.2	7.5	1.9	16.0	13.0
VAS comfort score	5	8	7	9	9	-	3	0	10	8
Main adverse effects	-	Regurgitation	Dry mouth	Eye irritation	Cervical and armpit discomfort	-	-	-	Cough	-
Number of days of utilization	2	2	5	4	7	1	1	1	2	5
ELMOcpap use outcome[b]	Failure	Success	Success	Success	Success	Failure	Failure	Failure	Success	Success
Total length of hospital stay before first ELMOcpap session, days	0	8	4	2	4	3	3	11	1	3
Total length of hospital stay, days	7	14	13	13	19	24	7	58	5	13
Clinical course assessed just before first ELMOcpap session	Worsening	Stable	Stable	Stable	Stable	Worsening	Improving	Worsening	Improving	Stable
Orotracheal intubation after ELMOcpap use	Yes	No	No	No	No	Yes	No	Yes	No	No
Outcome	Death	Discharge	Discharge	Discharge	Discharge	Death	Discharge	Discharge	Discharge	Discharge

ROX index = $(SpO_2/FIO_2)/RR$; VAS: visual analog scale to assess comfort of the interface (zero-most uncomfortable and 10-very comfortable). [a]Values expressed in n or median [IQR]. [b]Success: weaning from off oxygen supplementation delivered via ELMOcpap to that via nasal cannula at a flow ≤ 3 L/min via a nasal cannula or complete discontinuation of oxygen support. Failure: worsening of cardiorespiratory parameters during session, no improvement in breathing pattern, or patient rejection.

In our study, none of the patients developed pressure ulcers, but a few patients reported some discomfort in the cervical region and armpits, which could be alleviated with adjustments in the positioning of the silicone cervical collar and with the symmetrical positioning of the armpit braces with the use of underarm pads.

The analysis of the acute effects on gas exchange and cardiovascular function before and during the use of ELMOcpap revealed a significant improvement in all oxygenation parameters. Similar findings were reported by Coppadoro et al.,[14] who found that the PaO_2/FIO_2 ratio doubled from 100 to 200 mmHg and that the PaO_2/FIO_2 ratio remained constantly above 150 mmHg during the first week; this was associated with a probability of recovery without intubation of 91%.[14] A similar observation was made in the first hour of ELMOcpap use, with a significant increase in the PaO_2/FIO_2 ratio from 88 to 212 mmHg. This effect can be explained by the effect of CPAP on the recruitment of swollen and/or collapsed alveoli, with immediate improvement in the ventilation/perfusion ratio.[8] The positive pressure can favor a more even distribution of perfusion, diverting blood flow from lung areas with shunt and edema towards those with a high ventilation/perfusion ratio.[15]

We identified a decrease in respiratory alkalosis, which might have resulted from a combination of effects of CPAP application that decreased ventilatory drive: improvement of hypoxemia, a potential increase in lung compliance, reduced work of breathing, and greater comfort.[16,17] A study demonstrated that RR < 24 breaths/min on helmet-delivered CPAP for a few hours were associated with greater efficacy.[14]

As for cardiovascular function, we found a decrease in HR within the first hour of CPAP application with no significant changes in systemic blood pressure. However, a decrease in blood lactate levels was found in five of eight patients. These findings indicate a decrease in global oxygen consumption and a lower demand for oxygen supply.[18,19]

None of the patients in the present study had CO_2 rebreathing. Compared with face masks, helmets, due to their larger internal volume, might facilitate CO_2 rebreathing.[20] A group of authors[12] found that such a phenomenon is associated with two factors: the amount of CO_2 produced by the patient and the amount of gas passing through the helmet. Those researchers did not recommend the use of a helmet to deliver CPAP with a mechanical ventilator, the reason being that ventilators deliver CPAP with a gas flow equal to minute ventilation in healthy subjects; in the absence of a leak, there is no additional fresh gas flow to flush CO_2 during exhalation, which is thus retained inside the helmet.[12] Thus, the delivery of a continuous flow eliminates this problem, as we could see in the present study. In fact, during the development of ELMO, we demonstrated, using capnography, the degree of CO_2 rebreathing at different gas mixture flows (30, 40, 50, and 60 L/min). Flows > 40 L/min resulted in null or negligible CO_2 rebreathing,[11] which is in accordance with previous investigations.[7,21]

The success rate described in this study is similar to the one reported in a recent retrospective observational cohort study[14] involving 306 patients that showed that treatment with helmet-delivered CPAP of 10 cmH_2O was successful in 69% of the cases, its use being feasible for several days outside the ICU. Our slightly lower rate can be explained by the severity of hypoxemia in our patients. In that study,[14] the patients had an initial median PaO_2/FIO_2 ratio of 103 [79-176] mmHg receiving standard oxygen therapy, whereas our patients presented with an initial median PaO_2/FIO_2 ratio of 88.0 [80.5-126.0] mmHg. Another study[9] found that helmet-delivered CPAP failed in up to 44% of patients with moderate to severe AHRF caused by COVID-19 pneumonia. The authors reported that 55.4% of the patients with a median PaO_2/FIO_2 ratio = 136 mmHg avoided intubation and were then successfully weaned from CPAP to oxygen therapy.[9]

The present study has some limitations, such as the lack of a control group and the small sample size. The interface was developed to deliver CPAP with a continuous flow of gases during the peak of the COVID-19 pandemic, when resources were limited and CPAP application with ICU ventilators had yet to be studied. However, this pioneering investigation conducted in Brazil received formal approval by the Brazilian National Health Surveillance Agency for the manufacturing and sale of the ELMO interface in the country.

The clinical implications are many: first, the ELMO is relatively simple to set and apply; second, it may be particularly useful as an interesting alternative to treat AHRF in situations such as during the COVID-19 pandemic, which has overwhelmed health care systems worldwide and increased the demands for ICU beds and ventilators; third, it allows longer periods of CPAP application without causing adverse effects commonly seen with the use of conventional face masks, tolerance being a well-known limitation in NIV[22]; fourth, the continuous high-flow CPAP system was efficient in preventing CO_2 rebreathing, an effect that might attenuate the increments in ventilatory demand and respiratory drive, which are important issues for patients at risk of self-inflicted lung injury and ARDS progression[23]; fifth, the material used in ELMO manufacturing allows reprocessing it up to five times, reducing hospital costs, and the silicone collar allows a good seal,[11] preventing air leaks, dissemination of contagious aerosols around the patient, and the spread of diseases among health care professionals.

The results of this pivotal study support the development of further research to assess the use of ELMO in patients with AHRF caused by COVID-19 and other similar conditions, such as pneumonia, ARDS, and acute cardiogenic pulmonary edema, as well as to determine its impact on relevant outcomes, such as intubation rates, mortality, length of hospital stay, and survival rates. In a multicenter randomized clinical trial[24] involving 109 patients with COVID-19, the

use of helmet-delivered NIV (PEEP = 10-12 cmH_2O and pressure support = 10-12 cmH_2O) for at least 48 h, eventually followed by high-flow nasal oxygen (HFNO), was compared with the use of HFNO alone. The rate of orotracheal intubation was significantly lower in the helmet group (30%) than in the HFNO group (51%); however, no significant differences were found in mortality or in the median number of days free of respiratory support within 28 days (primary outcome).[24] Clinical trials are certainly needed to access and compare different helmet interfaces; for instance, those using CPAP with continuous flow, such as ELMOcpap, in comparison with those especially adapted for full NIV with pressure support and adapted to an ICU ventilator. Furthermore, it is important to identify the patients' characteristics associated with improved physiological and clinical response to this type of respiratory therapy.[25]

In conclusion, based on the results obtained, the use of the helmet device designated ELMO is believed to be feasible and effective in delivering high-flow CPAP to patients with COVID-19-related AHRF outside the ICU. No major adverse effects were found, and the patients considered its use as comfortable. The application of CPAP using the ELMOcpap system significantly improved oxygenation, contributing to the reduction of FIO_2 and eliminating CO_2 rebreathing. The overall success rate was 60% in this pilot study, and further clinical trials should be carried out in the future.

ACKNOWLEDGMENTS

The authors acknowledge the multiprofessional team at the Leonardo Da Vinci State Hospital for their support on data collection: Ana Paula Porto, André Castro Júnior, Cristiano Sousa, Erika Timbó, Francisco Pitombeira, Germana Magalhães, Gleyson Nunes, Mary Bezerra, Suzy Montenegro Pontes, and Wedla Santos. The authors also acknowledge Antônio Brazil Júnior for the statistical analysis. We are grateful to Carlos Roberto Sobrinho for the support in the development of the research. We acknowledge the ELMO TASK FORCE for their support in the development of ELMO: Ataliba Holanda Neto (consulting engineer at the the *Serviço Nacional de Aprendizagem Industrial* [SENAI, Brazilian National Service for Industrial Training], Carlos Eduardo Bastos de Salles (engineer director at Esmaltec S/A), Fábio Cisne Ribeiro (research engineer at the Federal University of Ceará), Francisco Clébio Silva (senior designer at Esmaltec S/A), Herbert Lima Santos da Rocha (professor and coordinator of the Research and Innovation in Cities Laboratory at the University of Fortaleza), Jarbas Aryel Nunes da Silveira (professor at the Federal University of Ceará), João Batista Furlan Duarte (research professor at the University of Fortaleza), Paulo André de Castro Holanda (regional director at SENAI), Rendex Ribeiro (engineering manager at Esmaltec S/A), and Tarcísio Bastos (innovation and technology manager at SENAI).

AUTHOR CONTRIBUTIONS

BST, GCG, JAL, and MAH: study design and drafting of the manuscript. DGAM, JBS, VF, LSJ, and the ELMO TASK FORCE: development of the ELMO device. BST, GCG, JAL, MSQF, and DLNL: data collection. BST, GCG, and JAL: guarantors of data integrity. BST, EDBP, and MAH: data analysis. All authors reviewed and approved the final manuscript.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210120
https://dx.doi.org/10.36416/1806-3756/e20210120

ORIGINAL ARTICLE

Evidence of the association between adherence to treatment and mortality among patients with COPD monitored at a public disease management program in Brazil

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Submitted: 22 March 2021.
Accepted: 28 September 2021.

Study carried out in the Serviço de Assistência Farmacêutica, Ambulatório de Pneumologia, Complexo Hospitalar Universitário Prof. Edgard Santos, Universidade Federal da Bahia, Salvador (BA) Brasil.

ABSTRACT

Objective: To evaluate the association between adherence to treatment and mortality among Chronic Obstructive Pulmonary Disease (COPD) patients treated in the Brazilian public health system. **Methods:** This is cohort study of moderate-to-severe COPD patients monitored in a public pharmaceutical care-based Disease Management Program (DMP). All subjects who died one year after the beginning of the cohort were age-matched with those who remained alive at the end of the cohort period. Treatment adherence was measured through pharmacy records. Patients who received at least 90% of the prescribed doses were considered adherent to treatment. **Results:** Of the 333 patients (52.8% age ≥ 65 years, 67.9% male), 67.3% were adherent to treatment (adherence rate, 87.2%). Mortality was associated with lack of adherence (p = 0.04), presence of symptoms (mMRC ≥ 2) and COPD treatment use. The death was associated with non-adherence, presence of symptoms and previous hospitalization. After adjustment, non-adherent patients to treatment were almost twice times likely to die compared to those adherents (Hazard Ratio (HR) 1.86; CI 1.16-2.98, p = 0.01). **Conclusion:** Non-adherence to treatment was associated with higher mortality among moderate-to-severe COPD patients treated in the Brazilian public health system. Strategies to monitor and optimize adherence should be strengthened to reduce COPD-related mortality.

Keywords: COPD; Treatment adherence; Mortality; Pharmaceutical care.

INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable disease which is characterized by persistent limitation in the airflow.[1] Currently, it is the main cause of morbimortality around the world, which results in a significant and growing economic and social burden.[1] In Brazil, only three conditions have a higher mortality. Additionally, it was the main cause of death from pulmonary disease in 2017.[2]

Adherence to drug treatment is one of the most important factors for disease management and its failure should be considered the main cause for inadequate treatment response.[1] Unsatisfactory adherence can lead to unfavorable disease outcome, including hospitalization and poor quality of life. Koehorst-Ter and collaborators,[3] using data from the COMIC study, found out that low adherence to inhaled corticosteroids (ICS) and tiotropium was associated with a greater risk of mortality in individuals with COPD.[4]

COPD treatment adherence rates are being reported in real-world studies between 16.0% and 67.0%.[5-9] In fact, the causes associated with the lack of adherence are being more commonly reported as level of schooling, pulmonary function, severity of disease and the presence of symptoms. However, few studies have explored the association between adherence to treatment in COPD patients and mortality.

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Financial support: None.

ISSN 1806-3756

Despite the free access to medication policy for the COPD treatment within the Brazilian public health system,[10] recent studies have shown high frequency of undertreatment.[11,12] Furthermore, there are limited data concerning adherence and risk factors for that. This study aimed to evaluate the association between adherence to treatment and mortality among patients with COPD monitored at a public disease management program in the Brazilian public health system.

METHODS

This is a cohort study involving patients previously diagnosed with COPD and referred from the public health care network to the referral outpatient clinic of the pharmaceutical care-based Disease Management Program (DMP) at Octávio Mangabeira Specialized Hospital in Salvador, in the state of Bahia, Northeast of Brazil. The objective of the program was associated with the improvement regarding clinical management and capacity for decision making for respiratory diseases (COPD, asthma, tuberculosis, acute respiratory infection, and lung cancer) within the scope of the public health system in the state of Bahia. The program activities could include medical and pharmaceutical care with free and continuous drug dispensing.

Patients

The present study selected individuals with COPD admitted to the DMP between June 2011 and January 2012 who were 40 years old or more, presenting a disease severity as Global Initiative for Chronic Obstructive Lung Disease II (GOLD II) (moderate), GOLD III (severe) or GOLD IV (very severe)[13] and a post-bronchodilator Forced Expiratory Volume$_1$/Forced Vital Capacity (FEV_1/FVC) ratio < 0.7 and post-bronchodilator FEV_1 < 80% of predicted, as measured by spirometry. Individuals with either (1) asthma, (2) refused to participate in the study or (3) could not provide written Informed Consent Form (ICF) were excluded from study.

Individuals who fulfilled the criteria for eligibility were included in the cohort and their treatment process was monitored for at least 12 months. Within this cohort, the individuals who completed at least one year of exposure to the program alive and during follow-up died before January 31st, 2019 (date set as the end of the cohort follow-up) was age-matched with those who remained alive until January 31st, 2019. Each death was matched with up to three live controls. Mortality was ascertained during active follow-up or through the Brazilian Ministry of Health's Mortality Information System. COPD-related deaths were defined according to the codes J40 - J44 of the 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) of the World Health Organization (WHO).[14]

Procedures

Enrollment and monitoring procedures details of the participants cohort were specified in a previous study.[11] In synthesis, the patients were admitted into the program and interviewed by two trained pharmacists and a pneumonologist, who used standardized questionnaires to obtain study data. Through these questionnaires, the investigators collected sex, age, self-reported skin color; years of schooling and per capita family income in minimum wages at the time of the study; smoking status, smoking load, duration of COPD in years, number of comorbidities and spirometry results (FEV_1, pre- and post-bronchodilator), emergency department visits/hospitalizations due to COPD in the last year and use of drugs other than for the COPD treatment in the past seven days.

The basal level of dyspnea was measured using the modified Medical Research Council (mMRC) dyspnea scale, those with score of two (2) or more were classified as symptomatic. The COPD spirometric severity classification followed the 2011 GOLD criteria,[13] to which 50% ≤ FEV_1 < 80% was considered as moderate COPD (GOLD II), 30% ≤ FEV_1 < 50% as severe (GOLD III) and FEV_1 < 30% as very severe (GOLD IV). Patients were classified in ABCD in accordance with the GOLD 2011 recommendations.[13] The spirometry (Koko Pneumotach model; PDS Instrumentation Inc., Louisville, CO, USA) was performed in accordance with the American Thoracic Society/European Respiratory Society recommendations.[15] The spirometric variables were expressed in percentage predicted, based on the Brazilian population reference values.[16]

The drugs referred being used as a response to the question "use of some medication for the treatment of COPD", were categorized as short-acting bronchodilators [Short-Acting Muscarinic Antagonists (SAMA), Short-Acting Beta Agonists (SABA) and their combinations]; long-acting bronchodilators [Long-Acting Muscarinic Antagonists (LAMA) and Long-Acting Beta Agonists (LABA), either isolated or combined with ICS]; ICS; and methylxanthines.

While participants were followed in the DMP, the pharmacists dispensed the medications and oriented them for treatment adherence, effectiveness and safety of physician prescribed drugs and the inhaled devices correct management. The drug dispensation occurred monthly, when dates of attendance, amount of medication given were recorded.

Ethical aspects

The study protocol was approved by the Research Ethics Committee of the Bahia State Department of Health (protocol n° CAAE: 17268313.8.0000.5030). All patients signed an ICF.

Sample size calculation

The sample size was calculated based on the following assumptions, i.e., the total number of the moderate-to-severe COPD patients in the state of

Bahia. Based on data from PLATINO[17] study, it was 45,900 patients; relative error margin of 5%; confidence interval of 95%; estimated adherence prevalence of 80%, considering the disease severity and the availability of free medication to all of the patients treated via the DMP and 20% loss to follow-up. From this rationale, a minimum sample of 294 individuals should be followed in the cohort study, to reach a representative sample of this population.

Statistical analysis

The rate of adherence was estimated using following formula: (ND ÷ NT) X 100**;** where ND = number of doses actually dispensed and NT = number of doses that should have been dispensed in the period. Patients who received at least 90% of the prescribed doses within the initial 12 months after admission to the program were considered adherence to treatment. The reason why this rate was higher than the ones recorded in the literature (80%)[5,7,18,19] was related to the fact that our patients sample presented greater disease severity and had free access to COPD drugs provided by DMP.

To analyze the date, the statistical package of IBM SPSS Software (Statistical Product and Service Solutions - IBM Corporation, Armonk, NY, USA) version 18.0 was used. The frequency of the categorical and nominal variables were calculated to describe the data; average and standard deviation for the continuous variables, or median and interquartile interval, when the variables did not meet normal distribution, was calculated. The Chi-square test was used to verify possible associations between categorical variables. For the continuous variables, the Student's *t* test and Mann-Whitney U-test were used to investigate the association between independent variables and adherence to treatment. Variables with $p \leq 0.10$ were included in an adjusted Cox regression model to evaluate their influence on mortality. In the regression model, the variable of time of duration of COPD was transformed into a logarithmic scale ($t\text{-}COPD_{lg}$) to obtain an approximately normal distribution. The Hazard Ratio (HR) was calculated with Confidence Intervals (CI) of 95% (95% CI).

RESULTS

A total of 441 patients were invited to participate in the study. Of these, 333 were included in the cohort to evaluate adherence to treatment and 257 in the matched analysis (Figure 1).

Most participants from the cohort were male (67.9%), elderly (52.8% ≥ 65 years) and their family income

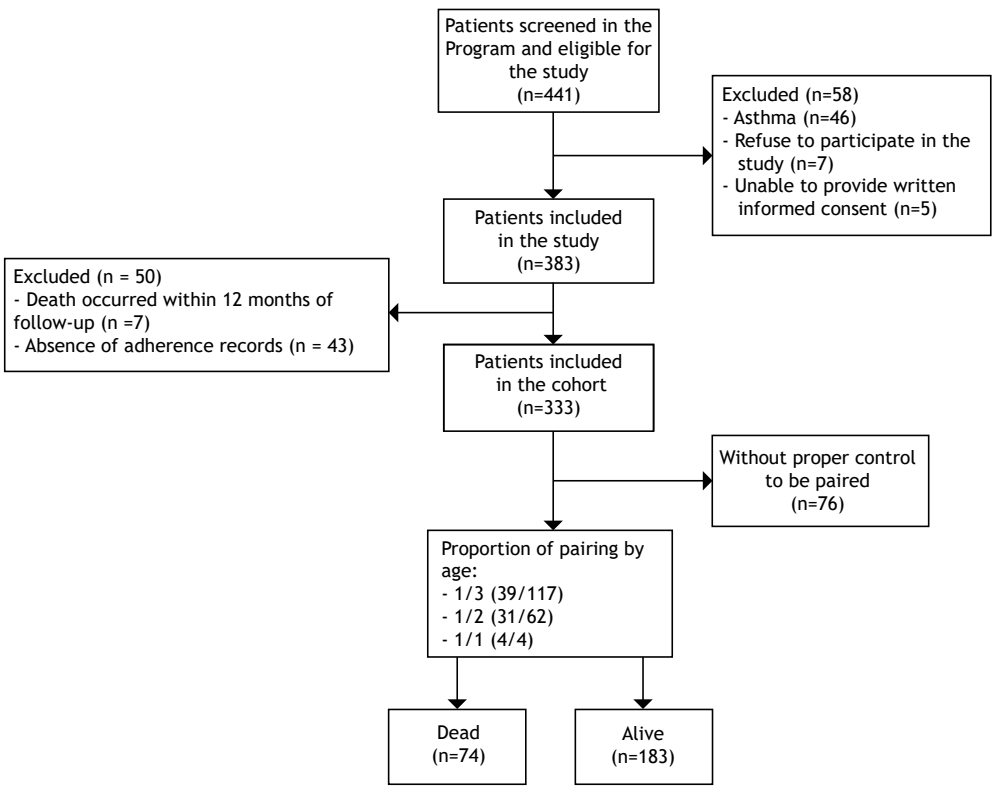

Figure 1. Flowchart of the participants' study.

was less than or equal to a minimum wage (81.7%). Almost half of them (44.7%) belonged to the GOLD D group. The general characteristics of the patients according to the non-adherent and adherent group to treatment are presented in Table 1.

The rate of adherence to treatment was 87.2%. Overall, 224 (67.3%) patients from the cohort were adherence to treatment. Adherence was associated with mMRC dyspnea grade (p = 0.02) and the previous use of some medication to the treatment of COPD (p = 0.03).

It could be noted that those adherent patients to treatment died less than those not adherence (20.1% *versus* 29.4%, p=0.04). Age at the beginning of the cohort was strongly associated with mortality (dead: mean age at the beginning 70.3 (11.7) years; alive: 64.6 (11.2), $p < 0.0001$). According to this result and in order to minimize the effect of age on mortality, matched by age was performed. The individuals more symptomatic (mMRC ≥ 2) (p = 0.03) and who were hospitalized (p= 0.02) died in greater proportion after a year of study monitoring (Table 2). The participants who had the disease for a greater length of time (p = 0.01) remained alive until the end of the monitoring period.

After adjustment, the likely of being dead at the end of the cohort's monitoring period was almost two times greater for those who did not adhere to treatment in the first 12 months (adjusted HR 1.86; CI 1.16-2.98, p = 0.01) (Table 3). After the first year of the monitoring, the survival mean time, in years, was greater within those who adhered to treatment (7.0 *versus* 6.4 years, p = 0.02). Figure 2 shows survival curves of mortality for adherent and non-adherent patients to treatment.

DISCUSSION

The rate of adherence to treatment of the cohort (87.2%) was greater than those observed in previous studies in the real world, in which values varied from 16.0% - 67.0%.[3,5,6,20,21] These results could be

Table 1. Comparison of the general characteristics of adherent (≥ 90%) and non-adherent (< 90%) patients to treatment in the cohort (n = 333).

Characteristics	Non-adherent (n=109)	Adherent (n=224)	*p*-value*
Male	67 (61.5%)	159 (71.0%)	0.05
Age ≥ 65 years	60 (55.0%)	116 (53.8%)	0.33
Age at cohort entry[a]	66.2 (11.1)	65.8 (11.8)	0.76
Less than nine years of schooling	92 (84.4%)	180 (80.4%)	0.23
One or less NMW per capita of family income	88 (80.7%)	184 (82.1%)	0.43
Pack-years smoking history[b]	30.0 (15.0-54.0)	30.0 (15.0-50.5)	0.90
Smoking status			
Never smoked	91 (83.5%)	199 (88.8%)	0.06
Former smoker	14 (12.8%)	11 (4.9%)	
Smoker	2 (1.8%)	9 (4.0%)	
COPD duration in years[b]	6.0 (3.0-14.0)	7.0 (3.0-10.0)	0.76
Five or more comorbidities	5 (4.6%)	17 (7.6%)	0.22
Pre-bronchodilator FEV_1 (% predicted)[a]	39.21 (±14.47)	36.56 (±12.90)	0.14
Post-bronchodilator FEV_1 (% predicted)[a]	42.41 (±15.66)	39.46 (±13.42)	0.15
mMRC dyspnea grade, ≥ 2	79 (72.5%)	186 (83%)	0.02
Mortality	32 (29.4%)	45 (20.1%)	0.04
Spirometric severity			0.21
Moderate	34 (31.2%)	51 (22.8%)	
Severe	46 (42.2%)	113 (50.4%)	
Very severe	29 (26.6%)	60 (26.8%)	
GOLD group			
A	9 (8.3%)	10 (4.5%)	0.16
B	8 (7.3%)	19 (8.5%)	
C	21 (19.3%)	28 (12.5%)	
D	71 (65.1%)	167 (74.6%)	
Emergency department visit	60 (55.0%)	116 (51.8%)	0.36
Hospitalization	25 (22.9%)	56 (25%)	0.39
Use of any previous medication to treat COPD	71 (65.1%)	170 (75.9%)	0.03

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced Expiratory Volume in the first second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; NMW: National Minimum Wage. Statistical analysis: Chi-square test. [a]student *t* Test: mean (standard deviation); [b]Mann-Whitney test: median (interquartile range); *A p-value < 0.05 was defined as statistically significant.

Table 2. Demographic clinical and functional characteristics of dead and alive individuals until January 31st, 2019.

Characteristics	Dead (n = 74)	Alive (n = 183)	*p*-value*
Male	51 (68.9%)	123 (67.2%)	0.46
65 or more years of age	53 (71.6%)	117 (63.9%)	0.15
Age at the beginning of the study[a]	69.4 (11.0)	67.4 (11.2)	0.19
Less than nine years of schooling	66 (89.2%)	146 (79.8%)	0.05
One or less NMW per capita of family income	61 (82.4%)	148 (80.9%)	0.46
Pack-years smoking history[b]	27.8 (9.5-59.3)	30 (15.00-51.5)	0.73
Smoking status			
Never smoked	4 (5.4%)	6 (3.2%)	0.73
Former smoker	63 (85.1%)	162 (88.5%)	
Smoker	7 (9.5%)	14 (7.6%)	
COPD duration in years[b]	5.0 (2.0-10.0)	8.0 (3.0-14.0)	0.01
Five or more comorbidities	5 (6.8%)	12 (6.6%)	0.57
Pre-bronchodilator FEV_1 (% predicted)[a]	35.6 (±14.9)	38.2 (±13.1)	0.18
Post-bronchodilator FEV_1 (% predicted)[a]	38.0 (15.1)	41.1 (±13.8)	0.11
mMRC dyspnea grade, ≥ 2	65 (87.8%)	141 (77.0%)	0.03
Adherence to treatment	43 (58.1%)	127 (69.4%)	0.06
Spirometric severity			0.31
Moderate	17 (23.0%)	51 (27.9%)	
Severe	31 (41.9%)	85 (46.4%)	
Very severe	26 (35.1%)	47 (25.7%)	
GOLD group			
A	2 (2.7%)	12 (6.6%)	0.24
B	6 (8.1%)	16 (8.7%)	
C	7 (9.5%)	30 (16.4%)	
D	59 (79.7%)	125 (68.3%)	
Emergency department visit	45 (60.8%)	92 (50.3%)	0.08
Hospitalization	27 (36.5%)	42 (23.0%)	0.02
Use of any previous medication to treat COPD	51 (68.9%)	130 (71.0%)	0.42

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; FEV_1: Forced Expiratory Volume in the first second; GOLD: Global Initiative for Chronic Obstructive Lung Disease; mMRC: modified Medical Research Council; NMW: National Minimum Wage. Statistical analysis: Chi-square test. [a]student *t* test: mean (± standard deviation); [b]Mann-Whitney test: median (Q1-Q3); *A *p*-value < 0.05 was defined as statistically significant.

associated with the fact that our sample consisted of mainly severe and symptomatic patients and who participated in a pharmaceutical care-based DMP, in which the interventions included monitoring and optimization of treatment adherence. Recent evidence has shown the benefits of the practice of pharmaceutical care on important outcomes for COPD, including improvement adherence to treatment.[22-29]

Generally, adherence rates near to 80% are found in clinical trials,[19] in which the study conditions are more controlled when compared with studies in the real world. Greater frequency of symptoms (mMRC ≥ 2) and greater disease severity can be associated with adherence to inhaled medications.[30-33]

Association between adherence and mMRC ≥ 2 ($p = 0.02$) was found by Boland and colleagues, in a 2-year cluster randomized trial,[19] showing that more symptomatic patients adhered more to the treatment than less symptomatic patients during the second trial-year. This finding strengthens our hypothesis that more symptomatic patients have a higher need for medication and as a result, they are more likely to be adherence to treatment.

Still with the cohort, the results showed an association between adherence and the previous use of some medication to treat COPD (75.9%, $p = 0.03$), demonstrating that those patients who were using inhaled medications, even if undertreated,[11] had more chances to maintain the therapy after being admitted to the DMP. The results of our analyses are in accordance with the findings of cohort studies which confirm previous adherence as the dominant predictor of future adherence.[5,34] In one of these studies, Ingebrigtsen and colleagues,[5] using an indirect method to estimate the adherence, found that previous adherence (adherence for ICS/LABA, LAMA and LABA during the first year) was associated with the increased adherence in COPD patients.

The association between non-adherence to treatment and increase in mortality evident in the multivariate analysis (adjusted HR 1.86; 95% CI 1.16-2.98, $p = 0.01$) adjusted for schooling, mMRC grade, hospitalization,

Table 3. Multivariate analysis adjusted by Cox regression of the mortality predictor variables.

Variables	*p*-value*	Adjusted Hazard Ratio	95% CI	
			Lower	Upper
Non-adherence to treatment	0.01	1.86	1.16	2.98
Less than nine years of schooling	0.09	1.92	0.92	4.04
Post-bronchodilator FEV_1, % predicted	0.24	0.99	0.97	1.01
mMRC dyspnea grade, ≥ 2	0.06	2.00	0.98	4.11
$t\text{-}COPD_{log}$	0.01	0.54	0.34	0.84
Emergency department visit	0.79	1.07	0.66	1.75
Hospitalization	0.03	1.72	1.06	2.82

Abbreviations: COPD: Chronic Obstructive Pulmonary Disease; mMRC: modified Medical Research Council; $t\text{-}COPD_{log}$: log of COPD duration; FEV_1: Forced Expiratory Volume in the first second; *A *p*-value < 0.05 was defined as statistically significant.

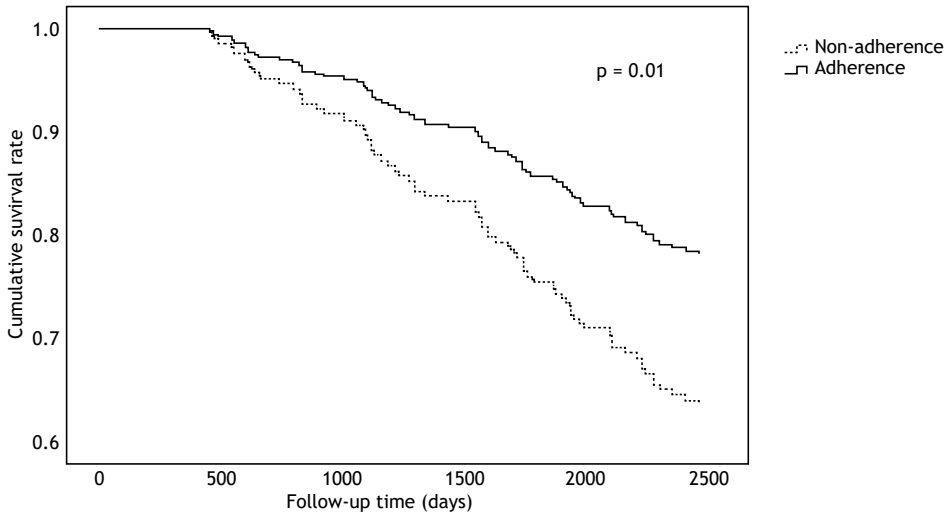

Figure 2. Survival curves of mortality showing a comparison between adherent and non-adherent to patients treatment by multivariate Cox-regression survival analysis.

post-bronchodilator $FEV_{1\%}$ and log of duration of COPD, was consistent with previous studies.[3,19,20] An analysis of the study entitled *Cohort of Mortality and Inflammation in COPD* (COMIC) performed in the Netherlands found an increase in risk of mortality among COPD patients with underuse of ICS and tiotropium compared to those in optimal use, with a HR equal to 5.3 (95% CI 3.3-8.5) *versus* 6.4 (95% CI 3.8-10.8), respectively.[3] A populational-based Italian study[20] involving 12,224 patients with moderate to severe COPD evaluated the impact of adherence to inhaled therapy on a survival period of 5 years; and showed that individuals who regularly used LABA had higher survival rates than those who occasionally used a combination of ICS/LABA (HR = 0.89, 95% CI 0.79-0.99). Further, a secondary analysis of the study *Towards a Revolution in COPD Health* (TORCH), a randomized clinical trial, involving 6,112 patients with moderate to severe COPD with a duration of 3 years,[19] showed an association between adherence and mortality (HR = 0.40, 95% CI 0.35-0.46, $p < 0.001$). Despite the difference in methodologies between the different studies, such findings showed the substantial impact of adherence to treatment on mortality and reinforced the importance of adequate evaluation of adherence to treatment in the daily clinical practices of these patients, with the aim of achieving suitable disease management.

Despite the high rate of adherence found in this study, it was evident that patients with COPD who had a low adherence rate in the first year in the DMP were those who had a higher risk of death after this period. Thus, this finding reinforces the necessity of implementing measures which promote changes in these patients' behavior, ensuring that they adhere to the prescribed treatment in order to achieve positive health results. Therefore, the implementation of initiatives based on pharmaceutical care in which interventions include encouraging consciousness raising about health conditions, including the identification of signals and symptoms to disease control; training about correct inhalation technique, as well as identification, treatment, prevention and monitoring of problems

related to medications. These are the recommended actions which have already had promising results around the world.[26-29]

There were some limitations in this study. The first was inherent to the indirect method of assessment of adherence used. Dispensation may not reflect adherence to the prescribed pharmacotherapy nor exact usage of the dispensed medicine.[35] However, studies showed high consistency between dispensation and consumption by patients.[36-38] Another limitation was that only one method for evaluating adherence was used, whereas recommendation is related to the use of more than one method.[39] However, studies showed that estimates for adherence obtained from records of medicine dispensing were comparable to those provided by direct methods such as electronic measures; therefore, those were a good estimate for adherence.[40]

To our knowledge, this was the first large-scale study carried out in a Brazilian population of COPD patients treated in the public health system that evaluated the adherence to treatment and patient-related determinants. However, new studies, combined with other methods to evaluate adherence using prospective designs, should be considered in order to identify predictive factors for adherence and the relation between adherence and morbidity and mortality related to the disease.

In conclusion, COPD patients monitored in a pharmaceutical care-based DMP of a public health system with free supply of drugs showed a high rate of adherence to treatment. Non-adherent individuals to treatment at the first year of follow-up were almost twice times likely to die compared to those adherents. Strategies to monitor and optimize adherence should be implemented to reduce COPD-related morbidity and mortality.

AUTHOR CONTRIBUTIONS

CRP, ACML, LAC and GSS: contributed to the design and concept of the study. CRP and ATAM: carried out the data collection. EMN and CRP: performed the statistical analyses and data interpretation. ATAM and CRP: drafted the manuscript. EMN, CRP and ACML: checked the final manuscript and revised it critically. All authors read and approved the final manuscript.

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J Bras Pneumol. 2022;48(1):e20210366
https://dx.doi.org/10.36416/1806-3756/e20210366

ORIGINAL ARTICLE

Prognostic features of sarcoidosis course in a Brazilian cohort

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Submitted: 3 September 2021.
Accepted: 3 November 2021.

Study carried out at Hospital São Paulo, Hospital do Servidor Público Estadual de São Paulo, and Clínica Dr. Carlos Alberto de Castro Pereira, São Paulo (SP) Brasil.

ABSTRACT

Objective: To identify predictive features associated with the course of sarcoidosis at initial evaluation and to develop a predictive score. **Methods:** This was a retrospective study involving pulmonary sarcoidosis patients, classified as having a self-limited or persistent course of disease, comparing data between the outcomes by univariate analysis. Features related to persistent disease were selected by multivariate analysis and a prognostic score was designed. **Results:** The sample comprised 200 patients (mean age = 49 years). The median duration of symptoms to diagnosis was 12 months, and delayed diagnosis (> 12 months) was found in 43% of the cases. The most common radiological stage was II; 37% had reduced FVC. Relevant systemic involvement was detected in 37% of the patients. Treatment for tuberculosis was prescribed in 44 patients prior to sarcoidosis diagnosis. Treatment for sarcoidosis was required in 77% of the sample, and the disease course was persistent in 115 cases. Excluding 40 patients with fibrotic disease, prognostic factors to persistent disease were parenchymal involvement, delayed diagnosis, dyspnea, relevant systemic involvement, and reduced FVC. On the basis of the analysis, a 3-letter scoring system (A, B and C) was developed according to the selected factors. The positive predictive values for persistent course for A (≤ 1 point) and C scores (≥ 4 points) were 12.5% and 81.8%, respectively. **Conclusions:** A score can be derived by selected features at initial evaluation, allowing the prediction of outcomes in a significant number of sarcoidosis patients.

Keywords: Sarcoidosis; Prognosis; Chronic disease; Tuberculosis.

INTRODUCTION

Sarcoidosis is a multisystem granulomatous disease with highly variable clinical expression, natural history, and prognosis.[1,2] It ranges from self-limited, often asymptomatic disease to one with severe loss of function that can lead to death.[1-3]

A number of studies derived models for predicting a higher risk of death, respiratory failure, or chronic disease.[3-14] Some have suggested complex classifications after a long-term follow-up period.[15-17] On an individual basis, it may be difficult to establish the prognosis of sarcoidosis, but it would be important to try to identify possible outcomes at diagnosis. Several manifestations are strongly associated with a worse prognosis. These include treatment-resistant pulmonary sarcoidosis phenotypes (e.g., fibrosis and pulmonary hypertension) and multiorgan sarcoidosis.[18,19] Other features are associated with chronic or persistent sarcoidosis in some studies, but not in others.[7,8,10,12,16,17,20] These include older age, male gender, smoking, respiratory/constitutional symptoms, race, level of dyspnea, absence of erythema nodosum, abnormal lung function, lung parenchymal involvement in the absence of fibrosis, and systemic involvement.[7,8,10,12,16,17,20]

The influence of duration of symptoms to diagnosis in sarcoidosis on outcomes is rarely reported. In a study involving the development of a score by experts, a greater time to diagnosis of sarcoidosis was associated to greater disease severity in the univariate analysis, but not in the multivariate analysis.[16] In another study, subacute and chronic course groups (i.e., if estimated disease duration was less or more than 2 years, respectively) had a similar mean duration of symptoms to diagnosis (2 months only).[9] In a North-American study,[21] sarcoidosis was not diagnosed in more than one fourth of the subjects within 6 months of initial symptoms. Those patients had lower FEV_1 (but not lower FVC) and more advanced stages of disease.[21] The median duration of symptoms to diagnosis was 12 months in a study in Brazil.[22] In the group of time to diagnosis > 12 months, both FVC and FEV_1 were lower, and tuberculosis was more commonly misdiagnosed.

The objectives of present study were to identify predictive features at initial evaluation associated with the clinical course of sarcoidosis and to develop a simple predictive prognostic score of disease outcome in routine practice. In particular, the role of delayed diagnosis and of treatment for misdiagnosed tuberculosis was analyzed.

METHODS

Patients with a diagnosis of pulmonary sarcoidosis were retrospectively evaluated at three specialized centers (two

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Financial support: None.

ISSN 1806-3756

tertiary hospitals and a private clinic) in interstitial lung diseases (ILDs) in the city of São Paulo, Brazil, between January of 1990 and December of 2015.

Diagnosis of sarcoidosis was based on a joint statement of the American Thoracic Society, the European Respiratory Society, and the World Association of Sarcoidosis and Other Granulomatous Disorders.[1] Patients with typical clinical features, patients unable to undergo biopsy procedures, and those without definite histological findings were diagnosed by a multidisciplinary team involving pulmonology and radiology experts in ILDs. Patients with complete initial evaluation within 3 months of initial treatment were included. Data were recorded using a standardized assessment form and included the following variables: age, sex, diagnostic procedure, symptoms, pulmonary function and chest radiological test results, systemic staging, treatment, and outcome. A previous diagnosis of tuberculosis was carefully reviewed. No bacteriological diagnosis was confirmed in the cohort. Rare cases of patients with presumed or confirmed sarcoidosis but having a definitive diagnosis of tuberculosis that were seen during the study period were excluded. Exclusion criteria included absence of thoracic involvement (stage 0) or missing data at diagnosis or regarding disease outcome.

Dyspnea was classified in accordance with Mahler and Wells' magnitude of task[23] and was considered relevant if present in moderate/light activities or at rest. Thoracic images were classified in accordance with the Scadding staging system,[24] based on CT findings. FVC was classified as abnormal using reference values for the Brazilian population.[25] Organ involvement was considered in the presence of definite or probable involvement using criteria from two reference studies.[1,26] Relevant systemic involvement was defined by the presence of extrathoracic sarcoidosis, excluding acute manifestations (facial palsy, peripheral adenopathy, orbital/salivary gland involvement, erythema nodosum, arthritis, or calcium metabolism disorders).

Physicians specialized in ILDs individually decided on the therapy. The records included type of drugs and time to initiation and duration of treatment, considered when performed for at least 3 consecutive months.

The disease course was classified as follows: self-limited—spontaneous involution within 2 years after diagnosis or stability at least for 1 year after a course of therapy; and persistent—treatment resistance, relapse after stopping treatment, maintenance treatment deemed necessary, or evidence of stable chronic disease 2 years after diagnosis.[27] In order to classify the disease course, a 1-year-interval from the latest outcome criteria was awaited. Some patients experienced relapse or treatment resistance during the last evaluation, and there was not enough time to determine whether the disease was chronically stable or whether it required permanent treatment.

Statistical analysis

The results were expressed as absolute and relative frequencies, mean ± standard deviation, or median and lower and upper quartiles (Q1 and Q3). The normal distribution of the variables was tested using the Kolmogorov-Smirnov test after visual inspection of the curves.

Time from first symptom to diagnosis was considered zero in asymptomatic patients (incidental diagnosis). Clinical, radiological, and functional data were compared between patients with self-limited and persistent courses by using Fisher's exact or Pearson's chi-square tests for categorical variables and by using Student's t-test and Mann-Whitney U test for continuous variables with normal and non-normal distribution, respectively.

Variables initially selected by univariate analysis with a p-value < 0.10 were entered in a multivariate analysis using the Wald method (forward stepwise technique) to calculate ORs and 95% CIs for independent features related to persistent course in the non-fibrotic sarcoidosis group.

After logistic regression, relative weights were assigned to significant OR values, and a prognosis score was developed, assigning points for each variable identified. Internal consistency of the final model was tested using the bootstrapping method (1,000 samples).

The analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA). The study was approved by the Research Ethics Committees of *Hospital São Paulo/Universidade Federal de São Paulo* (CAAE no. 55830016.0.1001.5505) and *Hospital do Servidor Público Estadual de São Paulo* (CAAE no. 55830016.0.2001.5463).

RESULTS

A total of 200 sarcoidosis patients with complete initial evaluation and follow-up were included in the study. Table 1 summarizes the baseline features and the comparative data between subjects with non-fibrotic and fibrotic sarcoidosis. Most of the subjects were female (63%), and the mean age at diagnosis was 49.4 years. The median duration of symptoms to diagnosis was 12 months. Cough and dyspnea were the most common pulmonary symptoms. Half of the sample manifested systemic symptoms (fever and/or weight loss).

Delayed diagnosis was characterized when diagnosis was confirmed more than 12 months after the onset of symptoms (in 43% of the cases). Delayed diagnosis was more common in females than in males (75% vs. 54%; $p < 0.01$), in patients over than 50 years of age (64% vs. 38%; $p < 0.01$), and in those presenting with wheezing (38% vs. 23%; $p = 0.02$) in comparison with non-delayed diagnosis (≤ 12 months).

The most common radiological staging was II, followed by stages I and IV, the latter ones with similar proportions. Mean FVC was below the lower limit of normal in 37% of the cases.

Treatment for presumed tuberculosis was performed prior to the diagnosis of sarcoidosis in 44 patients

Table 1. General features in the cohort of patients with sarcoidosis (N = 200) and comparison between the non-fibrotic and fibrotic disease groups.[a]

Features	Whole sample (N = 200)	Group		p
		Non-fibrotic disease (n = 160)	Fibrotic disease (n = 40)	
Gender, female	126 (63)	101 (63)	25 (62)	1.00
Age, years	49.4 ± 12.2	48.3 ± 11.5	53.6 ± 14.1	0.02
Granulomas on biopsy	176 (88)	147 (92)	29 (72)	< 0.01
Duration of symptoms to diagnosis, months	12 [4, 25]	10 [4, 24]	24 [8, 68]	0.01
Follow-up, months	80 [42, 123]	88 [40, 132]	77 [44, 96]	0.22
Smoking (current or former smoker)	68 (34)	48 (30)	20 (50)	0.02
Dyspnea	78 (39)	56 (35)	22 (55)	0.02
Cough	111 (56)	84 (52)	27 (60)	0.09
Wheezing	59 (30)	43 (27)	16 (40)	0.10
Weight loss	83 (42)	69 (43)	14 (35)	0.35
Fever	40 (20)	30 (19)	10 (25)	0.38
Relevant systemic involvement[b]	76 (38)	60 (38)	16 (40)	0.77
Treatment for presumed tuberculosis	44 (22)	33 (21)	11 (28)	0.35
Radiological staging, n				
I		38		
II		97		
III		25		
IV			40	
FVC, % predicted	84.9 ± 18.8	88.5 ± 16.8	70.7 ± 19.9	< 0.01
Reduced FVC	74 (37)	47 (29)	27 (68)	< 0.01
FEV_1 /FVC ratio	0.79 ± 0.09	0.78 ± 0.09	0.78 ± 0.10	0.56
Pharmacological treatment	153 (76)	113 (71)	40 (100)	< 0.01

[a]Values expressed as n (%), mean ± SD, or median [Q1, Q3]. [b]Excluding facial palsy, peripheral adenopathy, orbital and salivary glands involvement, erythema nodosum, arthritis, and calcium metabolism disorder.

(22%). Patients treated for presumed tuberculosis, in comparison with those who were not, were associated with weight loss (61% vs. 35%; p < 0.001) and parenchymal lung involvement (95% vs. 77%; p = 0.01). In this group, a longer duration of disease prior to sarcoidosis treatment was observed: median [Q1-Q3] = 17.0 [9.0-62.5] months vs. 9.0 [2.8-18.0] months; p = 0.024.

Systemic involvement is shown in Figure 1. Relevant systemic involvement (excluding acute manifestations) was present in 74 cases (37%).

During the course of the disease, 77% of the cases needed treatment, mainly corticosteroids (in 74%), followed by methotrexate and/or leflunomide (in 39%). Only 4% of the patients demanded TNF inhibitors. Two or more drugs were prescribed to 51% of the patients.

The analysis of features associated with the proposed outcomes was performed after excluding 40 patients in stage IV, since this stage is related to irreversible pulmonary lesions. In comparison with non-fibrotic sarcoidosis patients, those in stage IV (n = 40) were older, more often had a delayed diagnosis, more frequently had dyspnea, had lower FVC (in % of the predicted value), and more frequently had a smoking habit (p < 0.05 for all). All fibrotic patients needed treatment (82% of those with two or more drugs), and compared with those without fibrosis, also had a higher death rate (28% vs. 9%).

The final sample of patients with non-fibrotic pulmonary sarcoidosis was divided into self-limited (n = 85) and persistent (n = 75) course subgroups according to disease outcome (Figure 2). Prognostic features of the two subgroups were compared (Table 2). The univariate analysis associated the persistent course subgroup with parenchymal lung involvement (stages II and III), delayed diagnosis, dyspnea, relevant systemic involvement in two or more organs (but not in only one organ), reduced FVC, and treatment for presumed tuberculosis. Erythema nodosum was observed in 16 patients (10% of the cases), mainly in women (88%), but its presence was not associated with a better outcome (10 in the self-limited disease subgroup vs. 6 in the persistent disease subgroup). Smoking history was similar in the two subgroups. Other significant associations were as follows: 42/122 (34%) of the patients with parenchymal involvement had reduced FVC, compared with 5/38 (13%) of those without parenchymal involvement (p = 0,01); and 24/56 (43%) of the patients with dyspnea had reduced FVC, compared with 23/104 (22%) of those without dyspnea (p = 0,01). There was no significant association between parenchymal involvement and dyspnea (p = 0.29). Although there were significant associations among these variables, they were all selected for the final multivariate analysis.

In the final logistic regression model, two patients were excluded because they were considered discrepant

by the selected statistical model. The results of the multivariate analysis (OR and 95% CI) are shown in Table 3. Treatment for tuberculosis did not reach statistical significance. However, more patients treated for tuberculosis developed pulmonary fibrosis during follow-up. Evolution imaging was available in 154/158 of the non-fibrotic sarcoidosis patients; 15/32 (47%) and 31/122 (25%) of those who had and had not received tuberculosis treatment, respectively, developed fibrosis (p = 0.018).

By using the relative ORs of significant variables, a point score system was developed: reduced FVC, delayed diagnosis, and dyspnea—1 point each—parenchymal lung involvement and two or more relevant extrathoracic involvements—2 points each. By grouping the most relevant sum of points to distinct outcomes, three cutoff points and a staging system were developed: 0-1 point = stage A (24 patients); 2-3 points = stage B (90 patients); and ≥ 4 points = stage C (44 patients). Persistent course occurred in 12.5% (21/24) of the patients in stage A, in 38.9% (35/90) of those in stage B, and in 81.8% (36/44) of those in stage C (x^2 = 39.94; p < 0.001; Figure 3).

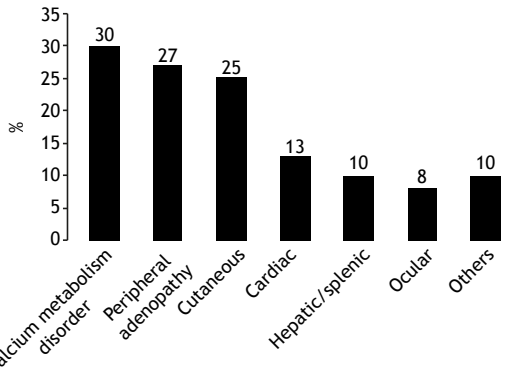

Figure 1. Proportion of systemic manifestations in the cohort (N = 200).

According to the proposed score, adding 40 cases of fibrotic disease (persistent course), the model would make a correct prediction in 97 of 200 cases (48%).

Internal validation of the staging system (bootstrapping resampling method) was performed, based in 1,000 samples, and statistically significant variables remained in the multivariate analysis (p < 0.05), except again for tuberculosis treatment (p = 0.16).

DISCUSSION

Predicting the course of sarcoidosis at initial evaluation is a hard task in clinical practice.[28,29] In the current study, we were able to identify prognostic features at presentation that were associated with self-limited or persistent course in patients with non-fibrotic pulmonary sarcoidosis in a significant, albeit limited number of cases. These included delayed diagnosis (> 12 months), presence of dyspnea, parenchymal lung involvement (stages II and III), reduced FVC, and relevant extrathoracic disease in two or more organs. Treatment for presumed tuberculosis in sarcoidosis patients was associated with delayed diagnosis and more persistent disease.

Patients with no thoracic involvement (stage 0) were excluded from the present study. In comparison with a large prospective North-American study, the present study included a smaller number of stage I cases and a larger number of stage IV cases, probably due to selection bias.[30]

Several factors have been associated with the outcome of sarcoidosis in different studies.[4-14] In the present study, the course of sarcoidosis was classified as self-limited or persistent.[27] At presentation, all patients with pulmonary fibrosis (stage IV) had persistent disease and demanded treatment. These patients were older, more often had a delayed diagnosis, more often reported having significant dyspnea, more frequently

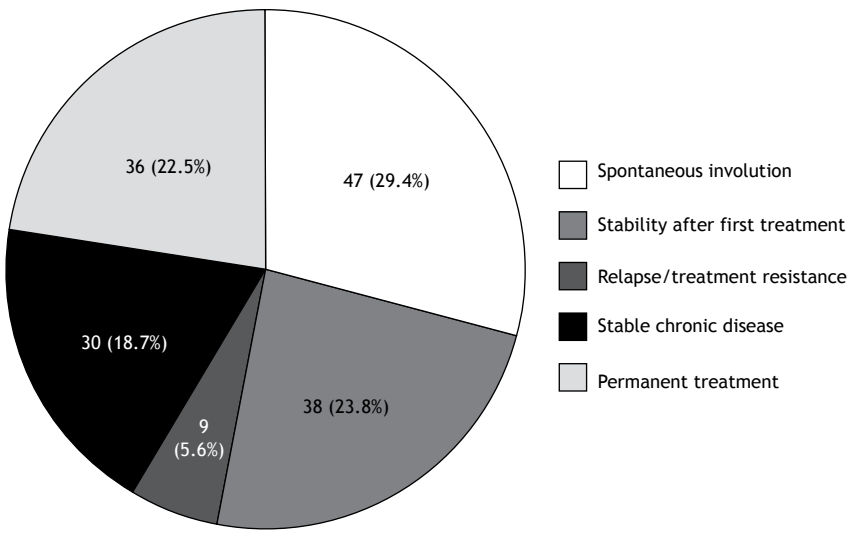

Figure 2. Outcomes in the non-fibrotic pulmonary sarcoidosis group (n = 160). Patients with spontaneous involution or stability after first treatment were classified as having self-limited disease, the remaining being classified as having persistent disease.

Table 2. General features of 160 patients with non-fibrotic pulmonary sarcoidosis classified as having a self-limited or persistent course.[a]

Feature	Group		p
	Self-limited course (n = 85)	Persistent course (n = 75)	
Female/male	55 (65)/30 (35)	46 (61)/29 (39)	0.74
Age, years	48.2 ± 12.8	48.5 ± 9.9	0.64
Time to diagnosis: early/delayed	60 (71)/25 (29)	38 (51)/37 (49)	0.01
Follow-up, months	76 [41, 114]	98 [40, 163]	0.20
Smoking (current or former smoker)	23 (27)	25 (33)	0.75
Dyspnea	23 (27)	33 (44)	0.03
Weight loss	37 (44)	32 (43)	1.00
Fever	15 (18)	15 (20)	0.84
Erythema nodosum	10 (12)	6 (8)	0.43
Tuberculosis treatment	10 (12)	23 (31)	< 0.01
Radiological staging			
I	27 (32)	11 (15)	
II	46 (54)	51 (68)	0.04
III	12 (14)	13 (17)	
Reduced FVC	17 (20)	30 (40)	< 0.01
FEV_1/FVC ratio	0.79 ± 0.09	0.79 ± 0.10	0.72
Two or more relevant extrathoracic involvements	4 (5)	13 (17)	0.01
Pharmacological treatment	38 (45)	75 (100)	< 0.01

[a]Values expressed as n (%), mean ± SD, or median [Q1, Q3].

Table 3. Independent predictive factors for persistent course in the non-fibrotic pulmonary sarcoidosis group at initial evaluation (n = 158 patients).[a]

Variable	OR	95% CI	p
Reduced FVC	2.35	1.05-5.15	0.038
Delayed diagnosis	2.37	1.50-4.93	0.020
Dyspnea	2.55	1.18-5.49	0.017
Parenchymal lung involvement	3.94	1.54-10.1	0.004
Two or more relevant extrathoracic involvements	5.78	1.66-20.2	0.006

[a]Ajusted for treatment for presumed tuberculosis. Two discrepant patients were excluded from the analysis.

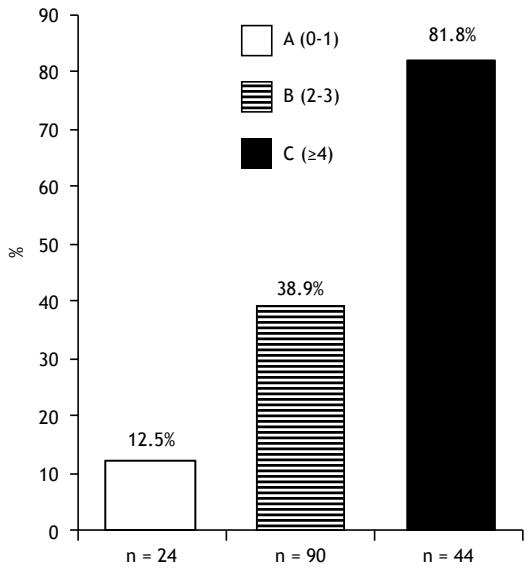

Figure 3. Positive predictive value in the non-fibrotic pulmonary sarcoidosis group (n = 158) for persistent course according to stages A (0-1 point), B (2-3 points) and C (≥ 4 points). p < 0.01.

were smokers or former smokers, and had lower FVC%. Weight loss was more common in those treated for misdiagnosed tuberculosis, but the presence of fever was not significantly different.

Smoking seems to have a protective effect on sarcoidosis development, but this is not a universal finding. In the present study, those subjects in radiological stage IV were most commonly smokers or former smokers, suggesting a higher risk for the fibrotic phenotype in smokers, similar to that observed in hypersensitivity pneumonitis.[31]

No influence of gender on prognosis was found. Race was not evaluated, due to the high interbreeding in the Brazilian population.

Spontaneous remission has been reported to occur in 90% of the patients in stage I, in 40-70% of those in stage II, and in 10-20% of those in stage III.[32] In the present study, patients in stage I more often presented with self-limited disease, but those in stages II and III had similar frequencies of self-limited and persistent courses and, consequently, were merged. The same was observed in the classic study by Neville et al.[2]

Parenchymal involvement, dyspnea, and reduced FVC remained significant predictors of disease outcome in the multivariate analysis. There is a dissociation among the level of dyspnea, pulmonary function results, and chest imaging in sarcoidosis.[33,34] We found that even stage I cases can have reduced FVC and relevant dyspnea, similarly to what has been reported in other studies.[8,32] Parenchymal lung disease can be present when HRCT is performed, even in the absence of radiographic abnormalities, demonstrating the higher sensitivity of CT.[35] We found that FVC below the lower limit of normal was a predictor of a persistent course of the disease. In one study, FVC < 80% of the predicted value was also a predictor of chronic disease.[36] The FEV_1/FVC ratio was similar between the two groups. Few studies have evaluated the role of dyspnea for predicting the course of sarcoidosis. In a study to determine features at initial presentation that are associated with continued treatment (2 years after onset), Baughman et al.[8] found that the level of dyspnea and predicted VC were significant features.

Dyspnea is multifactorial and can be the result of several aspects in sarcoidosis, not only due to pulmonary abnormalities. Conditions such as pulmonary hypertension, cardiac disease, anemia, musculoskeletal/neurological involvement, joint involvement, parasarcoidosis syndromes (chronic fatigue, anxiety, and depression), and hyperventilation can result in dyspnea.[37]

The diagnosis of sarcoidosis from the onset of symptoms is often delayed for several reasons, including a great number of health care visits prior to diagnosis.[21,22,38] The presentation of sarcoidosis is too diverse, the disease is uncommon, and very few physicians have training in and experience with the disease.

The influence of the delay in diagnosis on the outcomes has been rarely reported. In the present sample, half of the cases had the diagnosis delayed for more than 1 year, and most of these cases were associated with chronic disease. Delayed diagnosis was more common in females, older patients (> 50 years of age), those with wheezing, and those misdiagnosed with tuberculosis.

Persistent sarcoidosis was more common when relevant multiorgan, extrapulmonary involvement was present, a well-known association.[7,10,19,29,39]

In developing countries, due to the high incidence of tuberculosis, many patients who are diagnosed with sarcoidosis will have received treatment for tuberculosis. In our study, patients presenting with weight loss had more frequently been treated for tuberculosis. To the best of our knowledge, the impact of such decision on the final outcome of sarcoidosis has not been studied.

Although *Mycobacterium tuberculosis* does not seem to be the etiologic trigger for sarcoidosis, there is increasing evidence for mycobacteria to be a cause of at least some cases of sarcoidosis. In the present study, we found that a great number of patients treated for tuberculosis had a chronic course and developed imaging-confirmed fibrosis that was not present at initial evaluation. This suggests that treatment for presumed tuberculosis can worsen the course of the disease. A study postulated that the antigen(s) from this mycobacterium could be released during the death of the organism, with a complex of host and mycobacterial proteins in response to the infection leading to sarcoidosis.[40] That study also suggested that the failure to clear these antigen/protein complexes could lead to chronic disease in some patients.[40] There seems to be a bidirectional association between sarcoidosis and tuberculosis. Some patients with sarcoidosis have confirmed tuberculosis, before or after sarcoidosis. However, such cases were excluded from the present cohort.

Several studies have developed complex classifications for assessing the course of sarcoidosis after a long period of follow-up. Drug categories used in treatment were included in those classifications.[15-17]

A study carried out in Turkey evaluated the course of 275 patients with sarcoidosis separated according to disease course (subacute vs. chronic groups) and developed a model to predict the course using simple clinical and demographic variables.[9] Logistic regression indicated that erythema nodosum, arthralgia and/or arthritis, and stage I disease were more frequent in the subacute group, whereas respiratory/constitutional symptoms and stage II-III disease were more frequently seen in the chronic disease group. In our study, erythema nodosum was uncommon and did not have predictive values. Constitutional symptoms were not a predictor of outcome.

The major strengths of present study are the long-term follow-up period of the patients and the simplicity of the developed model. However, several limitations are present in our study. Patients were retrospectively evaluated and treated in referral centers, so they might not be representative of sarcoidosis at large. The derived model managed to estimate the prognosis in only half of the cases and must be reviewed using a validation cohort. Better markers of prognosis, including biomarkers, are necessary in sarcoidosis. DLCO measurements and investigation for pulmonary hypertension were performed in a limited number of cases and were not included in final analysis. Specific parenchymal findings on CT, which might be helpful in predicting the prognosis, were not evaluated. Finally, this study did not include a protocol for therapy.

In conclusion, a predictive score for sarcoidosis outcome can be derived by multiple variables at initial evaluation in order to predict the clinical course of the disease in a significant, albeit limited number of cases. The results should be confirmed in future studies involving a validation cohort.

ACKNOWLEDGMENTS

The corresponding author would like to thank the institutions and the participants involved the study, especially the *Universidade Federal de São Paulo*

for receiving her since the beginning of my medical residency program.

AUTHOR CONTRIBUTIONS

MDCC and CACP: conception and study design; data analysis and interpretation; drafting and critical revision of the manuscript for important intellectual content; and approval of the final version. MRS: expert advice and guidance at all stages of the study and during the manuscript preparation process; and approval of the final version.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210335
https://dx.doi.org/10.36416/1806-3756/e20210335

ORIGINAL ARTICLE

Are maximum respiratory pressures predictors of sarcopenia in the elderly?

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Submitted: 23 August 2021.
Accepted: 20 December 2021.

Study carrried out in the Núcleo de Estudos em Epidemiologia do Envelhecimento, Universidade Estadual do Sudoeste da Bahia – UESB – Jequié (BA) Brasil.

ABSTRACT

Objective: To compare maximum respiratory pressures and spirometric parameters among elderly individuals classified as having no sarcopenia, probable sarcopenia, and confirmed sarcopenia, and to test the ability of these variables to discriminate sarcopenia in a community-dwelling elderly population. **Methods:** This was a cross-sectional study involving 221 elderly (≥ 60 years of age) individuals of both sexes. Sarcopenia was diagnosed in accordance with the new consensus of the European Working Group on Sarcopenia in Older People. Maximum respiratory pressures and spirometry parameters were assessed. **Results:** The prevalences of probable sarcopenia and confirmed sarcopenia were 20.4% and 4.1%, respectively. Regardless of the sex, those with confirmed sarcopenia had significantly lower MEP than those with no sarcopenia and probable sarcopenia, whereas only males with confirmed sarcopenia presented with significantly lower MIP than did the other individuals. There was an inverse association of MIP and MEP with sarcopenia, indicating that the decrease by 1 cmH_2O in these parameters increases the chance of sarcopenia by 8% and 7%, respectively. Spirometric parameters were not associated with sarcopenia. Cutoff points for MIP and MEP, respectively, were ≤ 46 cmH_2O and ≤ 50 cmH_2O for elderly women, whereas they were ≤ 63 cmH_2O and ≤ 92 cmH_2O for elderly men, and both were identified as predictors of sarcopenia (area under the ROC curve > 0.70). **Conclusions:** Sarcopenia was associated with lower maximum respiratory pressures, but not with spirometric parameters. Maximum respiratory pressures can be used as markers of sarcopenia in a community-dwelling elderly population regardless of the sex.

Keywords: Aging; Sarcopenia; Maximal respiratory pressures; Spirometry.

INTRODUCTION

The current European Working Group on Sarcopenia in Older People (EWGSOP) consensus[1] defines sarcopenia as a muscle disease diagnosed when there is a decline in muscle strength and mass. Recent evidence indicates that sarcopenia can affect the respiratory muscles,[2] compromising their strength and impacting lung volumes and capacities,[1,3] which increases the risk of respiratory diseases.[3,4]

Although some respiratory parameters have already been shown to predict sarcopenia, PEF seems to be the spirometric parameter most frequently associated with this disease.[5-7] The decline in PEF with advancing age makes it useful for assessing the severity of sarcopenia in the respiratory muscles of longevous elderly individuals.[5] In addition, elderly people with sarcopenia have lower respiratory muscle strength, which is associated with the decline in strength and mass of peripheral muscles and physical performance.[8]

The change proposed by the EWGSOP[1] to diagnose sarcopenia, in which the assessment of muscle strength becomes a priority, has created a gap in the literature, justifying further studies that follow current guidelines. Thus, it will be possible to verify whether the proposed changes may affect the diagnosis and behavior of sarcopenia in relation to other health conditions.

We have started with the hypothesis that respiratory parameters can be predictors of sarcopenia in the elderly, and this appears to be the first study to evaluate the capacity of maximum respiratory pressures (MRPs) and spirometric parameters to discriminate sarcopenia within a community-dwelling elderly population, using as a diagnostic criterion the most recent proposal of the EWGSOP consensus.[1] Thus, research to investigate the relationship between sarcopenia and respiratory condition in the elderly can contribute to the health care of this population group, making it opportune to diagnose sarcopenia in the elderly undergoing respiratory tests.

This study aimed to compare MRPs and spirometric parameters in a sample of elderly people classified as having no sarcopenia, probable sarcopenia, and confirmed sarcopenia, and to test the ability of these variables

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Financial support: This study received financial support from the *Fundação de Amparo à Pesquisa do Estado da Bahia* (FAPESB, Foundation for the Support of Research in the State of Bahia; Grant no. BOL0603/2018).

ISSN 1806-3756

to discriminate sarcopenia in a community-dwelling elderly population.

METHODS

This was a cross-sectional study, with data from the project designated "Nutritional status, risk behaviors, and health conditions of the elderly in Lafaiete Coutinho-BA", which was approved by the Research Ethics Committee of the State University of Southwest Bahia (Protocol no. 491.661).

We had the support of the Municipal Health Department of Lafaiete Coutinho, a municipality in the state of Bahia, Brazil, which is 100% covered by the Brazilian Family Health Strategy, to locate the elderly (≥ 60 years of age) registered in the two Health Care Units in the urban area of the municipality. Thus, a census was carried out, and 331 individuals were identified in the initial screening. Of this total, 3 individuals refused to participate in the study and 10 were excluded because they were not located after three attempts. Therefore, 318 elderly people participated in the interviews. Participants whose information for the classification of sarcopenia was incomplete and those who did not undergo manometry and/or spirometry tests were excluded. The final sample of this study involved 221 elderly individuals (Figure 1).

Data collection took place in two occasions. Initially, a household interview was carried out using an instrument based on the Health, Well-being and Aging survey,[9] the International Physical Activity Questionnaire adapted for the elderly population,[10] and the Geriatric Depression Scale,[11] the latter two validated for use in Brazil. Tests were also applied to assess functional performance in the first occasion. In the second moment, the elderly participants were invited to attend the Health Care Unit where they were registered, at a previously scheduled time, to perform anthropometric measurements, the handgrip strength test, and respiratory tests.

Sarcopenia (dependent variable)

Sarcopenia was diagnosed based on the algorithm recently proposed by the EWGSOP consensus.[1] Initially, the elderly participants were classified as having no sarcopenia (adequate muscle strength, muscle mass, and physical performance); probable sarcopenia (insufficient muscle strength, but adequate muscle mass and physical performance); confirmed sarcopenia (insufficient muscle strength and muscle mass, but adequate physical performance); and confirmed severe sarcopenia (insufficient muscle strength, muscle mass, and physical performance). Then, the variable sarcopenia was retrieved, being considered for data analysis three categories: no sarcopenia, probable sarcopenia, and confirmed sarcopenia (including severe disease).

Muscle strength

Peripheral muscle strength was assessed through the handgrip strength test, using a hydraulic dynamometer (Saehan Corporation SH5001, Dangjin, South Korea).[12]

Insufficient muscle strength was defined according to sex and BMI.[13] The BMI was classified into three categories[14]: BMI < 22 kg/m^2 (low weight); 22 kg/

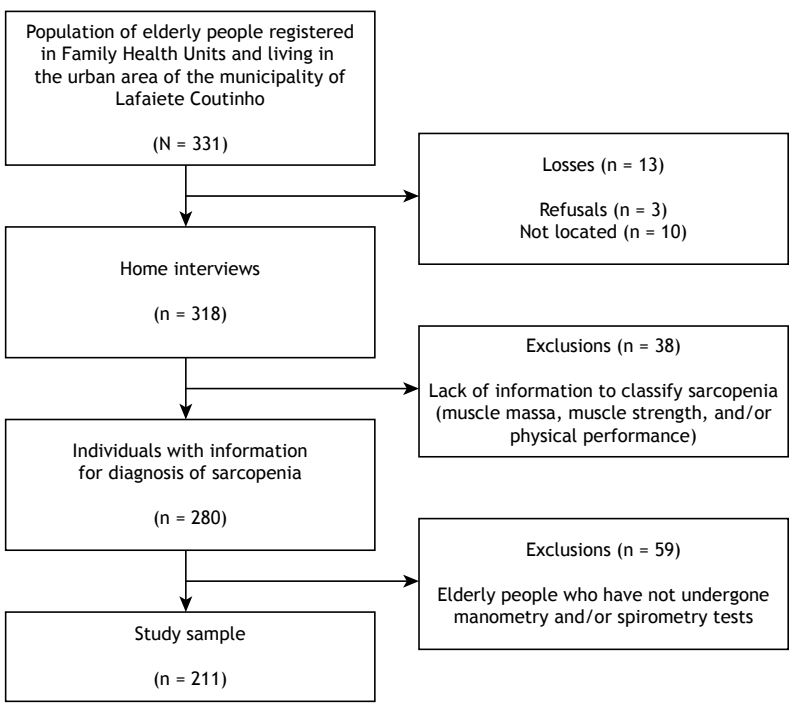

Figure 1. Flow chart of the participant selection process.

$m^2 \leq BMI \leq 27\ kg/m^2$ (adequate weight); and BMI $> 27\ kg/m^2$ (overweight). For each BMI category, the cutoff point for the handgrip strength test result was set at the 25th percentile. Thus, the participants were considered to have insufficient muscle strength when they presented values below the cutoff point related to their BMI category and sex. Those who during data collection were unable to perform the test due to physical limitations were classified as having insufficient muscle strength.

Muscle mass

The total muscle mass (TMM) was calculated using an equation proposed by Lee et al.[15] and validated for use in the Brazilian elderly population by Rech et al.[16]:

$$TMM\ (kg) = (0.244 \times BM) + (7.8 \times h) - (0.098 \times A) + (6.6 \times S) + (E - 3.3)$$

where BA is the body mass (in kg), h is the height (in m), A is the age (in years), S is the sex, and E is the ethnicity.

The values 0 for women and 1 for men were adopted for the variable sex, and the self-referred ethnicity was categorized adopting 0 for White (White, mixed race [except Black], and indigenous), 1.2 for Asian, and 1.4 for African descent (Black and Black mixed with another race).

From the TMM, the muscle mass index (MMI) was estimated as proposed by Janssen et al.[17]:

$$MMI = TMM/height^2$$

Finally, the 20th percentile of the MMI was used as a cutoff point to classify the participants as having insufficient muscle mass, stratified by sex.

Physical performance

Physical performance was assessed using the 2.44-meter walk test. Insufficient physical performance was defined using the criterion adapted by Guralnik et al.,[18] and, first, height was classified into two categories, according to sex, based on the median. Later, for each height category, the 75th percentile was used as the cutoff point for the time spent during the walk test. Thus, those elderly participants with values above the cutoff point for the time spent during the walk test and those who did not perform the test due to physical limitations were considered as having insufficient physical performance.

Independent variables

Respiratory muscle strength

The MRPs were evaluated following the guidelines of the American Thoracic Society[19] and the Brazilian Thoracic Association,[20] using a digital manometer (MVD 300; Globalmed, Porto Alegre, Brazil).

For data analysis, the highest values of MIP and MEP were used among the maneuvers considered acceptable and reproducible. The maneuvers were considered acceptable when no leaks occurred and when they were sustained for at least two seconds. In order to be considered reproducible, among the three acceptable maneuvers, the two with the highest values should not differ more than 10% between them. Up to five maneuvers could be performed, respecting an interval of one minute between them. This amount was exceeded only if the highest MRP was recorded in the last maneuver performed, ending the test when a lower pressure was generated.

Spirometric parameters

Spirometric parameters were collected using the CareFusion Microlab spirometer apparatus (Micro Medical Ltd., Rochester, England) in accordance with the Brazilian Thoracic Association guidelines.[20] The following measurements were collected: FVC, FEV_1, FEV_1/FVC ratio, PEF, and $FEF_{25-75\%}$. In addition to these measurements, the predicted values for the Brazilian population were estimated, as described by Pereira et al.[21] and calculated. For the statistical analysis, only the variables in percentage of the predicted values were considered.

Study population characteristics

The following variables were collected: sociodemographic variables (sex and age group); life habits (smoking and level of physical activity—using the long version of the International Physical Activity Questionnaire[10] and classifying the participants as active or insufficiently active, respectively, those who practiced ≥ 150 min or < 150 min of moderate/vigorous physical activity per week[22]; health condition (chronic diseases; hospitalization in the last 12 months; depressive symptoms [using the Geriatric Depression Scale])[11]; falls in the last 12 months; and functional capacity—in which the basic activities of daily living (BADL) were evaluated by means of the Katz et al. scales[23] and the instrumental ADL (IADL) in accordance with Lawton & Brody.[24] The participants were classified as independent when they were able to perform activities without help and as dependent when they needed help in at least one of the activities. Functional capacity was classified in a hierarchical manner[25] into three categories: independent, dependent on IADL only, and dependent on BADL and IADL.

Statistical analysis

Absolute and relative frequencies, as well as medians and amplitudes, were calculated. The Kolmogorov-Smirnov test was applied to assess the normality of data distribution.

The association between sarcopenia and the categorical variables was performed by means of the chi-square test (linear-by-linear association). To compare MIP, MEP, and spirometric parameters among no sarcopenia, probable sarcopenia, and confirmed

sarcopenia subgroups, the one-way ANOVA test was used, followed by Tukey's post hoc test for variables with normal distribution, and the Kruskal-Wallis test followed by the Mann-Whitney U test for variables with no normal distribution. The Mann-Whitney U test was also used for comparative analysis between the sexes.

The association between the sarcopenia profile and respiratory parameters was evaluated using multinomial logistic regression analysis and expressed as ORs and 95% CIs. In this analysis, adjustments were made for the sex variable and the covariates that had a significant association with the diagnosis of sarcopenia.

The diagnostic power of sarcopenia determined by MRP and spirometric parameters and the identification of the best cutoff points, differentiated between men and women, were evaluated using the parameters provided by a ROC curve: AUC, sensitivity, and specificity.

Significance was set at 5% ($p \leq 0.05$). All statistical analyses were performed with the IBM SPSS Statistics software package, version 21.0 (IBM Corporation, Armonk, NY, USA) and the MedCalc statistical package, version 9.1.0.1 (MedCalc, Mariakerke, Belgium).

RESULTS

The study population involved 221 elderly individuals, 54.3% being female, and 19.5% were ≥ 80 years of age. The characteristics of the sample according to the sarcopenia profile are presented in Table 1. The prevalence of probable sarcopenia was 20.4% and that of confirmed sarcopenia was 4.1%.

Table 2 shows that elderly men and women with confirmed sarcopenia had significantly lower MEP values than those with probable sarcopenia and no sarcopenia. Regarding MIP, only elderly males with confirmed sarcopenia had lower values in relation to those with probable sarcopenia and no sarcopenia ($p \leq 0.05$). In the no sarcopenia subgroup men had higher MIP and MEP values than women. In the probable

Table 1. Characteristics of the overall sample and according to sarcopenia profile subgroups.[a]

Variable	Total (n = 221)	% of answers	Subgroup			p
			No sarcopenia (n = 167)	Probable sarcopenia (n = 45)	Confirmed sarcopenia (n = 9)	
Sex		100				0,968
Female	120 (54.3)		91 (54.5)	25 (55.6)	4 (44.4)	
Male	101 (45.7)		76 (45.5)	20 (44.4)	5 (55.6)	
Age group, years		100				0.004
60-69	84 (38.0)		76 (45.5)	7 (15.6)	1 (11.2)	
70-79	94 (42.5)		61 (36.5)	29 (64.4)	4 (44.4)	
≥ 80	43 (19.5)		30 (18.0)	9 (20.0)	4 (44.4)	
Smoking		96.8				0.616
Never smoker	91 (42.5)		71 (43.6)	18 (41.9)	2 (25.0)	
Former smoker	101 (47.2)		75 (46.0)	22 (51.1)	4 (50.0)	
Current smoker	22 (10.3)		17 (10.4)	3 (7.0)	2 (25.0)	
Physical activity level		100				0.330
Active	157 (71.0)		122 (73.1)	30 (66.7)	5 (55.6)	
Insufficiently active	64 (29.0)		45 (26.9)	15 (33.3)	4 (44.4)	
Chronic diseases		94.6				0.049
None	26 (12.4)		21 (13.1)	2 (4.8)	3 (42.8)	
One	81 (38.8)		66 (41.3)	13 (31.0)	2 (28.6)	
Two or more	102 (48.8)		73 (45.6)	27 (64.2)	2 (28.6)	
Hospitalization in the last year		99.5				0.888
None	188 (85.5)		142 (85.5)	38 (84.4)	8 (88.9)	
One or more	32 (14.5)		24 (14.5)	7 (15.6)	1 (11.1)	
Depressive symptoms		99.5				0.566
No	187 (85.0)		143 (85.6)	36 (81.8)	8 (88.9)	
Yes	33 (15.0)		24 (14.4)	8 (18.2)	1 (11.1)	
Falls		98.2				0.035
No	176 (81.1)		139 (84.2)	31 (70.5)	6 (75.0)	
Yes	41 (18.9)		26 (15.8)	13 (29.5)	2 (25.0)	
Functional capacity		99.5				0.888
Independent	137 (62.3)		103 (62.0)	28 (62.2)	6 (66.7)	
Dependent for IADL	51 (23.2)		39 (23.5)	9 (20.0)	3 (33.3)	
Dependent for BADL and IADL	32 (14.5)		24 (14.5)	8 (17.8)	0 (0.0)	

IADL: instrumental activities of daily living; and BADL: basic activities of daily living. [a]Values expressed as n (%).

sarcopenia subgroup men also had higher MEP values than women ($p \leq 0.05$).

Table 3 shows that there were no significant differences between spirometric parameters in the sarcopenia profile subgroups or between the sexes ($p > 0.05$).

The adjusted analysis of the multinomial logistic regression model showed that MIP and MEP had an inversely proportional association with sarcopenia ($p \leq 0.05$), indicating that the increase of one unit (1 cmH_2O) in MIP and MEP reduced the chance of the outcome in the elderly by 8% and 7%, respectively. There were no associations of spirometric parameters in the probable and confirmed sarcopenia subgroups (Table 4).

The no sarcopenia and probable sarcopenia subgroups, because they neither presented significant differences between the medians nor associations in the adjusted model, were grouped together as "no sarcopenia" for the analysis of the ROC curve. Regardless of the sex, the results of the areas under the ROC curve of MIP and MEP indicated values above 0.70, which can be considered as having good predictive power. The cutoff points established to screen elderly women and men with sarcopenia, respectively, were MIP ≤ 46 cmH_2O and MEP ≤ 50 cmH_2O; and MIP ≤ 63 cmH_2O and MEP ≤ 92 cmH_2O. It should be noted that MEP showed a better predictive power for sarcopenia, regardless of the sex, as well as better sensitivity and specificity (Figure 2).

DISCUSSION

This study showed that MEP was lower in the confirmed sarcopenia subgroup than in the probable and no sarcopenia subgroups regardless of the sex, whereas MIP was lower only for men with confirmed sarcopenia. In a comparison between the sexes, it was possible to observe that men in the no sarcopenia subgroup had higher MIP and MEP values when compared with women in the same subgroup and that men in the probable sarcopenia subgroup had higher MEP values when compared with women in the same subgroup.

Ohara et al.[8] observed an association between sarcopenia and respiratory muscle strength and also identified that elderly individuals with sarcopenia had lower MIP and MEP values when compared with those without it. In addition, they noticed an association between the reduction in respiratory muscle strength and the decline in the components of sarcopenia. The

Table 2. Respiratory muscle strength according to sex and sarcopenia profile subgroups.[a]

Respiratory muscle strength, cmH_2O	Women			
	No sarcopenia (n = 91)	Probable sarcopenia (n = 25)	Confirmed sarcopenia (n = 4)	p*
MIP	58.0 (27.0)[†]	61.0 (26.0)	43.0 (10.0)	0.086
MEP	72.0 (31.0)[b,†]	71.0 (37.0)[b,†]	48.0 (3.0)[c]	0.033
Respiratory muscle strength, cmH_2O	**Men**			
	No sarcopenia (n = 76)	**Probable sarcopenia (n = 20)**	**Confirmed sarcopenia (n = 5)**	**p***
MIP	81.0 (47.0)[b,†]	65.5 (34.0)[b]	48.0 (23.0)[c]	0.050
MEP	111.0 (42.0)[b,†]	104.5 (64.0)[b,†]	71.0 (53.0)[c]	0.026

[a]Values expressed as median (IQR). [b,c]Different letters indicate statistical difference ($p \leq 0.05$) between the subgroups (Mann-Whitney U test). *Kruskal-Wallis test: [†]$p \leq 0.05$ between sexes (Mann-Whitney U test).

Table 3. Spirometric parameters according to sex and sarcopenia profile subgroups.[a]

Variable	Women			
	No sarcopenia[a] (n = 85)	Probable sarcopenia[a] (n = 22)	Confirmed sarcopenia[b] (n = 3)	p
FVC (% predicted)	69.0 (30.0)	63.5 (29.0)	47.0 (38.0)	0.404
FEV_1 (% predicted)	72.0 (31.0)	61.5 (37.0)	50.0 (32.0)	0.398
FEV_1/FVC	80.3 (19.0)	81.1 (25.0)	75.7 (11.0)	0.664
PEF (% predicted)	41.0 (26.0)	40.0 (32.0)	32.0 (17.0)	0.249
$FEF_{25-75\%}$ (% predicted)	61.0 (53.0)	55.0 (71.0)	43.0 (26.0)	0.376
Variable	**Men**			
	No sarcopenia[a] (n = 73)	**Probable sarcopenia[a] (n = 18)**	**Confirmed sarcopenia[b] (n = 5)**	**p**
FVC (% predicted)	72.0 (22.0)	67.0 (20.0)	69.0 (38.0)	0.065
FEV_1 (% predicted)	68.0 (22.0)	62.5 (22.0)	68.0 (49.0)	0.512
FEV_1/FVC	77.4 (18.0)	78.4 (18.0)	68.7 (38.0)	0.123
PEF (% predicted)	38.0 (27.0)	38.0 (21.0)	31.0 (26.0)	0.163
$FEF_{25-75\%}$ (% predicted)	62.0 (44.0)	51.5 (42.0)	38.0 (60.0)	0.118

[a]Values expressed as median and interquartile range. [b]Values expressed as median and range (difference between lowest and highest values).

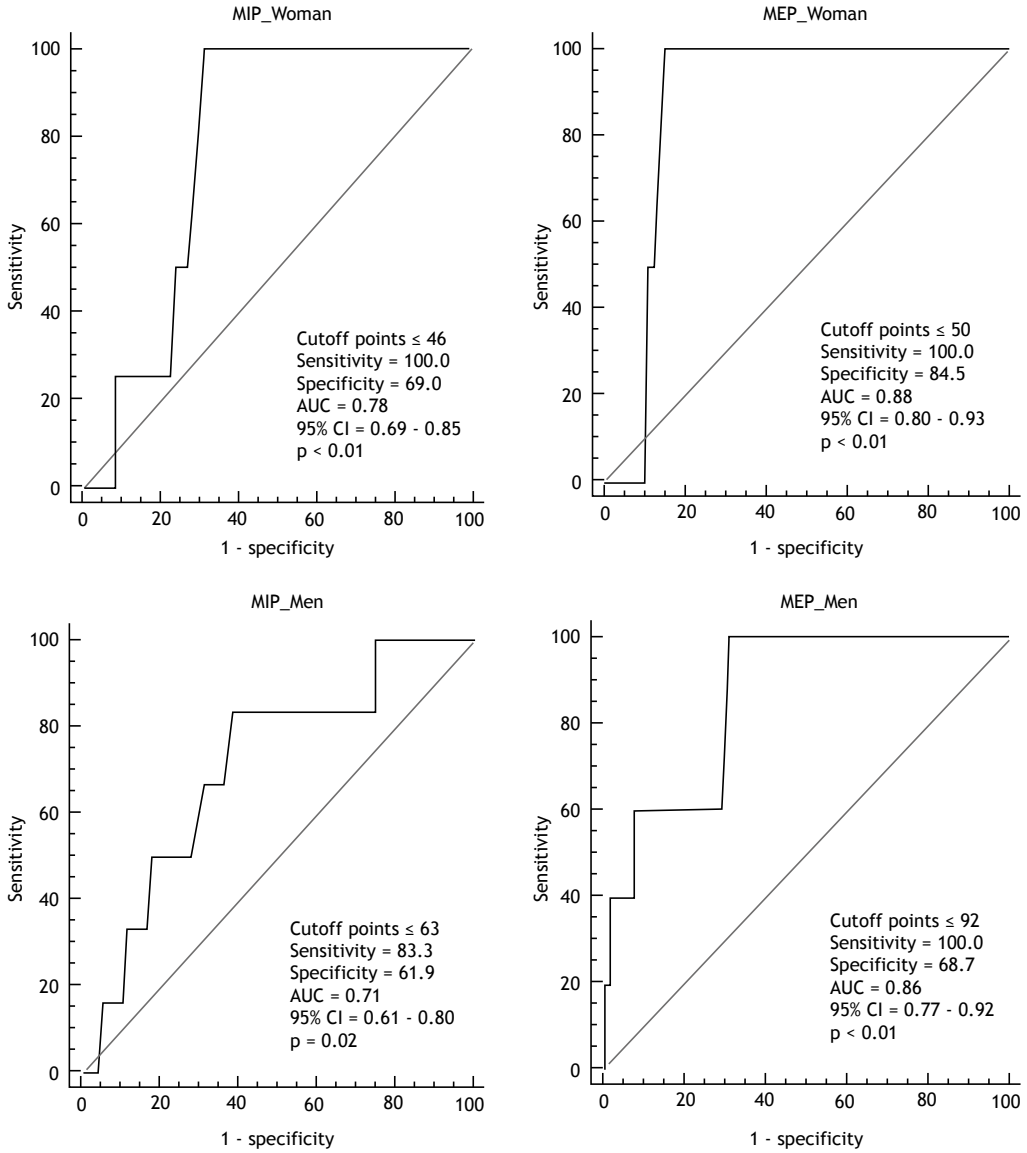

Figure 2. Cutoff points, sensitivity, specificity, and areas under the ROC curve for maximum respiratory pressures as discriminators of sarcopenia in elderly women and men.

physiological processes that accompany aging affect the muscle system of the elderly, so that weakness of the respiratory muscles is associated with the decline of peripheral muscles.[26]

Diaphragmatic sarcopenia impacts on the performance of this muscle to produce strength, which affects inspiratory capacity and also the ability to perform expulsive maneuvers that are important for airway hygiene.[27] This finding was reaffirmed in a review study that discussed the mechanisms related to the aging of diaphragmatic muscle fibers.[4] Thus, the findings of the present study corroborate the hypothesis described above. In addition, we highlight that aging is accompanied by accentuated thoracic kyphosis and increased rigidity of the rib cage, reducing elastic retraction capacity and lung compliance[28] and affecting respiratory muscle strength.[29,30]

In this study, men with confirmed sarcopenia showed better MIP and MEP than did women with the disease, and men with probable sarcopenia showed better MEP than did women in the same category, as reported in a previous study.[31] These findings can be explained by the differences that exist in the body composition of men and women: males tend to present greater muscle strength and mass.[26,32]

The results also showed that an increase of 1 cmH_2O in both MIP and MEP was able to reduce the chance of sarcopenia in the elderly by 8% and 7%, respectively. This reduction was higher than that reported in other studies.[8] These differences may be related to the profiles of populations related to social aspects and health conditions. Methodological differences in relation to the criteria used for the diagnosis of sarcopenia are also highlighted, since our study used the new

Table 4. Associations between probable and confirmed sarcopenia subgroups with maximum respiratory pressures and spirometric parameters.

Variable	Probable sarcopenia		Confirmed sarcopenia	
	Adjusted OR* (CI 95%)	p	Adjusted OR* (CI 95%)	p
MIP (cmH_2O)	1.00 (0.99-1.02)	0.403	0.92 (0.85-0.98)	0.018
MEP (cmH_2O)	1.00 (0.98-1.01)	0.882	0.93 (0.88-0.98)	0.011
FVC (% predicted)	0.99 (0.97-1.01)	0.522	0.68 (0.10-4.54)	0.691
FEV_1 (% predicted)	0.99 (0.97-1.01)	0.571	0.98 (0.94-1.03)	0.483
FEV_1/FVC	1.01 (0.98-1.04)	0.548	1.00 (0.94-1.08)	0.870
PEF (% predicted)	0.99 (0.97-1.01)	0.653	0.93 (0.86-1.01)	0.093
$FEF_{25-75\%}$ (% predicted)	0.99 (0.98-1.00)	0.348	0.99 (0.95-1.02)	0.484

*Sex, age group, chronic diseases, and falls.

EWGSOP consensus,[1] whereas Ohara et al.[8] based their study on previous recommendations. We add that Ohara et al.[8] used an analog manometer, and we used a digital device. Such differences may have influenced the values observed.

Another important finding of this study was the identification of cutoff points to assist in the screening of sarcopenia from the values obtained in manometry. In our study, we noted that the cutoff points for MIP and MEP showed better sensitivity values for both sexes and better specificity for women in relation to those in the study by Ohara et al.[8] Both studies had similar cutoff points for older women and suggested greater values for men, although the cutoff points for men were quite distinct between the two studies. These differences may also have occurred because of differences in the profile of elderly men samples, in addition to methodological differences between the two studies for the diagnosis of sarcopenia.[1,33] Comparisons with other national studies were not possible, since there are still few investigations proposing such cutoff points for diagnosing sarcopenia in the community-dwelling elderly population in Brazil.

The analysis of sensitivity of cutoff points for MEP, for both sexes, and MIP, especially in women, demonstrated that these parameters are very efficient in truly diagnosing sarcopenia in the community-dwelling elderly population. Furthermore, we found that the cutoff point for MEP also showed high specificity for elderly women.

Considering the repercussions that sarcopenia can generate in the lives of the elderly, such as functional decline and vulnerability to respiratory diseases, it is important to identify respiratory parameters capable of predicting sarcopenia by means of cutoff points with adequate sensitivity and specificity. With this information, health professionals will find one more opportunity to screen for sarcopenia in the respiratory assessment of the elderly, and manometry may provide useful information to establish early interventions and reverse or minimize the adverse effects of the disease.

There were no significant differences in spirometric parameters among the subgroups analyzed, nor was any association of spirometric parameters with the probable and confirmed sarcopenia subgroups. These results differ from those of Ohara et al.,[7] in which worse pulmonary function (FVC, FEV_1, and $FEF_{25-75\%}$) and worse muscle strength were evidenced in the elderly with sarcopenia than in those with no sarcopenia. In this study, spirometric parameters were presented as percentages of predicted values, whereas Ohara et al.[7] used the actual values (in L or L/s). The equations for calculating predicted values consider patient characteristics, such as sex, age, weight, and height, which are not considered in the analysis of actual values. These aspects can justify the different results found. In this sense, considering the divergences between the results and the small number of studies available in the literature that corroborate this discussion, it is suggested that more studies be carried out to investigate these aspects.

One limitation of the present study was the use of equations that consider anthropometric measurements to estimate muscle mass. Despite the choice of validated and useful equations to help diagnose sarcopenia in population-based studies, more complex imaging studies might produce more accurate measurements. Furthermore, we pointed out that the number of individuals in each group, according to the classification of sarcopenia,[1] may have influenced the results obtained.

Despite the limitations, this seems to be the first study to propose MIP and MEP cutoff points for the diagnosis of sarcopenia in a community-dwelling elderly population, considering the new EWGSOP consensus.[1] The use of the cutoff points presented in this study, either in clinical practice or as reference measures for other studies, may contribute to a more detailed investigation of the health condition of the elderly.

AUTHOR CONTRIBUTIONS

RBSP: literature search, data collection, study design, data analysis, manuscript preparation, critical review of the manuscript, and approval of the final version. MHF, TAB, PAP, and RSC: data collection, critical review of the manuscript, and approval of the final version. JAOC: data collection, study design, data analysis, critical review of the manuscript, and approval of the final version.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210290
https://dx.doi.org/10.36416/1806-3756/e20210290

ORIGINAL ARTICLE

Intra-breath oscillometry for the evaluation of lung function in children and adolescents with a history of preterm birth

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Submitted: 14 July 2021.
Accepted: 1 November 2021.

Study carried out at the Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To assess respiratory system impedance (Z_{rs}) and spirometric parameters in children and adolescents with and without a history of preterm birth. **Methods:** We evaluated a sample of 51 subjects between 11 and 14 years of age: 35 who had a history of preterm birth (preterm group) and 16 who had been born at term (full-term group). Lung function was measured by spirometry, spectral oscillometry, and intra-breath oscillometry. **Results:** Neither spirometry nor spectral oscillometry revealed any statistically significant differences between the preterm and full-term groups. However, intra-breath oscillometry demonstrated significant differences between the two groups in terms of the change in resistance, reactance at end-inspiration, and the change in reactance ($p < 0.05$ for all). **Conclusions:** Our findings suggest that abnormalities in Z_{rs} persist in children and adolescents with a history of preterm birth and that intra-breath oscillometry is more sensitive than is spectral oscillometry. Larger studies are needed in order to validate these findings and to explore the impact that birth weight and gestational age at birth have on Z_{rs} later in life.

Keywords: Oscillometry; Premature birth; Respiratory function tests; Respiratory mechanics; Spirometry.

INTRODUCTION

Approximately 15 million children are born prematurely every year, corresponding to 11% of all live births worldwide. Of those 15 million children, approximately 1 million die within the first month of life because of respiratory complications.[1] The intrauterine environment plays an essential role in lung growth and in subsequent respiratory health. The interruption of that development resulting from preterm birth may do harm to the respiratory system. Although advances in neonatal intensive therapy have extended the survival of preterm infants, respiratory morbidity is a common complication.[2] Monitoring the lung function of such children over the mid- and long-term seems to have great relevance for the continuation of their respiratory development.[3] In addition to spirometry and other widely used pulmonary function tests, such monitoring can be performed by oscillometry, a technique that measures the respiratory system impedance (Z_{rs}).[4] Although much is known about the lung function of children and adolescents who were born preterm, there are few data regarding their Z_{rs}.

Spirometry can aid in the decision-making process related to the control of the respiratory diseases, facilitating the diagnosis and allowing the quantification of ventilatory defects.[5] Previous studies using spirometry to assess preterm neonates throughout childhood have demonstrated that the degree of lung function impairment is inversely proportional to the gestational age (GA) at birth.[6]

Many authors have assessed patients who had been extremely preterm infants affected by respiratory diseases, mostly bronchopulmonary dysplasia, and have found lung function to be lower in such patients than in control subjects.[7-10] However, there have been few studies analyzing the lung function of individuals who had been moderately to late preterm infants and did or did not have neonatal respiratory diseases.[11-14]

Oscillometry is a noninvasive method to assess respiratory mechanics.[4,15] In comparison with spirometry, it has greater sensitivity and specificity in the evaluation of the peripheral airways.[16,17] Oscillometry measures the Z_{rs}, which is characterized by the combination of forces that oppose the movement of air in and out of the lungs.[4] The Z_{rs} is composed of respiratory system resistance (R_{rs}), which reflects the resistance to friction in the respiratory system, and by respiratory system reactance (X_{rs}), which expresses the sum of the elastic and inertial properties of tissues.

A comparative study of the applicability of oscillometry and spirometry in children and adolescents suggested that the former is more precise.[18] Previous studies have also demonstrated that oscillometry is more sensitive to the effects of environmental exposure, suggesting that it is ideal for epidemiologic studies.[18] A new modality, intra-breath oscillometry, has shown even greater sensitivity in children and adults with respiratory diseases. Intra-breath analysis shows high sensitivity for detecting

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Financial support: none.

ISSN 1806-3756

lung function impairment.[19,20] Oscillometry applied by the wave-tube technique provides new parameters for the analysis of ventilatory mechanics. Because it requires only passive cooperation from the patient, the technique has increasingly been used in children as a complement to the classic methods of pulmonary assessment.

We hypothesized that oscillometry, particularly the intra-breath technique, would be more sensitive than spirometry for the detection of respiratory abnormalities in children and adolescents with a history of preterm birth. To test that hypothesis, we applied both modalities is a sample of such subjects.

METHODS

For the purposes of this study, we recruited subjects from a cohort of preterm infants previously evaluated by our group.[21] In brief, the cohort consisted of children and adolescents who had been born preterm (at < 37 weeks of GA), consecutively, between June of 2004 and April of 2005, at São Lucas Hospital, operated by the Pontifical Catholic University of Rio Grande do Sul, in the city of Porto Alegre, Brazil. Through telephone contact, we recruited subjects from among the constituents of the cohort. To form a control group, we recruited healthy, age-matched subjects who had been born at ≥ 37 weeks of GA from among patients seen at the pediatrics outpatient clinic of the hospital. All of the subjects (in both groups) were between 11 and 14 years of age. Individuals who had been diagnosed with, or had signs and symptoms of, chronic lung disease were excluded from the control group, as were those with a history of recurrent wheezing (≥ 3 episodes ever), thoracic surgery, or heart disease. For both groups, individuals who presented with respiratory symptoms during sampling or who had impediments to performing forced expiratory maneuvers were excluded. After exclusions, there were 35 subjects who had been recruited from the cohort, collectively designated the preterm group, and 16 subjects who had been recruited from the pediatrics outpatient clinic, collectively designated the full-term group.

Because the forced maneuvers employed in spirometry have an impact on the R_{rs} and X_{rs}, all of the subjects underwent spectral and intra-breath oscillometry prior to undergoing spirometry. Before starting the examinations, the subjects remained at rest for 5-10 min, during which time we applied a questionnaire designed to collect clinical data. The procedures were carefully explained to the participants and their legal guardians, with an emphasis on the need to avoid leaks around the mouthpiece during the tests. For spirometry and oscillometry, the mouthpiece contained a bacterial/viral filter with minimal dead space. To prevent air leakage (during all procedures), a nose clip was used. All of the tests were carried out in a calm, private environment.

This study was approved by the Scientific and Research Ethics Committees of the Pontifical Catholic University of Rio Grande do Sul. Written informed consent was obtained from the parents or legal guardians, and all of the participants gave written informed assent. All procedures were performed in accordance with the ethical criteria for research involving human beings established in Brazilian National Health Council Resolution no. 466/2012.

Oscillometry

Oscillometry was performed in accordance with the European Respiratory Society Task Force guidelines.[15] The Z_{rs} was measured with custom-made equipment incorporating a wave-tube and a loudspeaker.[22] The wave-tube technique is a variant of classical oscillometry that allows the measurement of impedance in infants.[19] Intra-breath analysis was used because it is reported to be more sensitive than is spectral analysis for detecting lung disease.[22] To perform the test, participants remained seated, using a nose clip, with the head in a neutral position and the cheeks firmly supported by the examiner, maintaining spontaneous ventilation for 20 s. The cheeks were supported to reduce the effect of upper airway soft tissue compliance, which could generate mechanical impedance parallel to the Z_{rs}. As previously noted, the mouthpiece contained a bacterial/viral filter with minimal dead space. The estimated Z_{rs} was corrected for the filter resistance. The equipment measured the Z_{rs} in the spectral and intra-breath phases. Spectral oscillometry measures Z_{rs} throughout a signal of multiple frequencies ranging from 6 Hz to 32 Hz. Multifrequency analyses produce an average of the performance of respiratory mechanics over several respiratory cycles. In both phases, three to six curves were obtained, being considered reproducible if the coefficient of variation for R_{rs} was ≤ 10%. If four or more curves were obtained, the three that were most similar to each other were chosen and the results were calculated as the mean of those three. Intra-breath oscillometry uses a single frequency to assess alterations to the respiratory mechanics at different phases of each respiratory cycle. In our subjects, a frequency of 10 Hz was used. Curves in which there were artifacts (cough, glottal noise, swallowing, etc.) were deemed unacceptable. In such cases, the measurement was discarded and another curve was obtained, assuming that the maximum number of attempts was not exceeded.

Spirometry

Spirometry was performed in accordance with the recommendations of the American Thoracic Society/European Respiratory Society.[23] We used a Koko spirometer (PDS Instrumentation, Inc., Louisville, CO, USA) that was calibrated each morning before the tests. The subjects were instructed to perform a maximum inspiration followed by a rapid and sustained expiration, repeating that maneuver until the test was terminated by the examiner.[5] Each participant performed the test seated, with the head in a neutral position and using a nose clip. The following spirometric

parameters were assessed: FEV_1, FVC, the FEV_1/FVC ratio, and $FEF_{25-75\%}$. The spirometric data, presented in Z scores, were normalized to a reference equation.[24] It was considered necessary to have three acceptable and two reproducible curves. After acceptable curves (≥ 1 s plateau on the volume-time curve) had been obtained, reproducibility criteria were applied[24]: the two highest FEV_1 and FVC values should differ by less than 0.15 L. Tests were repeated until reproducible values were obtained, not exceeding eight attempts. The flow-volume and volume-time curves were analyzed during the test; those that did not meet the acceptance and reproducibility criteria were excluded at the time of sampling.

Statistical analysis

Statistical analysis was performed with the R Environment for Statistical Computing.[25] Values of $p < 0.05$ on two-tailed tests were considered statistically significant. The main variables of the study were assessed with the Kolmogorov-Smirnov test. Categorical variables are presented as absolute and relative frequencies, whereas numerical variables are presented as mean and standard deviation or as median and interquartile range. Categorical variables were analyzed with Fisher's exact test, and numerical variables were analyzed with a t-test or the Wilcoxon test, as appropriate, depending on the data distribution. Intra-breath values were compared by bootstrap resampling.

RESULTS

Sample characteristics

Demographic and anthropometric characteristics of the subjects are shown in Table 1, by group. There were no significant differences between the preterm and full-term groups in terms of those characteristics.

Perinatal data

Of the 35 subjects in the preterm group, 6 (17.1%) had presented some respiratory disease—defined as bronchopulmonary dysplasia, as hyaline membrane disease, or by the need for mechanical ventilation—in the neonatal period and 17 (48.6%) had subsequently been diagnosed with asthma. None of the subjects in the full-term group had presented neonatal respiratory disease. In terms of birth weight, 33 (94.3%) of the preterm group subjects were categorized as appropriate for GA, compared with 13 (81.2%) of those in the full-term group (Table 2).

Spirometry

The spirometry results are presented in Table 3. Although the values were lower in the preterm group than in the full-term group, the differences were not statistically significant.

Spectral oscillometry

Measures of resistance and reactance at frequencies of 6, 8, and 10 Hz did not differ significantly between the two groups ($p > 0.05$ for all). The overall mean values of resistance, compliance, inertance, and resonant frequency also did not differ significantly between the groups ($p > 0.05$ for all). Those data are shown in Table 4.

Intra-breath oscillometry

We observed differences in reactance at end-inspiration, the change in resistance (i.e., the difference between resistance at end-expiration and resistance at end-inspiration), and the change in reactance (i.e., the difference between reactance at end-expiration and reactance at end-inspiration), all of which were significant ($p = 0.027$, $p = 0.003$, and $p = 0.037$, respectively). In the intra-breath analysis, differences in resistance at end-inspiration, resistance at end-expiration, and reactance at end-expiration did not reach statistical significance ($p > 0.05$ for all). Those data are presented in Table 4.

DISCUSSION

In this study, we have demonstrated that intra-breath oscillometry is able to detect significant differences between children and adolescents with a history of preterm birth and those who were born at term. In contrast, we did not find significant differences between those two groups in terms of the variables obtained with spirometry and spectral oscillometry. Shackleton et al.[26] used spectral oscillometry to analyze Z_{rs} in preschool children who had been late preterm infants and found that the lung function of such children was comparable to that of preschool children who had been full-term infants. Their findings are in agreement with ours, given that we observed differences only when we used intra-breath oscillometry. This oscillometry

Table 1. Demographic and anthropometric characteristics of the subjects.[a]

Characteristic	Group		p
	Full-term (n = 16)	Preterm (n = 35)	
Age, years	12.90 (12.52-13.05)	12.88 (12.80-13.38)	0.167*
Female	13 (81.2)	18 (51.4)	0.041†
White	8 (50)	21 (60)	0.038†
Height, cm	158.5 (152.5-162.0)	158.0 (153.5-163.0)	0.831*
Weight, kg	50.95 (41.78-61.38)	49.50 (40.70-63.45)	0.935*

[a]Values expressed as median (IQR) or n (%). *Wilcoxon test. †Fisher's exact test.

Table 2. Perinatal characteristics of the subjects.[a]

Characteristic	Group		p
	Full-term (n = 16)	Preterm (n = 35)	
Gestational age, weeks	39.3 ± 3.1	33.5 ± 1.5	0.167*
Classification by gestational age			
Extremely preterm (< 28 weeks)	0 (0.0)	4 (11.4)	
Very preterm (28-31 weeks)	0 (0.0)	4 (11.4)	
Moderately preterm (32-33 weeks)	0 (0.0)	6 (17.1)	
Late preterm (34-36 weeks)	0 (0.0)	21 (60.0)	< 0.001†
Early term (37-38 weeks)	7 (43.8)	0 (0.0)	
Term (39-40 weeks)	6 (37.5)	0 (0.0)	
Late term (≥ 41 weeks)	3 (18.8)	0 (0.0)	
Birth weight, g	3,200 (2,795-3,397)	2,100 (1,780-2,530)	< 0.001‡
Classification by birth weight			
Extremely low (< 1,000 g)	0 (0.0)	3 (8.6)	
Very low (< 1,500 g)	0 (0.0)	3 (8.6)	0.001†
Low (< 2,500 g)	2 (12.5)	19 (54.3)	
Normal (≥ 2,500 g)	14 (87.5)	10 (28.6)	

[a]Values expressed as mean ± SD, n (%), or median (IQR). *t-test. †Fisher exact test. ‡Wilcoxon test.

Table 3. Spirometry results.[a]

Variable	Group		p*
	Full-term (n = 16)	Preterm (n = 35)	
FVC (Z score)	0.40 (−0.44 to 1.20)	−0.43 (−0.93 to −0.38)	0.109
FEV_1 (Z score)	0.12 (−0.42 to 0.83)	−0.43 (−1.12 to 0.28)	0.096
FEV_1/FVC (Z score)	−0.17 (−1.24 to 0.39)	−0.46 (−1.29 to 0.27)	0.670
$FEF_{25-75\%}$ (Z score)	0.08 (−1.06 to 0.68)	−0.34 (−1.70 to −0.10)	0.256

[a]Values expressed as median (IQR). *Wilcoxon test.

phase is known as the intra-breath phase because it describes the Z_{rs} oscillation in each respiratory cycle (R_{rs} and X_{rs} are measured at 0.1 s intervals), which makes the intra-breath analysis more sensitive than the spectral analysis.

In the present study, there were three variables for which differences between the preterm and full-term groups were found, all of them being identified by intra-breath oscillometry. One of those variables was the change in resistance. In a study aimed at identifying Z_{rs} descriptors with high sensitivity and specificity for the detection of airway obstruction in children, Czövek et al.[22] found that this same measure of lung function (the change in resistance) detected airway obstruction with 92% sensitivity and 89% specificity in children with acute wheezing.[22] Our data support the hypothesis that preterm birth and recurrent wheezing both have abnormal volume-dependent resistance (i.e., tidal changes in R_{rs} between the beginning and end of inspiration). Previous studies have also shown R_{rs} to be higher in children and adolescents who had been late preterm infants than in those who had been full-term infants.[27]

In the present study, we also found differences between the preterm and full-term groups in terms of reactance at end-inspiration and the change in reactance. Those variables describe pulmonary compliance, in accordance with previous studies demonstrating that pulmonary complacency tends to be reduced in individuals who were preterm infants, even those who were late preterm infants.[27,28] We found that reactance measured in the intra-breath phase was the most impaired oscillometric index in our preterm group subjects. That is in keeping with the findings of Lombardi et al.,[29] although those authors analyzed preschool children born very preterm and employed spectral oscillometry. We emphasize that, by using a highly sensitive technique, the effect of preterm birth on respiratory compliance can be detected up through adolescence.

It is noteworthy that nearly half of the subjects in our preterm group had been diagnosed with asthma. Although the diagnosis was reported by parents (or legal guardians), that information is important for the analysis of the results. However, we hypothesize that not all of those subjects actually had asthma; it is possible that they simply had a history of recurrent wheezing due to preterm birth.

Although premature birth may lead to alterations in pulmonary development after the neonatal period,[30] previous studies employing spirometry to evaluate subjects with a history of preterm birth have not demonstrated changes in lung function throughout

Table 4. Spectral and intra-breath oscillometry results.[a]

Characteristic	Group		p*
	Full-term (n = 16)	Preterm (n = 35)	
Spectral oscillometry			
R_{rs_6}, hPa·s·L^{-1}	4.14 (3.38-5.12)	4.49 (3.85-4.78)	0.465
R_{rs_8}, hPa·s·L^{-1}	4.14 (3.22-4.83)	4.25 (3.73-4.73)	0.685
$R_{rs_{10}}$, hPa·s·L^{-1}	4.04 (3.15-4.60)	4.14 (3.58-4.72)	0.556
X_{rs_6}, hPa·s·L^{-1}	−0.96 (−1.40 to −0.77)	−0.94 (−1.26 to 0.65)	0.503
X_{rs_8}, hPa·s·L^{-1}	−0.61 (−0.92 to −0.41)	−0.64 (−0.87 to −0.35)	0.887
$X_{rs_{10}}$, hPa·s·L^{-1}	−0.42 (−0.72 to −0.19)	−0.33 (−0.55 to −0.10)	0.477
R_{rs}, hPa·s·L^{-1}	3.98 (2.95-4.65)	4.17 (3.61-4.65)	0.383
C_{rs}, mL·hPa^{-1}	0.02 (0.02-0.03)	0.02 (0.02-0.03)	0.589
I_{rs}, mL·hPa^{-1}	0.01 (0.01-0.01)	0.01 (0.00-0.01)	0.612
f_{res}	13.83 (11.01-16.96)	12.82 (11.58-17.45)	0.935
Intra-breath oscillometry			
R_{eE}, hPa·s·L^{-1}	3.17 (2.71-4.34)	3.94 (3.16-5.16)	0.118
R_{eI}, hPa·s·L^{-1}	3.13 (2.66-4.13)	3.48 (2.72-3.88)	0.823
ΔR, hPa·s·L^{-1}	0.06 (−0.02 to 0.26)	0.46 (0.13-0.84)	0.003
X_{eE}, hPa·s·L^{-1}	−0.21 (−0.50 to 0.18)	−0.08 (−0.26 to 0.21)	0.477
X_{eI}, hPa·s·L^{-1}	−0.28 (−0.69 to −0.11)	−0.06 (−0.32 to 0.11)	0.027
ΔX, hPa·s·L^{-1}	0.15 (0.01-0.33)	0.04 (−0.11 to 0.16)	0.037

R_{rs6}: respiratory system resistance at 6 Hz; R_{rs8}: respiratory system resistance at 8 Hz; R_{rs10}: respiratory system resistance at 10 Hz; X_{rs6}: respiratory system reactance at 6 Hz; X_{rs8}: respiratory system reactance at 8 Hz; X_{rs10}: respiratory system reactance at 10 Hz; R_{rs}: respiratory system resistance; C_{rs}: respiratory system compliance; I_{rs}: respiratory system inertance; f_{res}: resonant frequency; R_{eE}: resistance at end-expiration; R_{eI}: resistance at end-inspiration; ΔR: change in resistance; X_{eE}: reactance at end-expiration; X_{eI}: reactance at end-inspiration; and ΔX: change in reactance. [a]Values expressed as median (IQR). *Wilcoxon test.

childhood and adolescence,[31,32] as was found in the present study. However, in studies evaluating children and adolescents who were born preterm and who had a more severe history, spirometry has shown differences between such subjects and control subjects who were born at term.[33-37]

The fact that we found the lung function of the subjects in the preterm group to be comparable to that of those in the full-term group may be related to the preponderance of individuals in the former group who had been late preterm infants. One study that used oscillometry to assess Z_{rs} in preschool children who had been late preterm infants demonstrated that the lung function of those children was comparable to that of healthy children who had been full-term infants, suggesting that data related to individuals who had been late preterm infants should be included in the normative reference data for oscillometry.[26] However, other studies analyzing children and adolescents who had been late preterm infants, in comparison with control subjects who had been full-term infants, have demonstrated that the former show lower lung function on spirometry[11,37] and a higher R_{rs} on impulse oscillometry.[37,38] Another possibility is that, during adolescence, with pulmonary development, adolescents who had been late preterm infants have already achieved lung function similar to that of those who had been full-term infants. One study, comparing the lung function of individuals who had been late or extremely to late preterm infants, at 8-9 years of age and at 14-17 years of age, with that of age-matched control subjects who had been full-term infants, showed that lung function was lower in those individuals than in the control subjects. However, the preterm group presented better FEV_1 at 14-17 years of age than at 8-9 years, suggesting that lung function improves during adolescence.[39]

Our study has some limitations. The main limitation is the sample size, which was smaller than it might have been because the coronavirus pandemic made it necessary to interrupt the data collection. One of the specific objectives initially proposed was to compare oscillometry and spirometry in terms of their accuracy for the detection of pulmonary alterations in adolescents with a history of preterm birth. However, that objective could not be met, because the small sample size prevented us from performing an accuracy analysis. In addition, the fact that the subjects in the preterm group were recruited from an existing cohort could constitute a selection bias, and the sample was relatively heterogeneous, both of which are potential limitations.

In summary, oscillometry is a viable method that is easily applicable in children and adolescents. In the analysis of lung function, the main advantage of the technique seems to be that it includes the intra-breath phase, which is sensitive enough to detect alterations in Z_{rs}. In the present study, we identified variables that differed significantly between the preterm and full-term groups in the intra-breath phase. These findings suggest that abnormalities in Z_{rs} persist in adolescents with a history of preterm birth and that intra-breath oscillometry is more sensitive than is spectral oscillometry.

Our findings underscore the need for further studies to investigate the impact that premature birth has on lung function measured by intra-breath oscillometry. Larger studies are needed in order to validate these findings and to explore the impact that birth weight and GA at birth have on Z_{rs} later in life.

AUTHOR CONTRIBUTIONS

BFA: study conception and design; data collection and analysis; drafting and revision of the manuscript; approval of the final version. FOF: data collection and analysis; revision of the manuscript; approval of the final version. ALC: study design; data collection; drafting of the manuscript; approval of the final version. JPR: data collection and analysis. MHJ: study design; data analysis; revision of the manuscript; approval of the final version.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210280
https://dx.doi.org/10.36416/1806-3756/e20210280

ORIGINAL ARTICLE

Effects of the breath stacking technique after upper abdominal surgery: a randomized clinical trial

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Submitted: 9 July 2021.
Accepted: 24 November 2021.

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ABSTRACT

Objective: To evaluate the effect of the association of the breath stacking (BS) technique associated with routine physiotherapy on pulmonary function, lung volumes, maximum respiratory pressures, vital signs, peripheral oxygenation, thoracoabdominal mobility, and pain in the surgical incision in patients submitted to upper abdominal surgery during the postoperative period, as well as to analyze BS safety. **Methods:** This was a randomized clinical trial involving 34 patients divided into a control group (CG; n = 16), who underwent conventional physiotherapy only, and the BS group (BSG; n = 18), who underwent conventional physiotherapy and BS. Both groups performed two daily sessions from postoperative day 2 until hospital discharge. The primary outcomes were FVC and Vt. The safety of BS was assessed by the incidence of gastrointestinal, hemodynamic, and respiratory repercussions. **Results:** Although FVC significantly increased at hospital discharge in both groups, the effect was greater on the BSG. Significant increases in FEV_1, FEV_1/FVC ratio, PEF, and $FEF_{25-75\%}$ occurred only in the BSG. There were also significant increases in Ve and Vt in the BSG, but not when compared with the CG values at discharge. MIP and MEP significantly increased in both groups, with a greater effect on the BSG. There was a significant decrease in RR, as well as a significant increase in SpO_2 only in the BSG. SpO_2 acutely increased after BS; however, no changes were observed in the degree of dyspnea, vital signs, or signs of respiratory distress, and no gastrointestinal and hemodynamic repercussions were observed. **Conclusions:** BS has proven to be safe and effective for recovering pulmonary function; improving lung volumes, maximum respiratory pressures, and peripheral oxygenation; and reducing respiratory work during the postoperative period after upper abdominal surgery.

Keywords: Abdomen/surgery; Pulmonary ventilation; Physical therapy modalities.

(ClinicalTrials.gov identifier: NCT 04418700 [http://www.clinicaltrials.gov/])

INTRODUCTION

The number of surgeries has exponentially grown in recent years and, among these, abdominal surgery is prominent.[1] Upper abdominal surgery (UAS), often used for the diagnosis and treatment of several diseases,[2] implies an incision in the upper quadrants of the abdominal region.[3] Certain aspects of UAS, such as anesthesia, incision, factors related to the surgical act, and individual characteristics of the patient,[4,5] may induce complications such as reflex inhibition of the diaphragm, pain, hypoventilation,[6] reduction in respiratory muscle strength, and inhibition of coughing.[4] The post-surgical respiratory pattern is predominantly characterized as restrictive, with a decrease in VT, VC, and functional residual capacity.[6,7] Therefore, the most common complications after UAS are atelectasis, hypoxemia, pneumonia,[8,9] tracheobronchial infection, acute respiratory failure, prolonged mechanical ventilation and/or intubation, bronchospasm,[4,9] pulmonary thromboembolism, pleural effusion, and respiratory failure.[10] These are identified as a direct cause of increased morbidity, mortality, length of hospital stay, and costs.[11]

In this regard, several techniques or mechanical devices have been utilized to encourage the patient to inhale deeply and promote lung expansion.[12-16] In 1990, with the technique developed by Marini et al.[17] to measure VC, it was demonstrated that patients with different diagnoses were able to generate and sustain greater inspiratory volumes than those achieved with incentive spirometry. This technique, designated breath stacking (BS), consists of successive inspirations

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Financial support: This study was financed in part by the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Funding Code 001).

through a unidirectional valve with an expiratory branch block. Successive inspiratory efforts with expiration impediment through BS increase chest volume, promoting the redistribution of air in areas with different time constants. Sustaining maximum inspiration causes an increase in transpulmonary pressure, recruiting collapsed alveoli and contributing to the increase in Pa_{O_2} and lung expansion.[17-19] BS has already been applied in patients with neuromuscular diseases,[20-24] acute lung injury,[25] obesity,[13,26] during the postoperative period of cardiac[19] and abdominal[27] surgery, in tracheostomized patients,[28] and in children,[20] showing promising results on lung function and respiratory mechanics.

To our knowledge, this is the first randomized clinical trial conducted to assess the efficacy and safety of the BS technique in patients after UAS. Therefore, this study aimed to evaluate the effect of the association of the BS technique with routine physiotherapy on pulmonary function, lung volumes, maximal respiratory pressures, vital signs, peripheral oxygenation, thoracoabdominal mobility, and pain in the surgical incision during hospitalization after UAS, as well as to analyze safety aspects of BS.

METHODS

This was a randomized clinical trial performed in the General Surgery Unit—Surgical Clinic at the University Hospital of Santa Maria, located in the city of Santa Maria, Brazil. The study was approved by the local research ethics committee. All participants signed an informed consent form at the beginning of the study.

Patients were randomly assigned to the control group (CG), which performed routine physiotherapy at the unit, or to the breath stacking group (BSG), treated with routine physiotherapy associated with the BS technique. The allocation into groups occurred after the end of the first evaluation by an independent researcher, using randomization at the random.org website at a 1:1 ratio. Evaluators were blinded concerning the type of intervention.

Sample size was estimated after FVC (in % of predicted values) results of the first 8 patients in each group at hospital discharge, using a power of 80% and an alpha error of 5%. Given that the difference between CG (60.9 ± 11.1%) and BSG (71.5 ± 9.7%) in FVC was 10.6%, the sample should have at least 16 patients in each group. The patients used for sample calculation were also included in the final statistical analysis. The sample size power was 89.2%.

Patients of both genders, between 18 and 65 years of age, and who underwent UAS with an incision in the upper quadrant of the abdominal region were included. Patients presenting with intolerance to the use of the BS mask, COPD, asthma, Crohn's disease, and severe liver trauma with hemodynamic repercussions were excluded, as were those who underwent esophagectomy, developed sepsis with hemodynamic complications during the postoperative period, required surgical reintervention, were admitted to the ICU, required mechanical ventilation after discharge from the recovery room, or had a cognitive disorder that precluded evaluations or intervention.

The medical records were analyzed to fill out the checklist with inclusion and exclusion criteria and to record laboratory test results and anthropometric, clinical, and surgical characteristics. The evaluations took place on the second postoperative day (between 24 and 48 h after surgery) and at hospital discharge. Primary outcomes were FVC and VT. Secondary outcomes were systemic blood pressure (BP), HR, RR, SpO_2, thoracoabdominal mobility, pain perception threshold, V_E, FEV_1, FEV_1/FVC ratio, PEF, $FEF_{25-75\%}$, MIP, and MEP.

Systemic BP and HR were measured using a stethoscope (Littmann; 3M, Maplewood, MN, USA) and a sphygmomanometer (Premium; Beijing Choice Electronic Technology, Beijing, China). SpO_2 was assessed with a portable pulse oximeter (G-Tech; Beijing Choice Electronic Technology). RR was measured by the movements of the rib cage during the respiratory cycles in one minute. Thoracoabdominal mobility was assessed using an anthropometric tape positioned at three anatomical landmarks: axillary fold, xiphoid appendix, and umbilical line. For each landmark, three measurements were taken, with one-minute intervals between each landmark. The measurements with the highest value for each landmark were selected.[29] To assess the pain perception threshold in the surgical incision, a digital pressure algometer (model FPX 50/220; Wagner Instruments, Greenwich, CT, USA), which determines the pressure pain threshold, was used. The evaluator exerted pressure with a 1-cm diameter rubber tip on the skin at a 90° angle, at a distance of 2-3 cm from the incision at three levels (upper, middle, and lower). Subsequently, the mean between the three values reported by the patient as painful discomfort was calculated.[30] Additionally, a visual analog scale was used in order to assess pain perception.

Measurements of V_T and V_E were obtained with the use of a Wright respirometer (British Oxygen Company, London, England). Spirometry variables (FVC, FEV_1, FEV_1/FVC ratio, PEF e $FEF_{25-75\%}$) were obtained using a portable spirometer (Spirobank II; Medical International Research, Rome, Italy), as recommended by international guidelines[31] and expressed as % of predicted values in accordance with Pereira et al.[32] Respiratory muscle strength (MIP and MEP) was evaluated using a digital manometer (MVD300; GlobalMed, Porto Alegre, Brazil), and the results were expressed as % of predicted values based on the equation by Pessoa et al.[33]

In order to analyze the safety of the BS technique, we assessed the following variables before and after the first session: degree of dyspnea (modified Borg scale),[34] SpO_2, RR, HR, BP, signs of respiratory distress (tachypnea, sweating, cyanosis, mental confusion,

and use of accessory muscles), and gastrointestinal symptoms (nausea, vomiting, and abdominal pain).

Patients in the CG received routine physiotherapy care, in two daily sessions, with the use of bronchial hygiene techniques, lung re-expansion, general mobilization, walking, and guidance for post-discharge care. In addition to routine physiotherapy, the BSG was treated with the BS technique, with the first intervention taking place between 24 and 48 h after surgery in two daily sessions until hospital discharge. BS was applied with a silicone face mask coupled to a unidirectional valve that allowed inspiration only (the expiratory branch was obstructed).[18] Patients performed the maneuver with successive inspiratory efforts for 20 s. Thereafter, the expiratory branch was unobstructed to allow expiration. This maneuver was repeated five times at each set, with intervals of 30 s between them, in three sets[19] (2-min interval between sets).[35] The technique was performed with the upper body inclined at an angle of 30° in relation to the horizontal plane. Total therapy time was up to 20 min. During the interventions, there was continuous monitoring by pulse oximetry to measure SpO_2 and HR.

Statistical analysis was performed using GraphPad Prism 5 (GraphPad Software Inc., San Diego, CA, USA). Data distribution was assessed with the Kolmogorov-Smirnov normality test. Fisher's exact test was used for categorical variables. For continuous variables, comparisons between the groups at baseline were performed using the unpaired Student's t-test or the Mann-Whitney test. Comparisons regarding the safety of BS were analyzed using the paired Student's t-test. Variables with more than two measures were compared by two-way ANOVA for repeated measures, followed by post-hoc Bonferroni test. Data are presented as mean ± SD, and the differences between groups were expressed as Δ and their respective 95% CIs. The level of 5% was considered significant ($p < 0.05$).

RESULTS

Between June 2020 and March 2021, 47 potentially eligible patients were screened, 36 of whom met the criteria and were randomized. However, 2 patients withdrew consent (1 from each group) during the study period. Therefore, the whole sample comprised 34 patients. Figure 1 demonstrates the flow chart of the patient selection process.

The groups were similar regarding anthropometric, clinical, and surgical characteristics, as well as protocol time and laboratory test results (Table 1). The most extensive surgeries were as follows: exploratory laparotomy, in 11 patients (32.5%); partial hepatectomy, in 6 (17.6%); splenectomy, in 4 (11.8%); and open cholecystectomy, in 3 (8.8%), with a similarity between the groups. The number of elective and emergency surgeries was also similar between the groups. The major clinical diagnoses were acute perforated abdomen due to trauma, in 6 patients (17.7%); liver neoplasm, in 6 (17.7%); rectal neoplasm, in 4 (11.8%); pancreatic neoplasm, in 3 (8.8%); and stomach cancer, in 2 (5.9%).

There was an increase in FVC in both groups, more markedly in the BSG. In addition, FEV_1, FEV_1/FVC ratio, PEF, $FEF_{25-75\%}$, Vt, and Ve significantly increased in the BSG but not in the CG (Table 2). Both groups showed a significant increase in MIP and MEP at hospital discharge, although the effect was higher on the BSG.

There was a significant decrease in RR and body temperature and a significant increase in SpO_2 in the BSG at hospital discharge, but not in the CG.

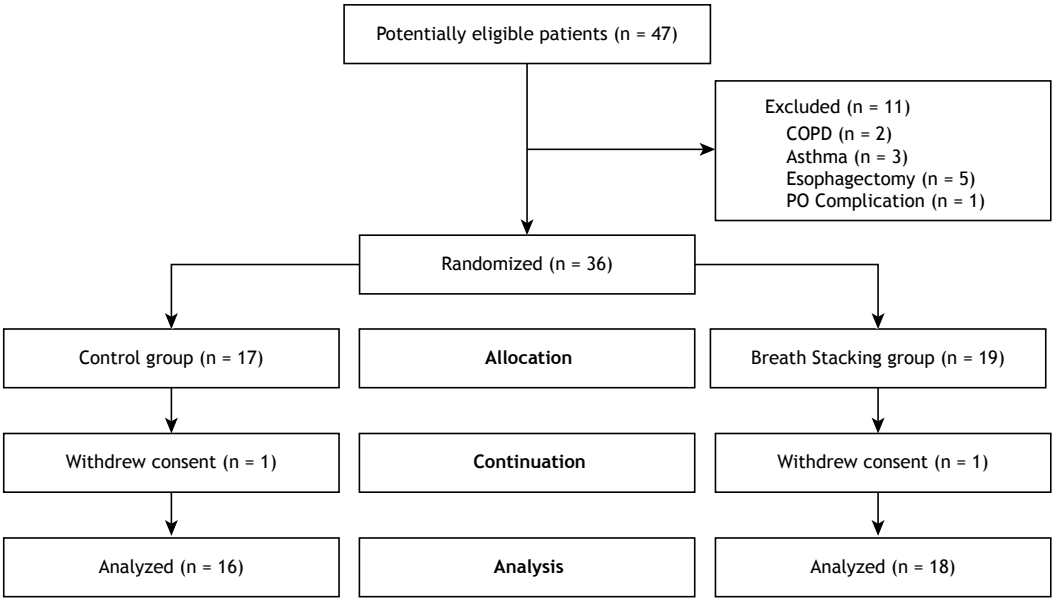

Figure 1. Flow chart of the patient selection process. PO: postoperative.

There were no changes in other vital signs in either group (Table 3).

Thoracoabdominal mobility and pain perception as assessed by algometry were similar in both groups. There was a significant decrease in pain perception using the visual analog scale in both groups but no significant difference between the groups (Table 4).

The findings related to the safety of BS are shown in Table 5. There was an increase in SpO_2 as an acute answer to BS; however, there were no changes in the degree of dyspnea or vital signs. There were no significant changes in signs of respiratory distress or gastrointestinal symptoms. Based on the reports, only 1 patient (2.9%) had mild abdominal pain before BS, which stopped shortly after its performance, and 2 remained with nausea (5.8%). During the study, there was no need to interrupt the protocol, and no adverse events related to the data collected were observed.

DISCUSSION

The main findings of this clinical trial demonstrated that the use of BS associated with routine physiotherapy after UAS favored the recovery of pulmonary function, improved maximal respiratory pressures and oxygenation, and reduced RR at hospital discharge.

Our results showed a significant recovery in FVC in both groups, but the effect was more significant in the BSG. In comparison with the CG, significantly favorable responses to BS were found in FEV_1, FEV_1/FVC ratio, PEF, and $FEF_{25-75\%}$ in the BSG. As suggested by Baker et al.,[18] BS allows the mobilization of larger lung volumes, probably due to increased lung compliance and decreased respiratory system resistance, thus resulting in the recruitment of collapsed alveoli and re-expansion of areas of atelectasis. Successive inspirations progressively increase lung volume until maximum inspiratory volumes are involuntarily reached, activating greater lung expansion from functional residual capacity to full pulmonary capacity.[13] In this context, the recovery of FVC seems to be related to the increase in the volume of mobilized air. The improvement in FEV_1 and FEV_1/FVC ratio in response to BS also suggests the ability of this technique to mobilize larger lung volumes.[22]

As demonstrated in a previous study,[23] the generation of higher expiratory flows seems to be related to the moment of maximum insufflation reached by the BS technique, which may explain the increase in PEF and $FEF_{25-75\%}$ after the technique. Once this is reached, the volume of compressed air is released under the force of the expiratory muscles, thus improving the explosive phase of coughing with the retraction of the lungs, distension of the chest wall, and stretching of the expiratory muscles,[23] that is, the greater the inspired volume is, the greater the elastic recoil pressure and PEF will be.[28] Because of this, the positive impact of the maneuver on the evolution of PEF and $FEF_{25-75\%}$ is evident in our study.

Other investigations have demonstrated the favorable effects of BS on FVC and peak cough flow in patients with amyotrophic lateral sclerosis[21] and on the decline in pulmonary function in those with Duchenne muscular dystrophy.[22] A study[19] involving patients submitted to cardiac surgery showed that BS promoted higher inspiratory volumes between postoperative days 1 and 5 when compared with standard and incentive spirometry procedures, but had a similar effect on FVC during the same period. Dias et al.,[27] in a crossover clinical trial, reported the acute effect of BS in generating and sustaining

Table 1. Clinical and anthropometric characteristics of the patients (N = 34).[a]

Variable	Group		p
	Control (n = 16)	Breath stacking (n = 18)	
Male, n (%)	8 (50.0)	10 (55.5)	0.75
Age, years	53.0 ± 13.1	45.6 ± 12.5	0.10
BMI, kg/m^2	26.7 (24.2-34.2)	25.0 (22.2-29.0)	0.08
Length of hospital stay, days	7.0 (6.0-8.8)	6.5 (5.0-8.3)	0.40
Protocol period, days	4 (3-5)	4 (4-4)	0.61
Operative time, min	177.0 ± 75.0	161.5 ± 59.2	0.50
Anesthesia time, min	229.7 ± 83.7	201.9 ± 62.7	0.28
Laboratory tests			
Hemoglobin, g/dL	12.1 ± 2.4	11.6 ± 2.3	0.55
Erythrocytes, × 10^5 mm^3	4.1 ± 0.7	4.1 ± 0.8	0.78
Leukocytes, ×10^3 mm^3	10,530 ± 6,355	9,611 ± 4,198	0.62
Platelets, ×10^3 mm^3	194 (151-286)	215 (169-307)	0.52
Creatinine, mg/dL	0.9 (0.8-1.2)	0.8 (0.7-1.3)	0.54
Urea, mg/dL	44.0 ± 21.5	35.7 ± 11.7	0.20
PT, s	14.3 (14.0-17.2)	15.3 (14.1-16.5)	0.83
PTT, s	37.6 (34.9-41.0)	36.7 (32.0-45.1)	0.90

PT: prothrombin time; and PTT: partial thromboplastin time. [a]Values expressed as mean ± SD or median (IQR), except where otherwise indicated.

Table 2. Comparison between control and breath stacking groups regarding lung function, ventilation, and respiratory muscle strength variables on postoperative day 2 and at discharge.[a]

Variable	Group						ΔBS – Control
	Control			BS			
	POD2	Discharge	ΔDischarge – POD2	POD2	Discharge	ΔDischarge – POD2	
FVC, %pred	47.0 ± 15.3	59.8 ± 26.0	12.8 (0.7-24.9)*	47.3 ± 18.1	77.7 ± 25.2	30.4 (19.0-41.8)*	17.6 (3.4-31.8)*
FEV_1, %pred	43.6 ± 15.0	55.6 ± 24.6	12.1 (−0.2 to 24.3)	42.4 ± 17.3	74.7 ± 17.1	32.3 (20.8-43.8)*	20.2 (5.9-34.5)*
FEV_1/FVC, %pred	99.0 ± 16.4	99.4 ± 11.8	0.4 (−7.0 to 7.8)	93.9 ± 15.6	104.0 ± 12.2	10.1 (3.1-17.1)*	9.7 (1.3-18.1)*
PEF, %pred	30.6 ± 10.9	34.1 ± 16.3	3.6 (−6.8 to 14.0)	31.3 ± 10.0	55.4 ± 12.3	24.1 (14.3-33.9)*	20.5 (8.3-32.7)*
$FEF_{25-75\%}$, %pred	39.9 ± 14.5	47.8 ± 19.6	7.9 (−4.2 to 20.0)	37.6 ± 17.1	64.3 ± 19.0	26.7 (15.3-38.1)*	18.8 (4.9 to 32.7)*
Ve, L/min	10.4 ± 3.0	11.7 ± 4.6	1.3 (−1.5 to 4.1)	9.0 ± 3.5	12.3 ± 5.9	3.3 (0.5-6.1)*	2.0 (−0.9 to 4.9)
Vt, L	0.6 ± 0.2	0.7 ± 0.3	0.1 (−0.1 to 0.2)	0.5 ± 0.3	0.7 ± 0.3	0.2 (0.0-0.3)*	0.1 (−0.1 to 0.2)
MIP, %pred	46.0 ± 33.3	59.0 ± 34.8	13.0 (0.1-25.9)*	48.8 ± 40.9	78.7 ± 38.1	29.8 (17.7-42.0)*	16.8 (2.4-31.2)*
MEP, %pred	23.1 ± 11.7	33.1 ± 19.4	10.0 (1.1-18.9)*	31.0 ± 20.0	51.5 ± 28.8	20.5 (12.1-28.9)*	10.5 (0.5-20.5)*

BS: breath stacking; POD2: postoperative day 2; and %pred: % of predicted value. [a]Values expressed as mean ± SD or Δ (95% CI). *p < 0.05.

Table 3. Comparison between the control and breath stacking groups regarding vital signs and peripheral oxygen saturation on postoperative day 2 and at discharge.[a]

Variable	Group						ΔBS – Control
	Control			BS			
	POD2	Discharge	ΔDischarge – POD2	POD2	Discharge	ΔDischarge – POD2	
HR, bpm	86.3 ± 13.9	83.8 ± 15.0	−2.5 (−9.0 to 4.0)	90.8 ± 12.8	85.1 ± 12.6	−5.7 (−11.8 to 0.5)	−3.2 (−10.7 to 4.3)
RR, breaths/min	17.8 ± 3.7	18.1 ± 3.4	0.3 (−1.5 to 2.0)	20.1 ± 3.3	18.4 ± 3.2	−1.7 (−3.3 to 0.0)*	−2.0 (−4.0 to 0.0)*
SBP, mmHg	134.4 ± 15.0	136.3 ± 18.9	1.9 (−9.9 to 13.7)	124.4 ± 16.9	127.8 ± 18.7	3.4 (−7.8 to 14.4)	1.4 (−11.8 to 14.6)
DBP, mmHg	80.0 ± 9.7	80.6 ± 12.9	0.6 (−8.3 to 9.5)	77.2 ± 15.3	81.7 ± 10.4	4.4 (−3.9 to 12.8)	3.8 (−6.1 to 13.7)
MBP, mmHg	98.1 ± 10.4	99.2 ± 13.5	1.1 (−8.2 to 10.3)	93.0 ± 15.2	97.0 ± 12.8	4.0 (−4.6 to 12.8)	3.1 (−7.2 to 13.4)
Body temperature, ºC	36.3 ± 0.4	36.3 ± 0.3	0.0 (−0.4 to 0.3)	36.5 ± 0.6	36.2 ± 0.4	−0.3 (−0.6 to 0.0)*	−0.3 (−0.7 to 0.1)
SpO_2, %	95.0 ± 1.8	95.4 ± 2.3	0.4 (−1.1 to 1.8)	95.1 ± 1.6	97.4 ± 1.9	2.3 (1.0-3.7)*	1.9 (0.3-3.5)*

BS: breath stacking; POD2: postoperative day 2; SBP: systolic blood pressure; DBP: diastolic blood pressure; and MBP: mean blood pressure. [a]Values expressed as mean ± SD or Δ (95% CI).*p < 0.05.

inspiratory volumes, which was shown to be superior to incentive spirometry on postoperative day 1 after UAS.

Our results also showed a trend toward an increase in Vt and Ve in the BSG. Knowing that Ve results from the product between Vt and RR, we can suggest that the increase in Ve after the BS technique is due to the elevation of Vt, since RR did not increase. The increase in Vt may result from the increase in the transpulmonary pressure gradient, which allows the re-expansion of collapsed alveoli, improving pulmonary ventilation.[36] This finding also seems to be related to the occlusion of the expiratory branch in the mask, which evokes compensatory mechanisms for Vt maintenance, progressively stimulating the respiratory center to accumulate lung volumes and favoring collateral ventilation.[17] Another study had already hypothesized that BS induced greater lung volumes than did incentive spirometry, because the unidirectional valve allows the inspiratory muscles to relax, without losing lung expansion.[35] In addition, it

Table 4. Comparison between the control and breath stacking groups regarding thoracoabdominal mobility and pain perception on postoperative day 2 and at discharge.[a]

Variable	Control			BS			ΔBS − Control
	POD2	Discharge	ΔDischarge − POD2	POD2	Discharge	ΔDischarge − POD2	
Axillary Cirt, cm	1.5 ± 1.4	2.0 ± 0.8	0.5 (−0.8 to 1.8)	1.9 ± 2.7	2.4 ± 1.6	0.4 (−0.8 to 1.7)	−0.1 (−1.5 to 1.3)
Xiphoid Cirt, cm	0.7 ± 1.2	1.3 ± 1.7	0.6 (−0.5 to 1.8)	0.6 ± 1.8	1.4 ± 1.9	0.8 (−0.3 to 1.9)	0.2 (−1.1 to 1.5)
Umbilical Cirt, cm	0.4 ± 1.5	0.3 ± 1.5	−0.2 (−1.5 to 1.2)	−0.1 ± 1.6	0.1 ± 2.8	0.2 (−1.0 to 1.4)	0.4 (−1.1 to 1.9)
Algometry, kgf/cm^2	1.4 ± 0.5	1.7 ± 1.1	0.3 (−0.2 to 0.9)	1.1 ± 0.6	1.6 ± 1.0	0.4 (−0.1 to 0.9)	0.1 (−0.5 to 0.7)
VAS	4.2 ± 2.0	2.4 ± 1.9	−1.8 (−3.1 to −0.5)*	4.7 ± 2.5	1.9 ± 2.0	−2.8 (−4.0 to −1.5)*	−1.0 (−2.5 to 0.5)

BS: breath stacking; POD2: postoperative day 2; Cirt: cirtometry; and VAS: visual analog scale. [a]Values expressed as mean ± SD or Δ (95% CI). *p < 0.05.

Table 5. Assessment of safety of the breath stacking technique.[a]

Variable	First intervention		ΔPost − Pre
	Pre	Post	
Borg scale	0.5 ± 0.8	0.2 ± 0.5	−0.3 (−0.7 to 0.1)
SpO_2, %	96.1 ± 1.7	97.3 ± 1.40	1.2 (0.5 to 1.8) *
RR, breaths/min	19.1 ± 2.7	19.4 ± 2.8	0.3 (−0.3 to 1.0)
HR, bpm	85.3 ± 9.9	85.6 ± 10.8	0.3 (−1.4 to 1.9)
SBP, mmHg	127.8 ± 15.1	125.6 ± 14.2	−2.2 (−5.9 to 1.5)
DBP, mmHg	82.2 ± 11.7	81.7 ± 11.0	−0.6 (−4.9 to 3.8)
MBP, mmHg	97.4 ± 11.5	96.3 ± 10.9	−1.1 (−4.8 to 2.6)

SBP: systolic blood pressure; DBP: diastolic blood pressure; and MBP: mean blood pressure. [a]Values expressed as mean ± SD or Δ (95% CI). *p < 0.05.

has been suggested that cumulative breathing allows the support of intrapulmonary pressure, redistribution of volume by interdependent forces, and opening of hypoventilated areas through collateral ventilation in the lung bases and peripheral regions, which are more predisposed to complications during the postoperative period.[35]

We observed an improvement in MIP and MEP after BS, which are indicators of respiratory muscle strength.[33] This finding can be explained, at least in part, due to the prolonged inspiratory time (hyperinflation) added to the pauses between inspiratory efforts during the BS maneuvers, which allow the phasic relaxation of the inspiratory muscles, especially the diaphragm, reducing the load imposed on this muscle and optimizing its performance.[18] It is plausible to suggest that BS may be beneficial to respiratory muscles after UAS. However, its effects on muscle strength as a primary outcome should be tested in future investigations.

The reduction in RR in response to the BS protocol can be explained by the decrease in energy requirements triggered by the increase in lung volume and in thoracic and pulmonary compliance, as well as by alveolar recruitment.[26] Therefore, it is suggested that the decrease in RR reflects in the reduction of respiratory work, in lower ventilatory muscle energy expenditure, and, consequently, in greater comfort for the patient at hospital discharge. Only the BSG showed significantly superior results in SpO_2 at hospital discharge. According to one group of authors,[37] the maximum inspiration generated by the application of the mask causes an increase in transpulmonary pressure and maintains alveolar pressure, contributing to the increase in Pao_2. Thus, it is likely that the improvement in SpO_2 reflects the effect of the mask on Pao_2, but this variable was not evaluated in our study.

There was no significant change in thoracoabdominal mobility at hospital discharge in either group. It is suggested that this small variation observed on cirtometry is due to the surgical procedure itself, because diaphragm dysfunction, pain, surgical incision, effect of anesthesia, and fear of the patient to take deep breaths are factors that contribute to its limitation.[38,39] The reduction in pain related to the surgical incision in both groups is an expected finding, especially due to the normal course of the postoperative period.[6] Furthermore, all patients were regularly prescribed analgesics. Thus, we observed that BS, despite recruiting greater lung volumes and capacities, did not induce greater pain at the incision site, which points to favorable aspects related to the safety and comfort of the technique. BS proved to be safe since the first intervention, as it induced no changes in perceived exertion, RR, HR, or BP, and

caused no greater respiratory or gastrointestinal symptoms. Improvement in SpO_2 soon after using the BS technique acutely points to its effectiveness.

Among the limitations of the study, we must report the short hospital stay after UAS in our hospital, with a consequent reduction in the number of BS sessions, which restricts our results to a short-term intervention. An increase in sample size may help reduce the 95% CIs in future studies. A specific demand from a patient could interfere with routine physiotherapy or BS, but this did not happen in our study. The sustained effects of the BS technique, evaluated after hospital discharge, may be considered in future investigations. The clinical applicability and external validity of this study can be considered, since the BS protocol was described in detail, is easy to apply, has low costs, and can be used safely and effectively in hospitalized patients following UAS, as well as in patients undergoing other types of abdominal surgery.

To our knowledge, the present study is the first randomized clinical trial that investigated the efficacy and safety of BS in patients submitted to UAS. BS proved to be a safe alternative, combined with routine physiotherapy, for the recovery of pulmonary function, improving lung volumes, maximal respiratory pressures, and peripheral oxygenation, as well as reducing respiratory work of patients submitted to UAS during the postoperative period.

AUTHOR CONTRIBUTIONS

DLF, LUS, and AMVS: study conception and planning; interpretation of evidence; writing and revision of preliminary and final manuscripts; and approval of the final version. NCR: study conception and planning; interpretation of evidence; and approval of the final version. LJRN, JMB, CMP, CZMR, and LFIN: study conception and planning; and approval of the final version.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210371
https://dx.doi.org/10.36416/1806-3756/e20210371

Incidental findings on lung cancer screening: pictorial essay and systematic checklist

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Submitted: 10 September 2021.
Accepted: 5 November 2021.

ABSTRACT

Lung cancer screening (LCS) programs are increasing worldwide. Incidental findings (IFs) on LCS are defined as low-dose CT findings unrelated to the primary purpose of identifying lung cancer. Most IFs on LCS are benign and clinically insignificant but are being increasingly recognized, and some require urgent referral for further diagnostic workup. Other findings are expected and are known as smoking-related comorbidities, including COPD, cardiovascular disease, emphysema, and interstitial lung disease, and their diagnosis can have a significant impact on patient prognosis. The purpose of this pictorial essay is to illustrate the most common IFs on LCS, organized by organ. We will discuss the current literature on IFs on LCS, focusing on their prevalence, appropriate communication, and triggering of clinical pathway systems.

Keywords: Diagnostic screening programs; Lung neoplasms; Incidental findings.

INTRODUCTION

With the increasing number of lung cancer screening (LCS) programs worldwide, incidental findings (IFs) have also increased significantly.[1-3] IFs on LCS can be defined as low-dose CT (LDCT) findings that can potentially affect the health of the patient and are unrelated to the primary purpose of identifying lung cancer.[1,4,5] Most IFs are benign and clinically insignificant—the most common being pulmonary findings (69%), cardiovascular findings (67%), and gastrointestinal findings (25%)—but some require urgent recognition and further management.[2]

The reported prevalence of IFs on LCS ranges from 1% to 19%, being as high as 94% in more recent reports.[2-6] This wide variation is explained by the lack of standards regarding the reporting and management of IFs on LCS. IFs are also a cause of stress and anxiety. In an ongoing interdisciplinary population-based long-term cohort study, a report of IFs is expected to be given to 10% of participants. The study participants have stated that they are highly interested in this report and that they would not have participated otherwise, even if admitting to increased levels of stress when receiving mail from the study.[7] It is a reasonable expectation, shared by both patients and referring colleagues, that significant IFs should be communicated effectively or acted upon.

Communication standards for urgent and unexpected findings are clear, as addressed by guidelines from the American College of Radiology (ACR) and the European Society of Radiology (ESR).[8,9] IFs, however, may not be urgent nor necessarily unexpected. The ACR Incidental Findings Committee has developed by consensus a series of white papers addressing IFs in multiple organs and systems, including the chest (mediastinal and cardiovascular findings), upper abdomen, and thyroid, although not specific to LCS. These serve as important guidance on reporting, communication, and management of IFs until specific guidelines are developed.[10-14]

Different communication strategies have been suggested for reporting IFs on LCS. The Lung CT Screening Reporting and Data System provides the S modifier for clinically significant or potentially clinically significant non-lung cancer findings[15] but does not specify which IFs should be reported or acted upon. The ESR and the European Respiratory Society (ERS) recommend that IFs that are clinically

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Financial support: None.

significant (i.e., with a major or adverse impact, or for which there is an established intervention that benefits the patient) and of general agreement (i.e., minimal interobserver variation) be reported and a recommendation for intervention be given. This recommendation falls within one of four categories (levels of management): immediate action, likelihood of nonpulmonary cancer, further investigation, and clinically insignificant (Table 1).[1]

Screening programs should develop a standard approach for the evaluation of these findings. Developing a standard approach to reporting and management of IFs on LCS would promote research into their impact on reducing overall mortality, as well as the development of automatic detection, measurement, and data-mining tools based on artificial intelligence. This evidence-based approach could inform public opinion and the political decision-making process, while optimizing the cost-effectiveness of LCS programs and the health gains to their participants.

This pictorial essay illustrates the systematic checklist proposed by the ESR/ERS position paper.[1] Our objective is to help radiologists familiarize with (and not to miss any) IFs, especially those with potential clinical relevance. Clinically significant IFs on LCS are summarized in Table 2.

NECK

The thyroid gland and neck lymphadenopathy

Depending on its anatomy or whether there is thyroid enlargement, the thyroid gland does not normally appear in its entirety on LDCT scans of the chest. Thyroid enlargement should be stated in the report if it causes deviation of the airway significant enough to cause respiratory symptoms (Figure 1). The most common IFs within the thyroid gland are calcifications, nodules, and cysts. The ACR white paper on incidental thyroid nodules recommends further ultrasound evaluation only for nodules larger than 1.5 cm with invasive behavior or associated with suspicious lymph nodes, because small incidental nodules are largely benign or represent indolent neoplasms (papillary carcinoma in most cases), with a 10-year survival rate of nearly 100%.[16]

Lower neck lymphadenopathy should be reported including size, morphology, shape, margins, and distribution. The criteria for lymphadenopathy include increased size (i.e., > 1 cm in short-axis diameter and on axial images); morphological changes (i.e., rounded shape; ill-defined, irregular margins; and replacement of normal fatty hila with necrosis, cystic change, suspicious calcification, or abnormal enhancement); and asymmetric distribution (i.e., prominent nodes or more than 3 contiguous and confluent lymph nodes along the drainage chain).[17,18]

THORACIC CAVITY

Trachea, bronchi, and bronchioles

Tracheal disease is usually clinically insignificant and is not commonly reported as an IF on LCS. It can present as changes in the tracheobronchial tree (e.g., diffuse dilation, stenosis, and collapse) or as focal lesions of the tracheal wall that can be benign, malignant, or non-neoplastic.[19]

In LCS, most diffuse tracheal changes are associated with COPD, including saber-sheath trachea (Figure 2), tracheocele, and tracheomegaly (Figure 3). Solid focal lesions of the trachea do require further evaluation.[19]

Bronchial wall thickening is common among smokers and usually reflects the chronic bronchitis form of COPD (Figure 3). Reference values for bronchial wall thickness, up to the segmental bronchi, are 1.2-1.4 mm and < 20% of the internal bronchial luminal diameter. This is found on approximately 39% of LDCT scans (Figure 4A).[2]

Bronchiectasis is also common in LCS because of the high prevalence of smoking and COPD (Figure 3), with cylindrical bronchiectasis being the most common type. Signs of infection (e.g., mucous plugging and tree-in-bud sign) should be mentioned in the report because the patient will benefit from further respiratory evaluation.[20]

Bronchial diverticula are also very common. They are mostly clinically insignificant and are not frequently reported.

Lungs

Pulmonary IFs are reported in 16-70% of LCS studies, with emphysema (Figure 5) being the most

Table 1. Levels of management of incidental findings on lung cancer screening, as recommended by the European Society of Radiology/European Respiratory Society.

Level of management		Action
1	Immediate action	Emergency referral (e.g., pneumothorax)
2	Likelihood of nonpulmonary cancer	Referral to a specialist (e.g., breast mass)
3	Noncancer findings	Referral to a specialist or a general practitioner (e.g., diffuse lung disease and dilated aorta)
4	Clinically insignificant	Prone to observer variation and, because there is no established beneficial intervention, do not need to be reported (e.g., minor atelectasis and renal, liver, or thyroid cysts)

Table 2. Checklist of clinically significant incidental findings on lung cancer screening (levels 1, 2, and 3). (Continued...)

Neck	Level of management	
Thyroid		
Nodules	Ultrasound if > 1.5 cm and invasive or suspicious lymph nodes	2
Enlargement	If airway deviation or compression	3
Lymphadenopathy	Size, morphology, shape, margins, and distribution	2
Chest		
Airways		
Bronchiectasis	+ Referral for respiratory evaluation	3
Lungs		
Emphysema	Type and severity	3
ILD/ILAs	+ Referral to ILD team/MDT	3
Infection		3
Pleura		
Pneumothorax	+ Emergency referral	1
Pleural plaques		3
Pleural effusion		3
Heart and Pericardium		
Coronary or valvular calcifications	+ Cardiovascular risk assessment	3
Stents, grafts, myocardial changes		3
Large pericardial effusion or cysts	May compress adjacent structures	3
Pericardial thickening (> 3-4 mm)		3
Esophagus		
Focal esophageal lesions	Smoking is a risk factor for esophageal cancer.	2
Diffuse wall thickening		3
Esophageal dilation		3
Mediastinum		
Pneumomediastinum	+ Emergency referral	1
Masses		2
Lymphadenopathy		2
Vessels		
Aortic aneurysm/ectasia	+ Referral to vascular MDT	3
Pulmonary artery dilation		3
Atheromatous disease		3
Diaphragm		
Complicated hernias	+ Emergency referral	1
Uncomplicated hernias		3
Diaphragmatic elevation		3
Breast		
New or previously undiagnosed lesion		2
Previous surgery		3
Abdomen		
Liver		
Focal lesion	Based on the hepatic risk profile	2
Biliary system		
Cholecystitis/thickening		2
Cholelithiasis		3
Biliary obstruction		2
Pneumobilia		3
Pancreas, Stomach, and Spleen		
Cysts		2
Solid masses		2
Splenomegaly		3
Kidneys		

ILD: interstitial lung disease; ILAs: interstitial lung abnormalities; and MDT: multidisciplinary team. Levels of management: (1) immediate action; (2) likelihood of nonpulmonary cancer; and (3) noncancer findings.

Table 2. Continued...

Neck		Level of management
Solid renal masses		2
Complex renal cysts		2
Stones >1 cm or in the upper pole		3
Adrenal glands		
Suspicious masses	if > 1 cm, > 10 HU, or growth	2
Masses	if < 1 cm, < 10 HU, or stable for > 1 year => no follow-up required	4
Peritoneum		
Nodules, infiltrative masses, omental haziness, ascites, and peritoneal thickening		2
Previous surgery		3
Bone/Joints		
Vertebral fractures		3
Low vertebral bone density		3
Suspicious bone masses		2
Skin/subcutaneous and Muscles		
New or previously undiagnosed lesion		2

ILD: interstitial lung disease; ILAs: interstitial lung abnormalities; and MDT: multidisciplinary team. Levels of management: (1) immediate action; (2) likelihood of nonpulmonary cancer; and (3) noncancer findings.

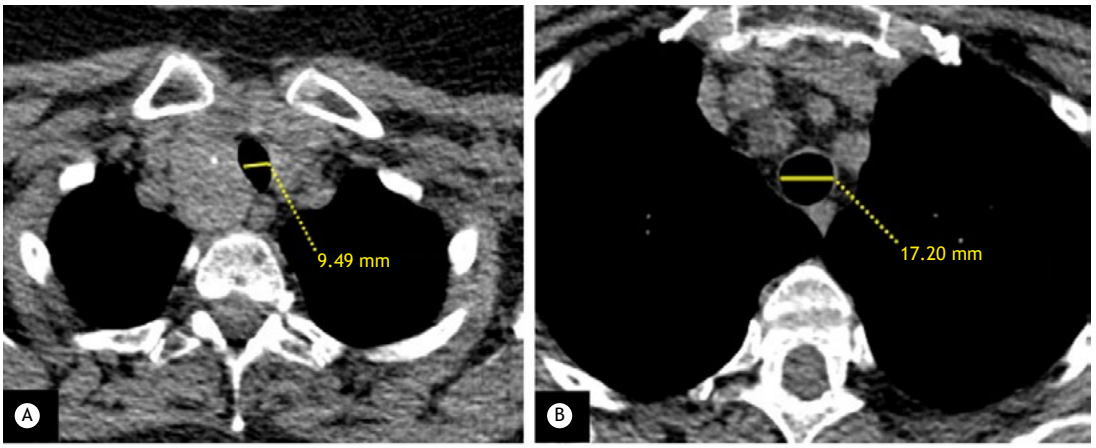

Figure 1. Goiter with tracheal compression. In A, axial image of the upper chest, showing enlargement of the left lobe of the thyroid gland, with coarse calcifications, causing displacement and narrowing of the trachea (tracheal lumen diameter, 9.49 mm). In B, tracheal lumen diameter is 17.20 mm.

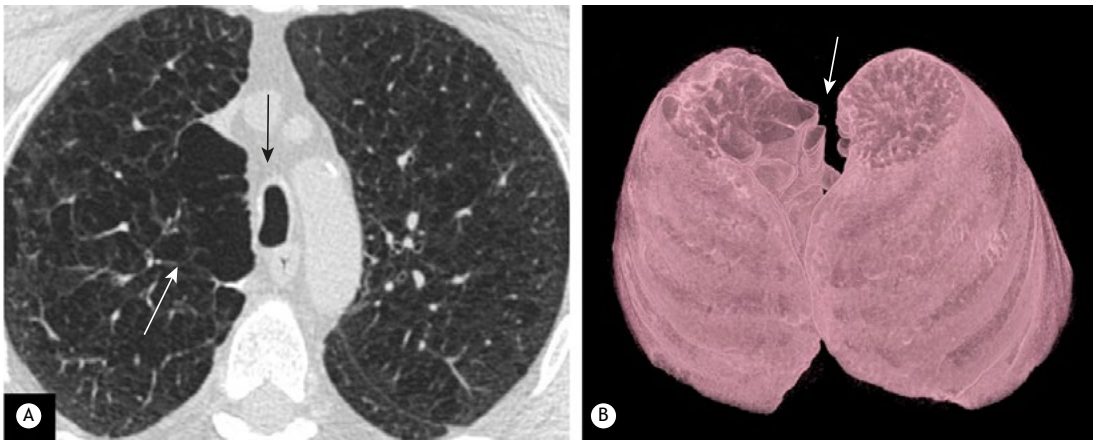

Figure 2. Saber-sheath trachea. In A, axial image of the proximal trachea, showing anatomical findings typical of a saber-sheath trachea (arrow). Note other morphological features of COPD (i.e., emphysema and bronchial wall thickening; white arrow). In B, 3D reconstruction showing decreased coronal diameter and increased sagittal diameter (white arrow).

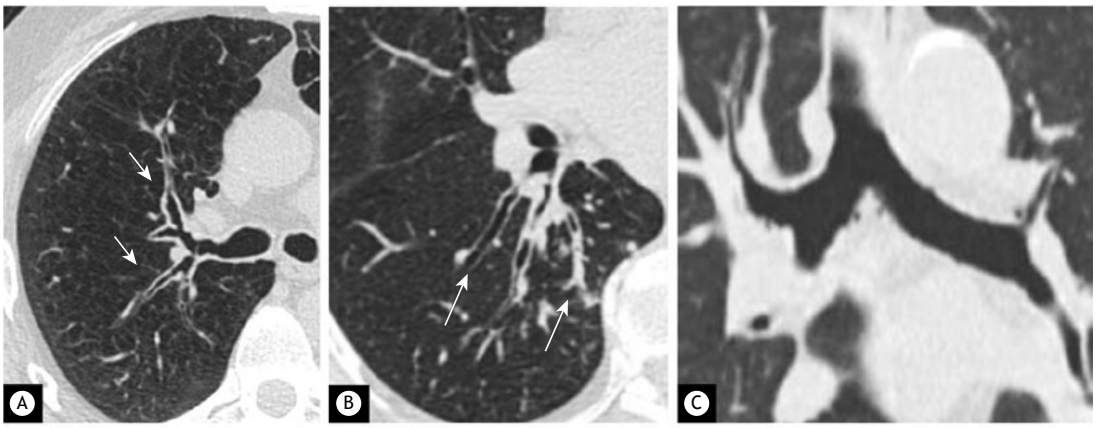

Figure 3. Airway manifestations of COPD. In A, axial image showing findings typical of pulmonary emphysema and bronchial wall thickening (arrows) in a COPD patient participating in a lung cancer screening program. In B, axial image of the right lower lobe, showing cylindrical bronchiectasis (arrows), some of which is filled with mucous plugging. In C, several subcarinal and bronchial diverticula in a heavy smoker.

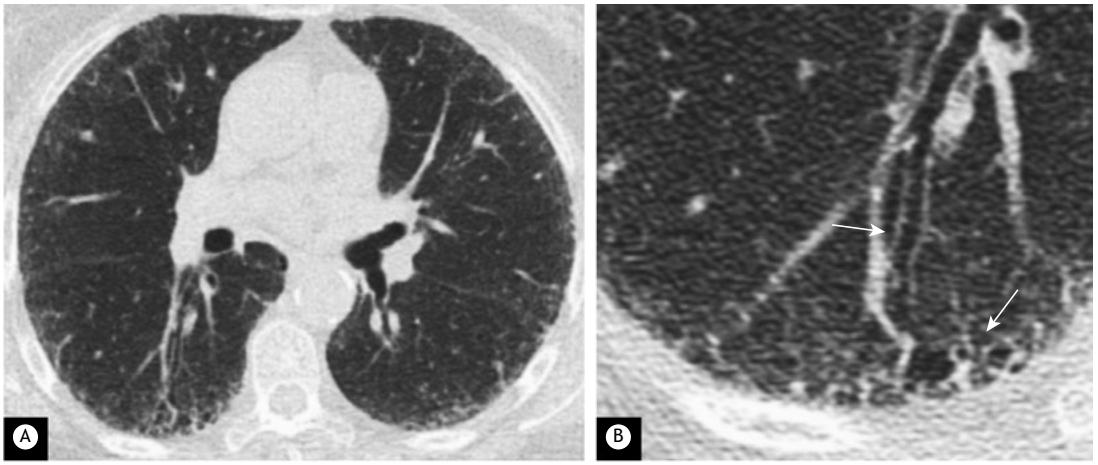

Figure 4. Interstitial lung disease. In A, axial image showing incidental findings of subpleural reticulation with honeycombing affecting the subpleural regions of the lower lobes. In B, a detail of the right lower lobe, showing traction bronchiectasis and mild honeycombing (arrows). The patient was referred for further evaluation, and the multidisciplinary team established a diagnosis of probable usual interstitial pneumonia.

common pulmonary IF.[2,6] According to some authors, emphysema should be interpreted as an expected (i.e., not incidental) comorbidity related to smoking.[2-6]

The LCS radiologist should report the type of emphysema (centrilobular, paraseptal, or panlobular) and grade its severity as trace (0.5% of a lung zone), mild (0.5-5%), moderate (45%), confluent (spanning several secondary pulmonary lobules), or advanced destructive (with hyperexpansion of secondary pulmonary lobules and architectural distortion).[21]

Interstitial lung disease (ILD) is an umbrella term used for a large group of diseases of the lungs (Figure 4) and should be reported, triggering an appointment with the respiratory team/multidisciplinary team. Smoking-related ILDs include smoking-related interstitial fibrosis, idiopathic pulmonary fibrosis, desquamative interstitial pneumonia, and respiratory bronchiolitis ILD.[21]

Osteophyte-induced lung fibrosis is a benign and focal form of fibrosis, seen in older patients as a localized ground-glass opacity, linear atelectasis, or a reticular pattern adjacent to osteoarthritic protrusions or spinal osteophytes, and does not appear to progress. Osteophyte-induced lung fibrosis should not be confused with ILD (Figure 5), especially usual interstitial pneumonia, which has a similar appearance but basilar predominance and is not restricted to a paraspinal location.[22]

Pulmonary infection has also been reported as an IF on LCS in approximately 6% of patients. Ground-glass opacities, consolidations, and tree-in-bud opacities (Figure 6) are nonspecific CT findings of infection and should be reported, prompting further clinical and laboratory evaluation.[21]

Atelectasis is another common IF on LCS. If it is linear and is not associated with a suspicious obstructive lesion, it is usually benign and does not require further evaluation.[21]

Intrapulmonary lymph nodes are common, benign findings within the lung parenchyma, with a prevalence of up to 66%, and do not require further evaluation, as per the recommendations of the British Thoracic Society, Fleischner Society, and ACR.[23,24] The morphological criteria for intrapulmonary lymph nodes are well-defined, noncalcified solid nodules with homogeneous, smooth margins and an oval, lentiform, or triangular shape, < 12 mm in diameter and located in the middle or lower lobes.

Pleura

The most common pleural IFs on LCS are pleural plaques (3.8%) and pleural effusion (1.2%). Pleural effusion may be due to benign conditions such as infection, pulmonary edema, autoimmune disease, and cardiovascular disease, but could also be a manifestation of primary or secondary malignancy and should always be reported and investigated. Pleural plaques are a marker of asbestos exposure (Figure 7). Pleural plaques should always be reported because there are important medical and legal implications to consider, and the patient should be referred to a respiratory specialist.[17]

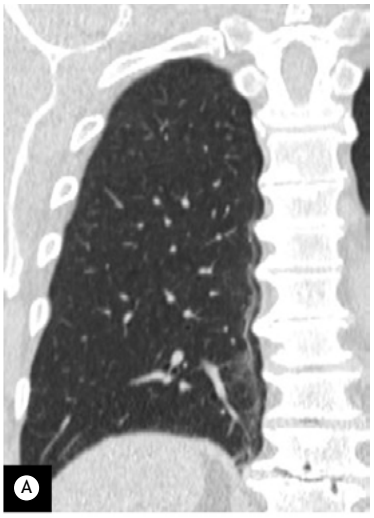

Figure 5. Osteophyte-induced lung fibrosis. Coronal image showing a line of fine fibrosis along the right paraspinal region. Progression of degenerative osteophytosis leads to compression of the adjacent lung parenchyma.

Pneumothorax is uncommon as an IF on LCS but should be treated as a medical emergency and mentioned in the report, triggering an emergency referral and activation of alert systems in place.[21]

Heart

Cardiovascular IFs on LCS are common, with some studies reporting coronary calcifications on 30-56% of LDCT scans and aortic valve calcifications on 21%.[2,3]

Smoking is a common risk factor for lung cancer and cardiovascular disease, and, as such, cardiovascular IFs on LCS should be considered smoking-related comorbidities. The risk of death from ischemic heart disease is estimated to be 3 times greater in current smokers in the 55- to 74-year age bracket than in nonsmokers.[17]

Coronary artery calcium (CAC) is highly correlated with plaque burden in coronary artery disease, and a CAC score of 1,000 is associated with a 10-fold increased risk of all-cause mortality. Recent studies on CAC and LCS have shown that LDCT can be used for low-cost, noninvasive parallel evaluation of cardiovascular risk in lung screening cohorts.[23-26] Some LCS software programs include identification and quantification of coronary artery calcifications (mild, moderate, or severe; Figure 8), and, in our experience, they should be reported because patients benefit from cardiovascular risk assessment and possible intervention.[17]

Pericardium

According to the ACR,[9] incidental pericardial findings include effusion, thickened pericardial layers, pericardial calcification (Figure 9A), and pericardial cysts. Small pericardial effusions are common and usually require no further workup, but large-volume effusions (Figure 9B) and thickening (> 3-4 mm) of pericardial layers should be reported and trigger further clinical evaluation. Pericardial cysts are the most common benign pericardial

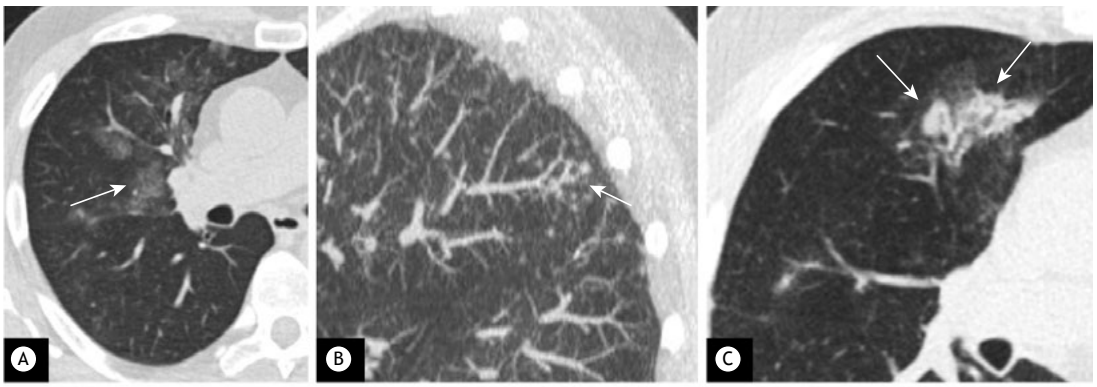

Figure 6. Pulmonary infection. In A, axial image of the right middle lobe, showing focal areas of ground-glass attenuation (arrow) with ill-defined nodularity. In B, a tree-in-bud pattern (arrow). The patient had clinically and microbiologically confirmed pneumonia. In C, axial image of a different patient, showing consolidation with air bronchogram in a predominantly peribronchovascular distribution (arrow). The patient was clinically diagnosed with bronchopneumonia.

masses, presenting with thin walls and located at the cardiophrenic angles. Low-attenuation cysts do not require follow-up, unless they are large enough to risk compression of adjacent structures.[9]

Esophagus

Evaluation of the esophagus on an unenhanced scan is limited, but significant luminal dilation should be reported and could be a sign of achalasia, scleroderma, or other inflammatory conditions. Diffuse esophageal wall thickening is seen in infectious or inflammatory conditions. Although not a common IF on LCS, focal lesions of the esophagus should be reported and trigger further diagnostic workup because smoking is a risk factor for esophageal cancer.[27]

Mediastinum

Mediastinal masses are an uncommon IF on LCS, with a reported prevalence of only 0.77% in high-risk smokers.[17] The most common mediastinal masses are anterior mediastinal masses originating from the thymus or thyroid gland. Masses in the posterior mediastinum are likely neurogenic in origin and should be further evaluated by magnetic resonance imaging.[27] When a mediastinal mass is present, location, texture, and invasive behavior should be reported and the patient should be referred for further evaluation.[9,17,27]

Mediastinal lymph nodes are a common normal finding on chest CT scans. Lymphadenopathy is frequently due to infection, edema, diffuse lung disease

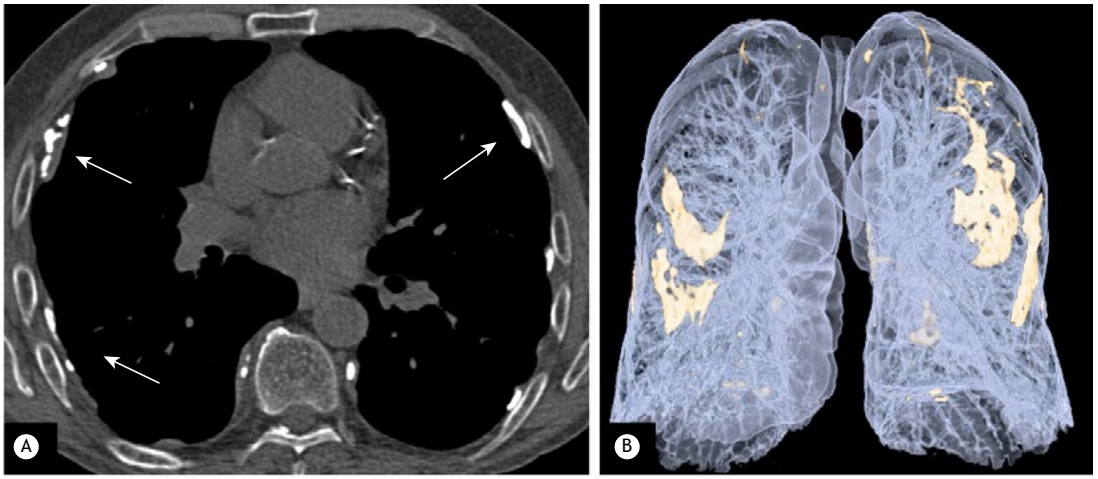

Figure 7. Pleural plaques. In A, axial image with bone window settings, showing several linear calcifications in the costal pleura (arrows). In B, 3D reconstruction of the same patient, showing that the pleural plaques are also affecting the mediastinal pleura and the diaphragmatic pleura.

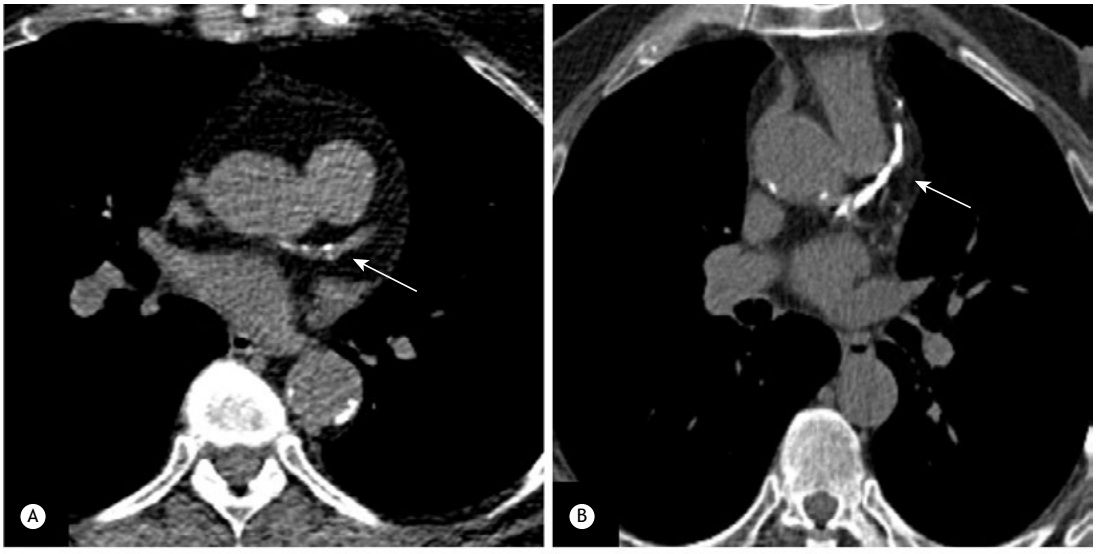

Figure 8. Coronary artery calcifications. In A, axial low-dose CT image showing mild scattered calcified plaques in the proximal left anterior descending coronary artery, findings that should be reported as mild calcifications of the coronary arteries (arrow). In B, severe calcifications of the coronary arteries with heavily calcified plaques distributed along the proximal and mid left anterior descending coronary artery, findings that should be reported as severe calcifications of the coronary arteries (arrow).

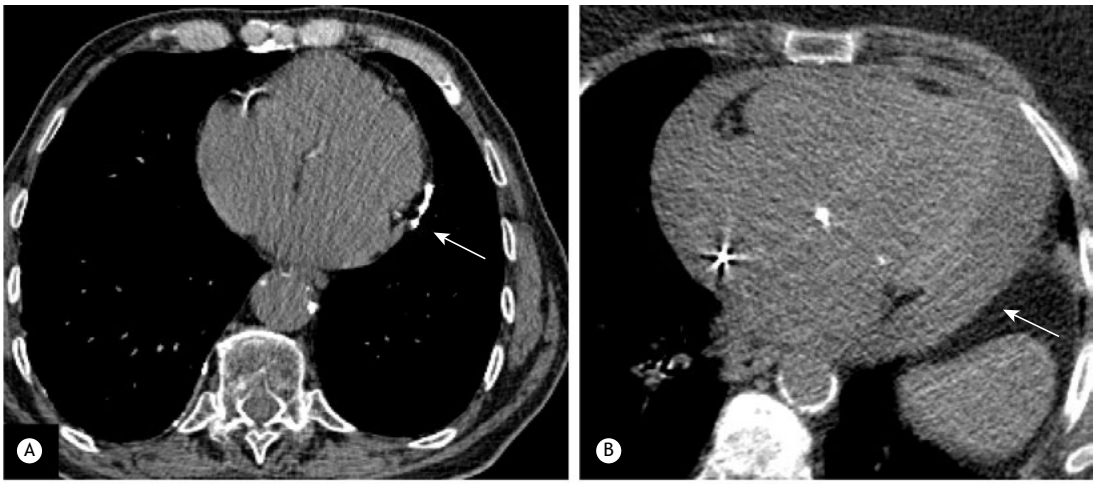

Figure 9. Pericardial effusion and calcifications. In A, axial image showing linear pericardial calcification (arrow), a finding that is likely related to a previous episode of pericarditis. In B, axial image showing a significant pericardial effusion (arrow). A review of the medical records showed that the patient had heart failure, with recent episodes of cardiac decompensation. The pericardial effusion was mentioned and triggered an alert to the cardiac team.

(e.g., sarcoidosis and fibrosis), and, less commonly, lymphoma or metastases. According to the ACR, incidentally detected lymph nodes of < 15 mm in short-axis diameter in patients with no other findings do not require further evaluation.[9]

Pneumomediastinum is not a common IF on LCS but is a medical emergency and requires immediate action from the radiologist, with emergency referral and activation of alert systems in place.

Vessels

Aortic disease is a common IF on LCS, with dilation of the aorta being reported in up to 8.1% of LCS studies.[2,17] Aortic dissection and significant ulcerations are usually undetectable on LDCT given its unenhanced nature.[9]

According to the ACR, the diameter of the aorta is influenced by sex, age, and body surface area.[9] The criteria for aortic aneurysm are more than 5 cm for the ascending aorta and more than 4 cm for the descending aorta. This should be reported, and the patient should be referred to a vascular specialist for further evaluation.

Pulmonary artery dilation has not been studied in the context of LCS but should be reported because an enlargement may reflect primary or secondary pulmonary arterial hypertension or be secondary to chronic pulmonary embolism or other pulmonary disease.[9] The criterion for a dilated main pulmonary artery is 3 cm or more in diameter, or equal in diameter to the ascending aorta.

Diaphragm

Diaphragmatic hernias can be either intrapleural (Bochdalek hernias) or mediastinal, the latter further divided into prevascular (Morgagni-Larrey hernias) or visceral (pericardial or hiatal hernias). Hiatal hernia is the most common transdiaphragmatic IF on LCS, being reported in 9-14% of patients.[2,28]

Most hiatal hernias are not significant but should be reported if they are large enough to cause cardiac compression. Diaphragmatic paralysis from phrenic nerve injury results in an asymmetric position of the diaphragmatic dome and does not need any special mention in the report.

ABDOMINAL CAVITY

A systematic review of the included upper abdomen is mandatory to exclude potentially significant clinical findings (e.g., malignancy) requiring urgent referral (Table 2). The ACR white papers on incidental abdominal findings provide useful guidance for lesions requiring further follow-up.[11-14]

Liver

The most commonly encountered benign hepatic lesions are hepatic cysts, hemangiomas, and focal nodular hyperplasia, usually seen on LDCT scans as a focal hypodense lesion.[12]

In a recent study of IFs on LCS, hepatic cysts were present in 34% of patients (Figure 10A) and are of little or no clinical significance.[28] The need for further characterization of focal liver lesions other than simple cysts is based on patient risk profile and lesion size, with known malignancy (primary liver cancer or other primary malignancy known to metastasize to the liver), hepatic dysfunction, and hepatic risk factors being taken into consideration.[12]

Gallbladder

The gallbladder does not always appear in its entirety on LCS scans depending on the field of view, patient body habitus, and patient height. In our experience,

the most common findings are gallstones, with no further complications.

Pancreas, stomach, and spleen

Pancreatic IFs on LCS are reported in approximately 5% of LCS studies, including pancreatic calcifications (Figure 10B) and cancer.[2] According to the ACR, all incidental pancreatic cysts should be presumed mucinous in nature.[13] Pancreatic cysts and pancreatic solid masses should be reported and further evaluated.[13] Likewise, any gastric or splenic mass, splenic cyst, or splenomegaly should be referred for further evaluation.

Kidneys

Renal cancer has been reported as one of the most common extrapulmonary malignancies in LCS studies.[2,28] Any solid renal lesion should be reported and trigger further specialist evaluation and diagnostic workup (using a renal-mass CT protocol or magnetic resonance imaging study), especially if the lesion is accompanied by suspicious findings such as thick or irregular wall, mural nodule, septa, and calcification. Lesions smaller than 1 cm are likely benign, even if they are solid lesions. Well-defined homogeneous lesions smaller than 3 cm with high density (above 70 HU) can be confidently diagnosed as hyperattenuating cysts (Bosniak category II cysts) according to the ACR.[14] Simple cystic renal lesions are a common IF on routine imaging and are usually easy to recognize because of their water attenuation (0-20 HU).

Renal stones are also common findings on imaging studies. The prevalence of asymptomatic lithiasis in LCS is 10%, and renal stones are considered clinically irrelevant.[17] However, renal stones larger than 10 mm or located in the upper poles tend to be associated with an increased risk of symptoms and benefit from surgical evaluation (and should therefore be reported). If hydronephrosis is identified, it also requires further evaluation.

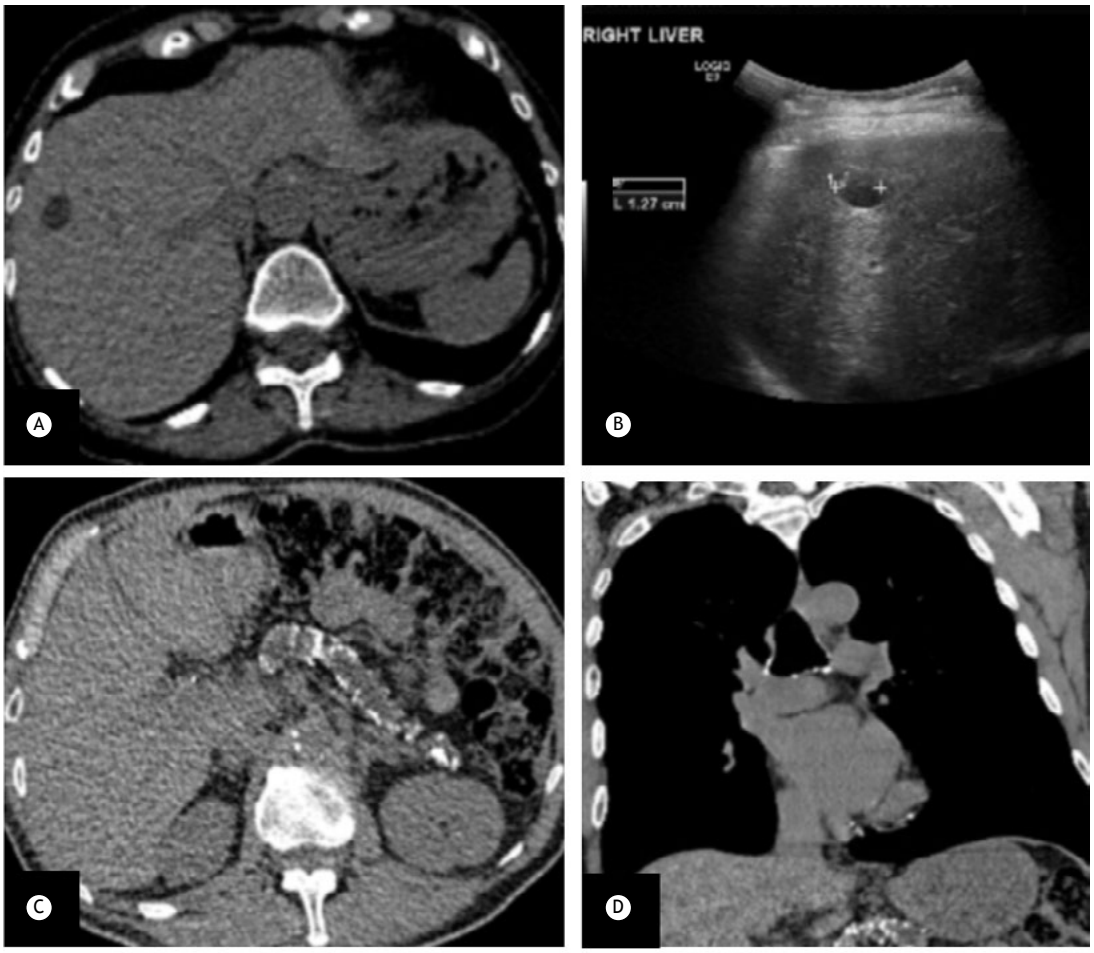

Figure 10. Incidental abdominal findings. In A, axial image showing a focal hypodense liver lesion of 13 mm. Density was found to be inaccurately measured by low-dose CT. This was mentioned in the report, and the medical team decided to request an ultrasound scan. In B, ultrasound scan showing the benign features of a cyst. In C and D, axial and sagittal images of a different patient, showing another incidental finding, i.e., several coarse calcifications in the atrophic pancreatic parenchyma, with dilated pancreatic duct, in keeping with chronic pancreatitis. Pancreatic disease is not commonly depicted on low-dose CT scans for lung cancer screening, because low-dose CT has reduced sensitivity for pancreatic lesions and because the usual field of view does not cover the pancreas.

Adrenal glands

Non-hyperfunctioning adenomas are the most common adrenal lesions in the general population and are seen on as much as 13% of LCS scans.[28] According to the ACR, incidental adrenal lesions smaller than 1 cm in short-axis diameter, containing macroscopic fat, and with average attenuation of less than 10 HU or stable for more than 1 year should be considered benign and do not require follow-up.[11]

Peritoneum

Suspicious signs of peritoneal disease, such as nodules or infiltrative masses in the peritoneal cavity, omental haziness, ascites, and peritoneal thickening, should be reported, and the patient will require referral for specialist and further diagnostic evaluation.[29]

BONE/JOINTS

Incidental osseous findings on LCS include diffuse diseases such as osteoporosis, thoracic kyphosis, osteophytosis, and diffuse idiopathic skeletal hyperostosis, as well as focal lesions, both benign and malignant.[30]

SKIN/SUBCUTANEOUS AND MUSCULAR SYSTEM

In one study of IFs on LCS, the presence of soft-tissue or muscular findings was very low, with incidental sebaceous cysts having only a 1% frequency, despite the fact that sarcopenia is a known smoking-related comorbidity.[28]

The breast is a special soft-tissue compartment, with lesions being seen on up to 7% of LCS scans, with variable clinical significance, despite the fact that LDCT is not a good imaging modality for breast evaluation.[3,28] Breast IFs on LCS include primary and secondary malignancies, as well as benign lesions such as calcifications, fibroadenomas, and lipomas. Breast malignancy is the most worrying finding, and, as such, any new lesion or any lesion not previously documented as benign should be reported and referred for further evaluation.

FINAL CONSIDERATIONS

Clinically significant IFs on LCS are common, and their potential impact should be taken into consideration in the shared decision-making process. LCS programs should develop a standard approach for the evaluation of these findings.

AUTHOR CONTRIBUTIONS

DP and EP made substantial contributions to the conception and design of the work, as well as to the collection of the illustrations used. KI, CM, EM, LTB, BH, SR, and HK made substantial contributions to the review of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICT OF INTEREST

None declared.

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

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Submitted: 24 September 2021.
Accepted: 2 November 2021.

ABSTRACT

Objective: Studies in the literature regarding the use of remdesivir to treat COVID-19 patients have shown conflicting results. This study sought to answer questions related to the use of remdesivir for the treatment of patients hospitalized with moderate to severe COVID-19. **Methods:** This was a systematic review and meta-analysis including phase 3 randomized clinical trials (RCTs) and observational cohort studies selected from various databases, comparing patients hospitalized with moderate to severe COVID-19 receiving remdesivir and controls. **Results:** A total of 207 studies were retrieved, 9 of which met the eligibility criteria and were included in the study. The meta-analysis using RCTs alone showed no statistically significant differences regarding mortality or use of mechanical ventilation/extracorporeal membrane oxygenation between remdesivir and control groups, and the quality of evidence was moderate and low, respectively. The use of remdesivir increased the recovery rate by 6% (95% CI, 3-9); p = 0.004) and the clinical improvement rate by 7% (95% CI, 1-14); p = 0.02). Additionally, no significant differences in mortality were found between remdesivir and control groups when the meta-analysis used observational cohort studies alone (risk difference = −0.01 (95% CI, −0.02 to 0.01; p = 0.32), the quality of evidence being moderate, and the risk of adverse events was 4% ([95% CI, −0.08 to 0.01]; p = 0.09). **Conclusions:** The use of remdesivir for the treatment of patients with moderate to severe COVID-19 had no significant impact on clinically important outcomes.

Keywords: Antiviral agents; COVID-19; SARS-CoV-2.

INTRODUCTION

In March of 2020, the WHO declared that the current COVID-19 pandemic had spread worldwide, with 200,840,000 people being infected by the new SARS-CoV-2 and resulting in 4,265,000 deaths.[1] In Brazil, until August of 2021, there were 20,026,000 diagnosed cases and 559,607 deaths,[2] with a mortality rate of 3.81%. An increased risk of mortality is associated with the presence of comorbidities and the need for mechanical ventilation.[3]

The main mechanism underlying the development of ARDS is related to the binding of the viral surface glycoprotein, called a spike glycoprotein, to angiotensin-converting enzyme 2, the most abundant receptor in alveolar type II epithelial cells in the lungs, allowing viral entry.[4]

Remdesivir is an intravenous broad-spectrum antiviral drug developed in 2017 as a compassionate treatment option for the Ebola virus infection and was later tested for Middle East respiratory syndrome and SARS coronavirus.[5] Remdesivir is a direct-acting nucleotide-analog prodrug that inhibits RNA by incorporating triphosphates and interfering with viral RNA polymerase activity.[6] The in vitro efficacy of remdesivir against SARS-CoV-2 has previously been demonstrated.[7] In a rhesus monkey model of SARS-CoV-2 infection, treatment with remdesivir, which was started shortly after inoculation, resulted in lower viral load in the lungs and reduced lung damage in comparison with control animals.[8]

Remdesivir has been approved by the U.S. Food and Drug Administration for use in hospitalized adult and pediatric patients (≥ 12 years and weighing ≥ 40 kg) infected with SARS-CoV-2 and has further received conditional marketing authorization from the European Medicines Agency for use in patients with SARS-CoV-2-related pneumonia receiving supplemental oxygen. In Brazil, remdesivir was approved by the Brazilian National Health Surveillance Agency for use in hospitalized COVID-19 patients not on mechanical ventilation. However, the existing evidence from systematic reviews and meta-analyses are conflicting[9-11] and justify a living systematic review approach. Therefore, this systematic review sought to identify, describe, evaluate, and synthesize evidence regarding clinical outcomes of the use of remdesivir in hospitalized COVID-19 patients.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[12]

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Financial support: None.

ISSN 1806-3756

Eligibility criteria

The protocol of this study was based on the PICO methodology (Patients of interest, Intervention to be studied, Comparison of intervention, and Outcome of interest). Therefore, the PICO framework in the present study was Patients: adult patients with COVID-19; Intervention: use of remdesivir; Comparison: comparison between standard of care (SOC) and placebo; and Outcomes: all-cause mortality rate in 29 days, recovery rate in 29 days, patient clinical improvement rate in 29 days, need for mechanical ventilation or extracorporeal membrane oxygenation (ECMO), and adverse events. Intermediate outcomes, such as length of hospital stay (in days), were excluded.

Phase 3 randomized controlled trials (RCTs) and observational cohort studies with at least 24 days of follow-up were considered eligible for the study. We imposed no restrictions on the date of publication, language, or full-text availability.

Information sources and search strategy

Two of the authors developed a search strategy that was revised and approved by the team, selected information sources, and systematically searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov. Specific search strategies were used for each database: ("COVID-19" OR "COVID" OR "coronavirus" OR "SARS-CoV-2") AND ("remdesivir" OR "Adenosine nucleoside triphosphate analog" OR "Adenosine Monophosphate") AND (Therapy/narrow[filter] OR Prognosis/narrow [filter] OR "Comparative study" OR "Comparative studies"). Cochrane Central Register of Controlled Trials: (COVID-19 OR COVID OR CORONAVIRUS OR SARS-CoV-2) AND (remdesivir). The search strategy included studies published until October 18, 2021.

Study selection

Two independent researchers selected and extracted the data from the studies included. First, the articles were selected on the basis of their titles and abstracts. Second, full texts were evaluated to be included or excluded, and disagreements were resolved by consensus.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (remdesivir or control), absolute numbers of each outcome, and follow-up period were extracted from the studies.

Risk of bias and quality of evidence

The risk of bias for RCTs was assessed using the Cochrane risk-of-bias (RoB 2)[13,14] tool, as were other fundamental elements, which were expressed as very serious, serious, or not serious. For cohort studies, the risk of bias was assessed using the current tool recommended by the Cochrane Collaboration to estimate the effectiveness and safety of nonrandomized interventional studies—Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I).[15] ROBINS-I assesses seven domains of bias, classified by the time of occurrence. The assessment of risk of bias was conducted by two independent reviewers, and, in case of disagreement, a third reviewer deliberated on the assessment. 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 as very low, low, or high; for meta-analyses, the quality of evidence was described by the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada) as very low, low, moderate, or high.

Synthesis of results and analysis

Categorical outcomes were expressed by group (remdesivir or control), number of events, and calculated risk (in %) for each group (by dividing the number of events by the total number of patients in each group). If the risk difference between the groups was significant, a 95% CI was expressed on the basis of the number needed to treat (NNT) or the number needed to harm. We used the fixed-effect or random-effect model in the meta-analysis to evaluate the effect of remdesivir vs. control on the outcomes when these data were available in at least two RCTs or observational cohort studies. The effects of meta-analyses were reported as risk differences (RDs) and corresponding 95% CIs; a 95% CI including the number 0 in its range meant that there was no difference in the outcome effect between the remdesivir and control arms. The use of RD shows 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. The heterogeneity of effects among studies was quantified using the I^2 statistic ($I^2 > 50\%$ indicates high heterogeneity). For the meta-analysis, we used the Review Manager software, version 5.4 (Cochrane, Oxford, United Kingdom). The results were presented using a methodological design (RCT or observational cohort study).

RESULTS

A total of 207 studies were retrieved from the selected databases (Figure 1). After eliminating duplicates and including studies that met the eligibility criteria, 14 studies were selected for full-text assessment. Of these, 5 were excluded (Figure 1); therefore, six RCTs[16-21] and three observational cohort studies were selected.[22-24] The characteristics (Table 1), results, risk of bias, quality of evidence, and synthesis of evidence of these studies are described below (Tables 2-4). No publication bias was identified.

The total population comprised 12,379 hospitalized moderate-to-severe COVID-19 patients (8,044 from the six RCTs and 4,335 from the three observational cohort studies); 5,722 patients received remdesivir,

and 6.657 received SOC or placebo. In regards to the risk of bias in the RCTs,[16-21] two had randomization and blinded allocation, showing a risk of bias,[17,20] four were single-blinded, with no blinding of the observer,[16-19] and one RCT did not use intention-to-treat analysis,[17] which was considered a risk of bias (Table 3).

Regarding the risk of bias in the three nonrandomized studies, only one had a moderate bias due to missing data. Overall, the studies were considered to have a low risk of bias (Figure 2 and Table 4).[22-24]

Qualitative description of included results

Beigel et al.[16] conducted a placebo-controlled RCT including adult patients hospitalized with COVID-19 and pulmonary impairment in the USA, Denmark, United Kingdom, Greece, Korea, Mexico, Spain, Japan, and Singapore. The patients were stratified according to the severity of pulmonary impairment (use of mechanical ventilation or supplemental oxygen). Intervention was treatment with remdesivir 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v. from days 2 to 10 or until discharge/death. The primary outcome was time to recovery, defined on the basis of an 8-point ordinal scale (1: not hospitalized and no limitations of activities; 2: not hospitalized, with limitations of activities, home oxygen requirement, or both; 3. hospitalized, not requiring supplemental oxygen, and no longer requiring ongoing medical care—used if hospitalization was extended for infection control or other nonmedical reasons; 4. hospitalized, not requiring supplemental oxygen, but requiring ongoing medical care—related to COVID-19 or other medical conditions; 5. hospitalized, requiring any type of supplemental oxygen; 6. hospitalized, requiring noninvasive ventilation or use of high-flow oxygen devices; 7. hospitalized, receiving invasive mechanical ventilation or ECMO; and 8. death). Time to recovery was defined as the first day, during the 28-day follow-up period after enrollment, on which a patient met the criteria for category 1, 2, or 3. Secondary outcomes were time to improvement of one category and of two categories from the baseline ordinal score; the incidence and duration of new oxygen use, of noninvasive ventilation or high-flow oxygen, and of invasive ventilation or ECMO; number of days of hospitalization up to day 29; and mortality at 14 and 28 days after enrollment. Safety outcome

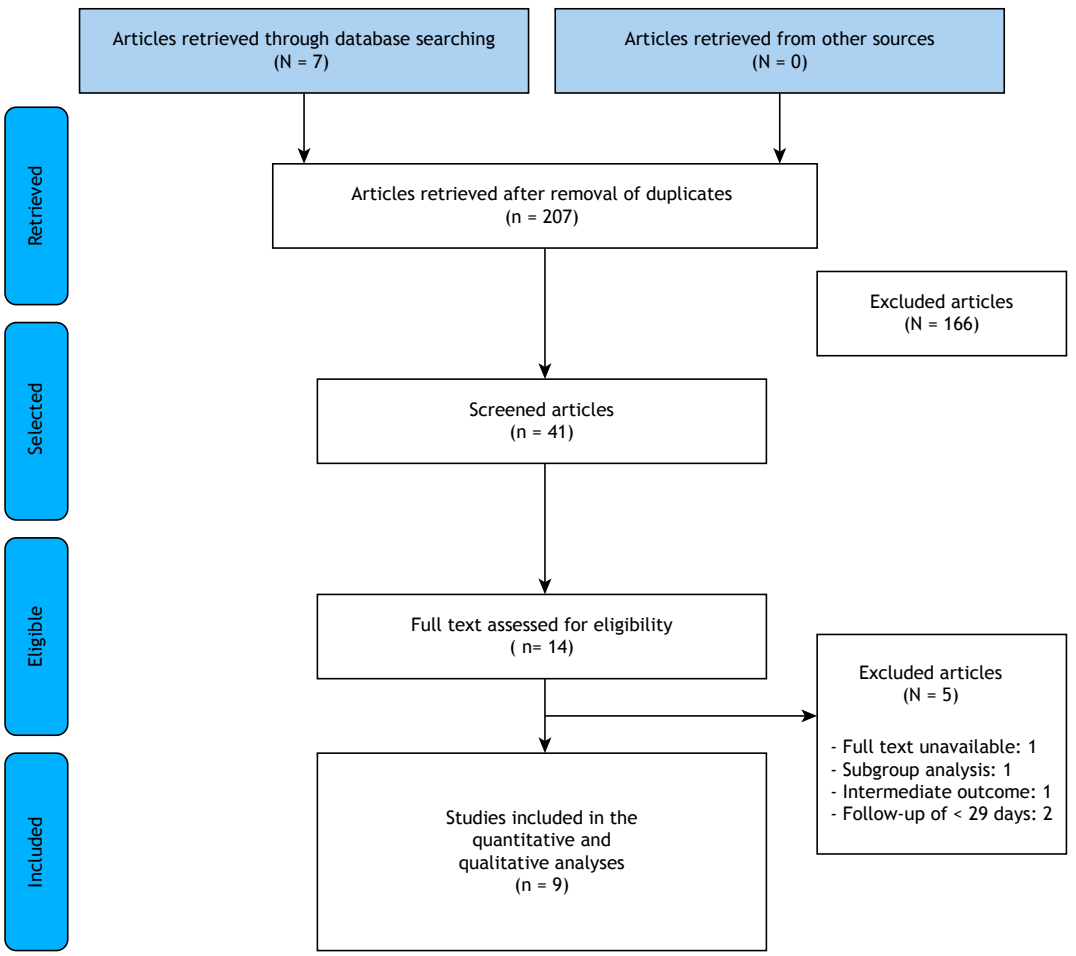


Figure 1. Flow chart of study selection based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[12]

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

Study	Design	Population	Intervention	Comparator	Outcome	Follow-up
Beigel et al.[16]	RCT	Adults hospitalized with COVID-19 with pulmonary impairment Different severity levels of COVID-19	(N = 541) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg on days 2-10 or until discharge or death	(N = 521) Placebo	Mortality in 15 and 29 days Mechanical ventilation or ECMO Time to recovery (discharge or hospitalization for infection control) Clinical improvement (recovery scale) Severe adverse events	29 days
Spinner et al.[19]	RCT	Patients hospitalized with SARS due to COVID-19 (pulmonary abnormalities and SpO_2 < 94% on room air = moderate to severe disease)	(N = 197) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10 (N = 199) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-5	(N = 200) Standard of care corticosteroid, hydroxychloroquine, azithromycin, lopinavir-ritonavir	Mortality Mechanical ventilation or ECMO Recovery rate (recovery scale) Clinical improvement (recovery scale) Severe adverse events	28 days
Wang et al.[20]	RCT	Adult patients hospitalized with COVID-19 and onset of symptoms by 12 days SpO_2 < 94% on room air, PaO_2/FIO_2 ratio < 300, or radiological viral pneumonia Severe COVID-19	(N = 158) Remdesivir: 200 mg i.v. on ICU day 1, followed by 100 mg i.v. on days 2-10 Concomitant use of lopinavir-ritonavir, interferon, and corticosteroids	(N = 79) Placebo	Mortality Clinical improvement (recovery scale or discharge) Severe adverse events	28 days
WHO Solidarity Trial Consortium et al.[18]	RCT	Adult (≥ 18 years) patients hospitalized with COVID-19 Different severity levels of COVID-19	(N = 2,750) Remdesivir: 200 mg on day 0, followed by 100 mg on days 1-9	(N = 4,088) Standard of care, corticosteroids, convalescent plasma, anti-IL-6 drug	Mortality Mechanical ventilation or ECMO	28 days

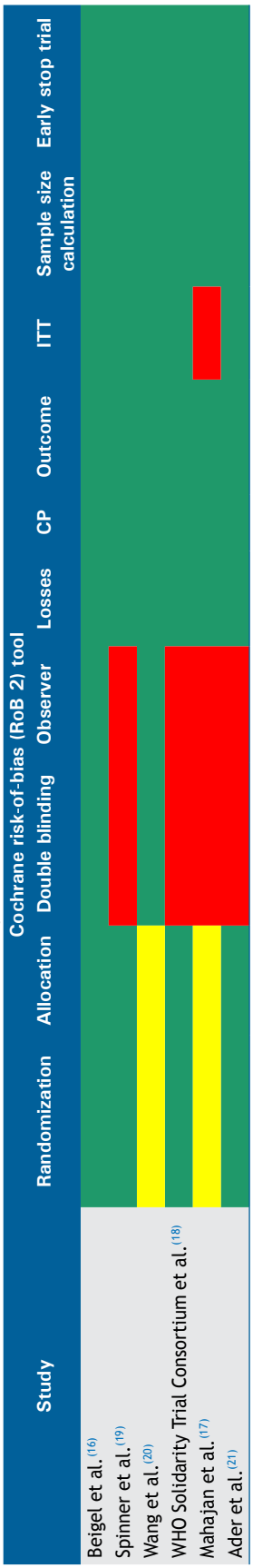
Continue...▶

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

Study	Design	Population	Intervention	Comparator	Outcome	Follow-up
Mahajan et al.[17]	RCT	Adult (18-60 years) patients hospitalized with moderate to severe COVID-19 within the last 4 days with viral pneumonia, RR > 24 breaths/min, and SpO_2 < 94%, not on mechanical ventilation or presenting with multiple organ failure	(N = 34) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg on days 2-5 Concomitant use of heparin and corticosteroids	(N = 36) Standard of care, corticosteroids, heparin	Mortality Mechanical ventilation Recovery rate (recovery scale) Adverse events	24 days
Ader et al.[21]	RCT	Adult (≥ 18 years) patients hospitalized with moderate to severe COVID-19, based on clinical assessment and SpO_2 < 94% or requiring supplemental oxygen, noninvasive ventilation, or mechanical ventilation	(N = 414) Remdesivir: 200 mg i.v. on day 1, followed by 100 mg i.v. on days 2-10	(N = 418) Standard of care, corticosteroids, heparin	Clinical status at days 15 and 29 Time to improvement Time to hospital discharge Mortality	29 days
Kalligeros et al.[22]	OCS	Adult patients hospitalized with COVID-19 and SpO_2 < 94% or requiring supplemental oxygen Pulmonary abnormalities, creatinine clearance > 50 mL/min, AST and ALT < 5 upper limit unit of normal	(N = 99) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10	(N = 125) Standard of care, corticosteroids, convalescent plasma, hydroxychloroquine	Mortality Clinical improvement Length of hospital stay	28 days
Ohl et al.[23]	OCS	Positive test for SARS-CoV-2 within 14 days prior to or during hospitalization Creatinine clearance > 50 mL/min, AST e ALT < 5 upper limit unit of normal	(N = 1,172) Remdesivir	(N = 1,172) Standard of care, corticosteroid, hydroxychloroquine, azithromycin, heparin	Mortality Length of hospital stay	30 days
Olender et al.[24]	OCS	Adult (≥ 18 years) patients hospitalized with COVID-19, SpO_2 < 94% or requiring supplemental oxygen Pulmonary abnormalities, creatinine clearance > 50 mL/min, AST e ALT < 5 upper limit unit of normal	(N = 268) Remdesivir: 200 mg on day 1, followed by 100 mg on days 2-10	(N = 1,399) Standard of care, azithromycin, biologic agents, HIV protease inhibitors, hydroxychloroquine, ribavirin	Mortality	28 days

RCT: randomized clinical trial; and OCS: observational cohort study.

Table 2. Risk of bias of the randomized controlled trials included in the analysis.



CP: characteristic prognosis; and ITT: intention to treat.
Observation: red = risk of bias; yellow = not clear; green = no risk of bias.

measures included adverse events and serious adverse events.[16]

Mahajan et al.[17] conducted a single-center RCT including adult patients hospitalized with COVID-19 (confirmed RT-PCR within the last 4 days), RR > 24 breaths/min, SpO_2 < 94%, and no mechanical ventilation use or multiple organ failure. The intervention group received remdesivir 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v. once a day from days 2 to 5. The outcomes were mortality, use of mechanical ventilation, and recovery rate.

The WHO Solidarity Trial Consortium et al.[18] conducted an RCT that included hospitalized COVID-19 patients ≥ 18 years of age who had neither been known to have received any trial drug nor were expected to be transferred elsewhere within the following 72 h. The trial drugs were remdesivir, hydroxychloroquine, lopinavir, and interferon. The controls for a drug were patients assigned to receive SOC at a time and place in which that drug was locally available. One of the intervention groups received remdesivir 200 mg i.v. on day 0 and remdesivir 100 mg from days 1 to 9. The primary objective was to assess the effects of the drug on in-hospital mortality, regardless of whether death occurred before or after day 28. Secondary outcomes were initiation of mechanical ventilation and length of hospital stay.[18]

Spinner et al.[19] conducted an RCT in the USA, Europe, and Asia using three different groups randomly assigned in a 1:1:1 ratio to receive up to a 5-day course of remdesivir, up to a 10-day course of remdesivir, or SOC. Randomization was not stratified. They included patients hospitalized with SARS due to COVID-19 infection (pulmonary abnormalities and SpO_2 < 94% on room air). All patients randomized to one of the remdesivir groups received 200 mg i.v. on day 1, followed by remdesivir 100 mg i.v., infused between 30 and 60 min, once a day on the subsequent days. Prespecified exploratory endpoints were time to recovery (improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7); time to modified recovery (improvement from a baseline score of 2-4 to a score of 5-7, improvement from a baseline score of 5 to a score of 6-7, or improvement from a baseline score of 6 to a score of 7); time to clinical improvement (≥ 2-point improvement from baseline on the 7-point ordinal scale); time to improvement by 1 or more points; time to discontinuation of any oxygen support; and all-cause mortality.[19]

Wang et al.[20] conducted an RCT in ten hospitals in Wuhan, China, including adult patients hospitalized with COVID-19 and confirmed pneumonia by chest imaging, SpO_2 ≤ 94% on room air or PaO_2/FIO_2 ratio ≤ 300 mmHg, and symptom onset ≤ 12 days. The primary clinical endpoint was time to clinical improvement within 28 days after randomization. Clinical improvement was defined as hospital discharge or a 2-point reduction from baseline admission score on a 6-point ordinal scale (6: death; 5: hospital admission for ECMO or

Table 3. GRADE analysis of remdesivir compared with placebo/standard of care in patients hospitalized with moderate to severe COVID-19 in randomized clinical trials.

No. of studies	Study design	Certainty assessment					No. of patients		Effect		Certainty	Importance
		Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Remdesivir	Placebo/SOC	Relative (95% CI)	Absolute (95% CI)		
Mortality in 29 days												
5	Randomized trials	very serious[a]	not serious	not serious	not serious	none	390/3669 (10.6%)	397/3543 (11.2%)	RR 0.94 (0.82 to 1.07)	7 fewer per 1,000 (from 20 fewer to 8 more)	⊕⊕⊕◯ MODERATE	IMPORTANT
Recovered patients in 29 days												
3	Randomized trials	very serious[b]	not serious	not serious	very serious[c]	none	579/768 (75.4%)	525/757 (69.4%)	RR 1.09 (1.03 to 1.15)	62 more per 1,000 (from 21 more to 104 more)	⊕⊕◯◯ LOW	IMPORTANT
Clinical improvement in 29 days												
2	Randomized trials	very serious[d]	not serious	not serious	very serious[c]	none	277/351 (78.9%)	211/278 (75.9%)	RR 1.10 (1.01 to 1.19)	76 more per 1,000 (from 8 more to 144 more)	⊕⊕◯◯ LOW	IMPORTANT
Mechanical ventilation or ECMO in 29 days												
5	Randomized trials	very serious[a]	very serious[e]	not serious	not serious	very serious[f]	354/3268 (10.8%)	375/3152 (11.9%)	RR 0.76 (0.46 to 1.26)	29 fewer per 1,000 (from 64 fewer to 31 more)	⊕◯◯◯ VERY LOW	IMPORTANT
very serious adverse events in 29 days												
3	Randomized trials	not serious	not serious	not serious	very serious[c]	None	169/880 (19.2%)	201/794 (25.3%)	RR 0.75 (0.63 to 0.90)	63 fewer per 1,000 (from 94 fewer to 25 fewer)	⊕⊕⊕◯ MODERATE	IMPORTANT

GRADE: Grading of Recommendations Assessment, Development and Evaluation; SOC: standard of care; and RR: risk ratio.
Explanations
a. Three of the five studies were not blinded by the researcher. Two studies showed risk of bias related to randomization and allocation, with some concerns.
b. Two of the three studies were not investigator's blinded studies, and one study had a risk of bias for randomization and blind allocation, with some concerns.
c. Large confidence interval
d. One of the two included studies was not blinded by the researcher, and one had a risk of bias for randomization and blind allocation with some concerns.
e. High heterogeneity (I^2 = 71%).
f. Publication bias.

Table 4. GRADE analysis of remdesivir compared with placebo/standard of care in patients hospitalized with moderate to severe COVID-19 in observational cohort studies.

No. of studies	Study design	Certainty assessment: Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	No. of patients: Remdesivir	SOC	Effect: Relative (95% CI)	Absolute (95% CI)	Certainty	Importance
Mortality in 28 days												
3	Observational study	not serious	Severe[a]	not serious	not serious	none	194/1639 (11.8%)	367/2696 (13.6%)	RR 0.85 (0.56 to 1.28)	20 fewer per 1,000 (from 60 fewer to 38 more)	⊕⊕⊕◯ MODERATE	IMPORTANT

GRADE: Grading of Recommendations Assessment, Development and Evaluation; SOC: standard of care; and RR: risk ratio.

Explanations

a. High heterogeneity (I^2 = 76%).

mechanical ventilation; 4: hospital admission for noninvasive ventilation or high-flow oxygen therapy; 3: hospital admission for oxygen therapy; 2: hospital admission but not requiring oxygen therapy; and 1: discharged or having reached discharge criteria). Secondary outcomes were all-cause mortality at day 28 and frequency of invasive mechanical ventilation.[20]

Ader et al.[21] conducted an RCT in France, Belgium, Austria, Portugal, and Luxembourg. They included adult patients hospitalized with COVID-19 with evidence of rales or crackles on clinical examination and SpO_2 ≤ 94% on room air or requirement of supplemental oxygen, high-flow oxygen devices, noninvasive ventilation, or mechanical ventilation. Remdesivir was administered intravenously at a dose of 200 mg on day 1, followed by a dose of 100 mg (1-h infusion once daily for up to 10 days). The primary outcome measure was clinical status at day 15 as measured on the 7-point ordinal scale of the WHO Master Protocol (1: not hospitalized, no limitations on activities; 2: not hospitalized, limitations on activities; 3: hospitalized, not requiring supplemental oxygen; 4: hospitalized, requiring supplemental oxygen; 5: hospitalized, on noninvasive ventilation or high-flow oxygen devices; and 7. hospitalized, on invasive mechanical ventilation or ECMO). Secondary outcome measures were clinical status and change from baseline clinical status at day 29; time to improvement by 1-2 points as measured on the 7-point ordinal scale or hospital discharge by day 29; length of hospital stay; time to new mechanical ventilation; in-hospital mortality; and mortality at day 28.[21]

Kalligeros et al.[22] conducted an observational study in the USA including adult (≥ 18 years) patients hospitalized with COVID-19 ≤ 4 days prior and SpO_2 ≤ 94% or needing oxygen supplementation and presenting with pulmonary infiltrates. The patients received remdesivir 200 mg i.v. on day 1, followed by a daily maintenance dose of 100 mg from days 2 to 10 or until hospital discharge or death. The primary outcome was the impact of remdesivir on all-cause in-hospital mortality by day 28. Secondary outcomes were time to clinical recovery, time to clinical improvement, and time to discharge.

Ohl et al.[23] conducted a retrospective observational study including patients who tested positive for SARS-CoV-2 within 14 days prior to or during hospitalization at institutions pertaining to the U.S. Veterans Health Administration. The primary outcome was 30-day mortality from remdesivir treatment initiation.

Olender et al.,[24] based on an RCT and a longitudinal real-world study, conducted a prospective study including patients hospitalized with COVID-19 and SpO_2 ≤ 94% on room air or requiring supplemental oxygen and presenting with pulmonary infiltrates. The intervention group received remdesivir 200 mg on day 1, followed by remdesivir 100 mg/day either on days 2-5 or on days 2-10. The outcomes were clinical recovery after treatment initiation and 28-day all-cause mortality.

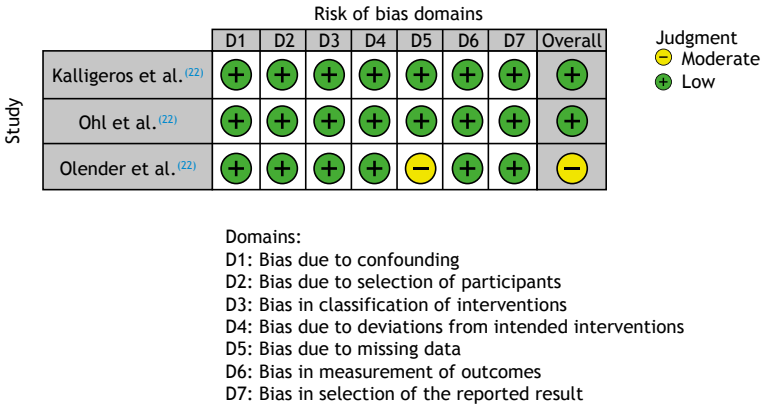


Figure 2. Risk of bias for nonrandomized studies.[a]
[a]In accordance with the Risk Of Bias In Nonrandomized Studies of Interventions (ROBINS-I) tool.[15]

RCT results

Mortality

The analysis of 29-day mortality included six RCTs (8,044 patients).[16-21] No statistical difference was found between the remdesivir/SOC and SOC/placebo groups (RD = −0.01 [95% CI, −0.02 to 0.01]; p = 0.32; I^2 = 0%; Figure 3A). The quality of the evidence was moderate.

Recovery rate by day 29

The definitions of recovery differed among the studies. Beigel et al.[16] considered recovery when the patient had a score of 1-3 based on the criteria of an 8-point ordinal scale. Mahajan et al.[17] used a 6-point ordinal scale (1: does not require hospitalization; 2: hospitalized, not requiring supplemental oxygen; 3: hospitalized, requiring supplemental oxygen; 4: hospitalized, requiring high-flow oxygen or noninvasive ventilation; 5: hospitalized, requiring/receiving mechanical ventilation; and 6: death). Spinner et al.[19] used a 7-point ordinal scale whereby recovery was improvement from a baseline score of 2-5 to a score of 6 or 7 or from a baseline score of 6 to a score of 7. Ader et al.[21] used the 7-point ordinal scale of the WHO Master Protocol.

Based on these four studies (N = 2,357),[16,17,19,21] the use of remdesivir/SOC, when compared with placebo/SOC, increased the recovery rate by 6% (RD = 0.06 [95% CI, 0.03-0.09]; p = 0.004; I^2 = 0%), and the NNT was 17 patients for 1 patient to show recovery (95% CI, 11-33; Figure 3B). However, the quality of evidence was low.

Clinical improvement rate in 29 days

Clinical improvement was defined according to the study protocol. Spinner et al.[19] considered an improvement of at least 2 points from baseline on a 7-point ordinal scale (1 = death and 7 = hospital discharge). Wang et al.[20] used a variation of a 2-point reduction in the baseline 6-point ordinal scale score or hospital discharge, whichever came first.

Two studies evaluated the outcome of clinical improvement within 29 days (n = 629).[19,20] Comparing remdesivir/SOC and placebo/SOC groups, there was a 7% increase in the rate of patients with clinical improvement, favoring remdesivir (RD = 0.07 [95% CI, 0.01-0.14]; p = 0.02; I^2 = 0%; NNT = 14 [95% CI, 7-100]; Figure 3C). However, the quality of evidence was low.

Mechanical ventilation or ECMO in 29 days

Six studies were included to assess the combined outcome of mechanical ventilation or ECMO use within 29 days (n = 7,252). No statistically significant difference was found between remdesivir/SOC and placebo/SOC groups (RD = −0.02 [95% CI, −0.05 to 0.00]; p = 0.08; I^2 = 68%; Figure 3D). The quality of evidence was low.[16-21]

Severe adverse events in 29 days

Four studies, with a total of 2,498 participants, were used to assess severe adverse events.[1619-21] When comparing remdesivir/SOC and placebo/SOC groups, we found that remdesivir use had no influence on the risk of serious adverse events. The risk of adverse events was 4% (RD = −0.04 [95% CI, −0.08 to 0.01]; p = 0.09; I^2 = 41%; Figure 3E). The quality of evidence was moderate.

Observational cohort study results

Mortality

Three cohort studies evaluated mortality within 24-28 days, with a total of 4,335 participants.[22-24] No statistically significant difference was found between remdesivir/SOC and placebo/SOC groups (RD = −0.02 [95% CI, −0.07 to 0.03]; p = 0.37; I^2 = 76%; Figure 4). These studies had a moderate quality of evidence.

Quality of evidence of RCTs and observational cohort studies

The quality of evidence in the analysis of the remdesivir/SOC groups vs. control groups, including

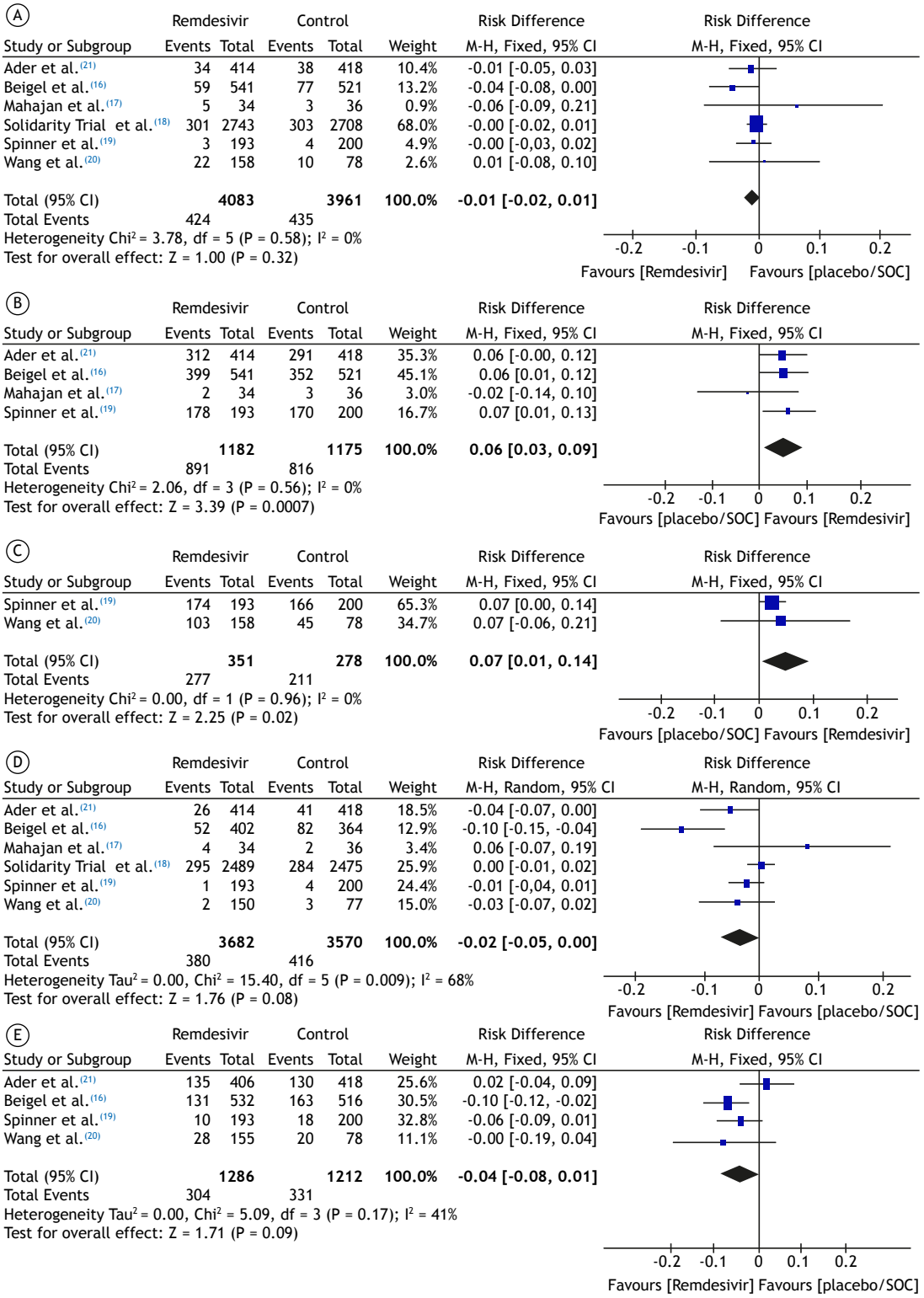


Figure 3. Meta-analyses and forest plots (based on randomized clinical trials) between intervention (remdesivir/standard of care [SOC]) and control (placebo/SOC) groups regarding mortality in 29 days (in A); patient recovery rate in 29 days (in B); clinical improvement rate in 29 days (in C); use of mechanical ventilation/extracorporeal membrane oxygenation in 29 days (in D); and severe adverse events in 29 days (in E). RDV: remdesivir; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

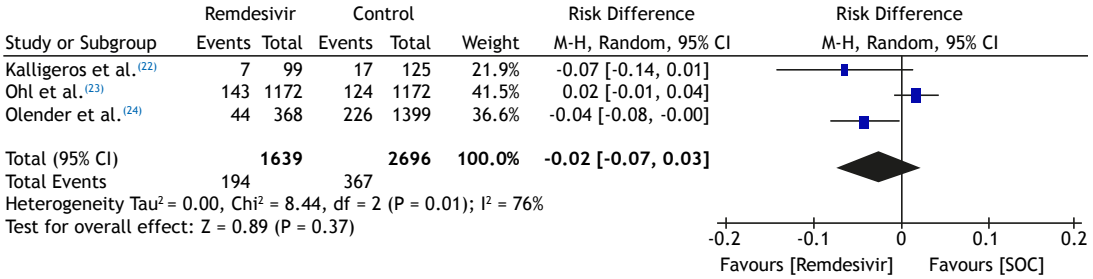


Figure 4. Meta-analysis and forest plot (based on observational cohort studies) between intervention (remdesivir/standard of care [SOC]) and SOC groups regarding mortality in 28 days. RDV: remdesivir; M-H: Mantel-Haenszel (method); and df: degrees of freedom.

only RCTs, varied according to the analyzed outcome during a follow-up period of up to 29 days, in accordance with the GRADE terminology: death (moderate), recovery rate (low), clinical improvement (low), and serious adverse events (moderate; Table 3).

The three cohort studies included only all-cause mortality as an outcome, allowing for the meta-analysis, and had a moderate quality of evidence within the 24-to 28-day follow-up period (Table 4).

DISCUSSION

The main results of this systematic review were that remdesivir had no effect on reducing mortality, the use of mechanical ventilation/ECMO, or severe adverse events in hospitalized patients with moderate to severe COVID-19. However, we identified increased rates of clinical improvement and recovery in those patients.

Regarding the mortality outcome, our results are similar to those of a previous systematic review published in the literature.[9,11,25,26] In studies that revealed a lower risk of mortality using remdesivir, we observed differences in methodological characteristics; those meta-analyses pooled observational studies together with RCTs or assessed the mortality rate on day 14.[10] These aspects can directly affect the results and influence treatment decisions. In the present systematic review, we used robust methods, such as RD, to consider the critical outcomes (mortality and use of mechanical ventilation) and demonstrated the direct effect of the intervention. Additionally, we divided the pooled results considering the design of the pooled studies.

With regard to clinical improvement and recovery rates, the use of remdesivir demonstrated a positive influence on hospitalized patients in the present meta-analysis. On the other hand, even with positive results, we need to consider the differences between studies that used different scales of disease severity that could directly affect the outcome response, leading to an uncertain benefit in clinical improvement. Different from our results, the literature consistently demonstrates a reduced rate of severe adverse events associated with the use of remdesivir,[9,25,26] which is a clinically important factor and should be considered when making treatment decisions. However, when we compare the importance of different outcomes, we must consider the patients' opinions. Even when the mortality rate is similar, knowledge of clinical improvement can influence treatment decisions.

The early use of remdesivir in patients hospitalized with moderate to severe COVID-19 can be relatively associated with clinical improvement and recovery rates. However, we need to evaluate this affirmation by considering the interactions of different treatments. A higher proportion of patients in the RCTs included in this systematic review received other COVID-19 treatment options, such as corticosteroids, convalescent plasma, and immunotherapy. The interaction of different pharmacological interventions and different respiratory support systems with comorbidities needs to be explored in the main results. However, this requires a greater number of patients because the subgroup analysis failed to demonstrate the efficacy of remdesivir in decreasing the mortality rate.[9] The transposition of this information to modify clinical practice needs to be balanced with the NNT, costs, and effects. In the case of low- and middle-income countries, the impact of high costs of COVID-19 treatment per patient needs to be considered using the best medical evidence.

The strength of this systematic review lies in the methodological characteristics adopted, with the separation of RCTs from observational cohort studies, revealing the influence of remdesivir use on the selected outcomes. The certainty of the present results is dependent on novel RCTs involving a larger population for analysis. Therefore, we cannot affirm whether the present results can be used as modifiers in the future. However, to reduce publication bias, we used a comprehensive search strategy. Nevertheless, this systematic review has limitations that need to be addressed.

In conclusion, the results of this systematic review demonstrated no benefit from the prophylactic use of remdesivir in the treatment of COVID-19.

FINAL CONSIDERATIONS

On the basis of the evaluation of the RCTs included in this systematic review, in patients hospitalized with moderate to severe COVID-19, the use of remdesivir/

SOC is equivalent to conventional treatment by day 29 and showed no differences regarding the risks of death or severe adverse events, the quality of evidence being moderate. However, an increase in the number of recovering patients by 6% (NNT = 17) was observed, but the quality of evidence was low. Furthermore, the number of patients showing clinical improvement increased by 7% (NNT = 14), but the quality of evidence was low. There was no difference in the risk of requiring mechanical ventilation/ECMO (low quality of evidence). On the basis of the evaluation of the observational cohort studies included in this systematic review, in patients hospitalized with moderate to severe COVID-19, treatment with remdesivir/SOC is equivalent to conventional treatment within 24-28 days and did not modify the risk of death, the quality of evidence being moderate.

AUTHOR CONTRIBUTIONS

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

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210337
https://dx.doi.org/10.36416/1806-3756/e20210337

Diagnostic performance of VEGF-D for lymphangioleiomyomatosis: a meta-analysis

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Submitted: 19 August 2021.
Accepted: 16 November 2021.

ABSTRACT

Objective: VEGF-D is a potential biomarker for lymphangioleiomyomatosis (LAM); however, its diagnostic performance has yet to be systematically studied. **Methods:** We searched PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library to identify primary studies on VEGF-D in relation to the diagnosis of LAM. The quality of the studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2). Summary estimates of diagnostic accuracy were pooled using a bivariate random effects model. Subgroup and sensitivity analyses were performed to explore possible heterogeneity. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was applied to rate the quality of evidence and indicate the strength of recommendations. **Results:** Ten studies involving 945 patients were of high risk in quality, as assessed using the QUADAS-2. The pooled diagnostic parameters were indicated as follows: sensitivity = 0.82 (95% CI, 0.71-0.90); specificity = 0.98 (95% CI, 0.94-0.99); and diagnostic OR = 197 (95% CI, 66-587). The AUC of summary ROC analysis was 0.98. The subgroup and sensitivity analyses revealed that the overall performance was not substantially affected by the composition of the control group, prespecified cutoff value, the country of origin, or different cutoff values ($p > 0.05$ for all). A strong recommendation for serum VEGF-D determination to aid in the diagnosis of LAM was made according to the GRADE. **Conclusions:** VEGF-D seems to have great potential implications for the diagnosis of LAM in clinical practice due to its excellent specificity and suboptimal sensitivity.

Keywords: Lymphangioleiomyomatosis/diagnosis; Vascular endothelial growth factor D; Biomarkers; Meta-analysis.

INTRODUCTION

Lymphangioleiomyomatosis (LAM) is a rare systemic neoplastic disease that primarily affects women of reproductive age. It is characterized by progressive and multiple cystic destruction of the lung and abnormalities of lymphatic system.[1,2] Histologically, LAM lesions are characterized by the proliferation of neoplastic smooth muscle-like cells (LAM cells) in small clusters located on the edges of lung cysts and along blood vessels and lymphatics. LAM cell infiltration causes airway obstruction, vascular wall thickening, lymphatic vessel disruption, venous occlusion, and hemorrhage, leading to the deterioration of lung function and eventually respiratory failure.[3-6]

Given the deadly harm of LAM and the advances in disease-specific treatments, such as sirolimus, it is increasingly important to make an early correct diagnosis.[7,8] However, the diagnosis of LAM remains challenging. According to the European Respiratory Society (ERS), a definite diagnosis of LAM depends on the typical changes in the findings of HRCT plus lung biopsy in the absence of compatible clinical presentations, such as renal angiomyolipoma, chylothorax, or tuberous sclerosis complex.[9] In fact, several patients do not have these typical clinical features, and biopsy is often needed to achieve a definite diagnosis.[10] However, biopsy methods, either transbronchial lung biopsy or video-assisted thoracic surgery, are invasive, technically difficult, and operator-dependent. Furthermore, invasive diagnostic procedures are unsuitable for screening for LAM in high-risk groups.[11] Thus, searching for noninvasive and effective methods to aid in the diagnosis of LAM has become imperative, among which disease-specific biomarkers, has become imperative.

VEGF-D, a glycoprotein produced by LAM cells, has been found to promote the lymphangiogenesis via VEGF receptor 3.[12,13] In 2006, Seyama et al.[14] first found increased serum VEGF-D levels in patients with LAM. Consequently, an increasing number of studies have

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Financial support: This study was supported by the National Key Development Plan for Precision Medicine Research (2017YFC091004), the National Natural Science Foundation of China (81670023, 81870027, and 81920108002), Science and Technology Foundation of Sichuan Province (2018SZ0167), and 1.3.5 Project for Disciplines of Excellence-Clinical Research Incubation Project, West China Hospital, Sichuan University (2018HXFH016).

investigated the diagnostic value of VEGF-D levels for LAM; however, the results have not entirely been consistent. For example, in the study by Xu et al.,[15] VEGF-D levels demonstrated an excellent diagnostic performance with an AUC of 0.99; in another study,[16] VEGF-D levels for diagnosing LAM had an AUC of 0.75. Although a threshold of 800 pg/mL is indicated by the American Thoracic Society (ATS),[6] serum VEGF-D levels appear to vary at different dosages or cutoff values. The optimal cutoff value for VEGF-D levels differed across studies, ranging from 440 pg/mL to 1,239 pg/mL.[16] Identification of an appropriate threshold for VEGF-D levels in patients with LAM, especially those with characteristic lung cysts on HRCT but without additional clinical findings, is essential. To date, no studies have systematically pooled these data to estimate the overall diagnostic performance of VEGF-D levels for LAM or further explore potential issues that impact on its diagnostic accuracy. Therefore, we performed a meta-analysis based on the currently available evidence to establish summary estimates for the diagnostic accuracy of VEGF-D levels for LAM, which would yield relevant implications in clinical practice.

METHODS

This study was a meta-analysis in design whose protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO, Protocol no. CRD42020164137), an international database of prospectively registered systematic reviews. Our study was conducted and the findings were reported in accordance with the methods recommended by the Cochrane Diagnostic Test Accuracy Working Group and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Chart S1).[17-19] Ethical approval was not required owing to the retrospective nature of the meta-analysis.

Search strategy and selection criteria

Two reviewers independently searched the following databases: PubMed, EMBASE, Scopus, Web of Science, and Cochrane Library (until June 26, 2021) to identify related studies. The combinations of the following search strings were used: ("lymphangioleiomyomatosis" or "LAM") AND ("endothelial growth factor-D" or "VEGF-D"). References listed in the considered articles or review articles were also manually checked to obtain additional relevant articles. LAM was described and defined in accordance with the ATS/Japanese Respiratory Society (JRS) guidelines (Chart S2)[6] and the ERS guidelines (Chart S3).[9] Studies were incorporated into the meta-analysis when they met all of the following criteria: 1) original studies that examined the diagnostic ability of VEGF-D for LAM; 2) sufficient data for constructing a two-by-two table of true positive, true negative, false positive, and false negative outcomes; and 3) studies that included at least 20 subjects (studies with smaller sample sizes may be vulnerable to selection bias). There were no limitations on languages, and the lowest date limit was restricted to 1997, when VEGF-D was first identified.[20] Only the data associated with the best diagnostic performance were included from the studies in which several different cutoff values were used.

Data extraction and quality assessment

Two reviewers independently assessed the included studies. The following information was extracted: first author, publication year, country of origin, test method, cutoff value, diagnostic standard, and two-by-two tables for true positive, false positive, true negative, and false negative outcomes. We contacted the corresponding authors to identify additional information if necessary.

Quality Assessment of Diagnostic Accuracy Studies, version 2 (QUADAS-2)[21] was applied to evaluate the methodology of the included studies. It covers four main domains to evaluate the risk of bias: patient selection, index test, reference standard, and flow and timing. Concerns regarding applicability were also assessed in patient selection, index text, and reference standard domains. The tool provides signaling questions to help rate different studies in the abovementioned domains. The questions are answered as "yes," "no" or "unclear." If the answers to all signaling questions for a domain are "yes," then an overall judgment of a "low risk of bias" can be made. If any signaling question is answered as "no," potential bias exists. If data provided by the primary study are insufficient in one or more domains to permit a judgment, the "unclear" category should be used. We further assessed the following information as a supplement for methodology evaluation: study registration, real-world design, institutional review board, sample size calculation, prospective data collection, consecutive data collection, inclusion/exclusion criteria (stringent or lenient), multicenter study, and conflicts of interest.

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) was applied to evaluate the certainty of evidence. It classifies the quality of evidence into four levels (high, moderate, low, and very low). The GRADE system starts with a "high quality" rating and then it is downgraded by one level for each of the five factors considered: risk of bias, indirectness, inconsistency, imprecision, and publication bias.[22] The risk of bias was evaluated using the QUADAS-2. To evaluate indirectness, we considered our evaluation of applicability concerns and the directness of VEGF-D test results on patient-important outcomes. Inconsistency was evaluated according to interstudy heterogeneity (assessed using the chi-squared-based Q-test and inconsistency index). The width of 95% CI was considered when evaluating imprecision: 95% CI < 10% was considered as "not serious"; 10% ≥ 95% CI < 20% was considered as "serious"; and 95% CI ≥ 20% was considered as "very serious."

The GRADE system offers two grades of recommendations: "strong" and "weak." When the effects of an intervention clearly outweigh the undesirable effects, or clearly do not, it offers strong recommendations. When the trade-offs are less certain, weak recommendations become mandatory.[22] Any discrepancies in study selection, data extraction, and quality assessment were resolved by a third reviewer.

Statistical analysis

The meta-analysis was performed using a bivariate model.[23,24] We analyzed the overall diagnostic test accuracy by calculating the following indices: sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic OR. We also calculated the AUC, which suggests the degree of accuracy of a diagnostic tool (poor, 0.50-0.75; good, 0.75-0.92; very good, 0.93-0.96; and excellent, > 0.97).[25] Furthermore, we combined the hierarchical summary ROC (HSROC) model to conduct the meta-analysis, because we expected that the studies would use different thresholds to dichotomize test results measured on a continuous scale. The method can denote whether a threshold effect is present when the cutoff value is non-prespecified. It is better to summarize the results than to use a single joint summary estimate of sensitivity and specificity.[26,27] We further applied Fagan's nomogram to estimate the extent to which the results of the diagnostic test change the possibility that a patient has a certain disease, which is based on the following equivalent formula:

log(post-test odds) = log(likelihood ratio)+ log(pre-test odds)

To detect the inter-study heterogeneity, we applied the chi-squared-based Q-test and inconsistency index (I^2). A p value of < 0.10 was used to suggest the presence of heterogeneity beyond what would be expected by chance, and an I^2 value of > 50% was used to quantify the degree of heterogeneity. We further performed subgroup and sensitivity analyses to explore potential issues that may affect the diagnostic performance of VEGF-D for LAM. Publication bias was assessed by Deeks' funnel plots.[28]

Stata, version 15.0 (Stata Corp LP, College Station, TX, USA), Review Manager 5.2 (The Cochrane Collaboration, Copenhagen, Denmark), and Meta-Disc (XI Cochrane Colloquium, Barcelona, Spain) were used, and a two-sided $p < 0.05$ was considered statistically significant.

RESULTS

Study characteristics

After title and abstract review of the 115 records identified in the initial screening, we selected 33 articles for full-text review, of which 3 studies were excluded because of duplicate data. In addition, 14 of these studies were excluded because they did not include a control group, and another 6 studies were further excluded because two-by-two tables could not be constructed, although the authors of those studies had been contacted. Finally, 10 studies were included in the meta-analysis (Figure 1).

The included studies were conducted between 2009 and 2019. The average sample size was 95 (range, 33-173), yielding a total population of 945 patients. Two studies were conducted in North America,[16,29] 4 in Europe,[30-33] 3 in Asia,[15,34,35] and 1 in South America.[36] The mean age of the patients in the included studies ranged from 30 to 55 years.

All included studies were conducted in tertiary hospitals, and serum was used as the sample to test VEGF-D levels; the human VEGF-D enzyme-linked immune sorbent assay kit (R&D System Inc., Minneapolis, MN, USA) was used in 8 studies.[15,16,29-31,34-36] The diagnostic standard of LAM met the diagnostic criteria of definite LAM according to the ERS guidelines[9] in 8 studies,[15,16,29-32,35,36] while part of the included patients met the diagnostic standard for probable LAM in 2 studies.[33,34] All included studies described the composition of the control group in detail. The control groups (Table 1) consisted of patients with other polycystic lung diseases such as pulmonary Langerhans cell histiocytosis, Birt-Hogg-Dubé syndrome, and Sjögren's syndrome in 3 studies,[29,31,35] healthy individuals in 4 studies,[15,16,30,36] and patients with other polycystic lung diseases as well as healthy participants in 3 studies.[32-34]

Methodological quality assessment

We used the QUADAS-2 tool to evaluate the methodological quality of the included studies. A high risk may exist in the patient selection and index test domains. The studies had a high or an unclear risk of bias because of the following: 1) 90% of the included studies did not describe in detail whether participants were enrolled consecutively or whether they used random sampling[15,16,29-32,34-36]; 2) 4 studies did not avoid a case-control design[15,16,30,36]; 3) 4 studies did not avoid inappropriate exclusion, in which healthy subjects, rather than patients with a disease that needs to be differentiated from LAM, were recruited as controls[15,16,30,36]; and 4) the cutoff value of VEGF-D in serum was prespecified in 33.3% of the included studies.[29,32,36] In the reference standard domain, all included studies were at a low risk. In the flow and timing domain, 1 study showed a high risk of bias because not all of the patients in the studies were included in the analysis.[16] With regard to applicability concerns, 5 studies were of high concern owing to deficiencies in patient selection,[15,16,30,34,36] and 1 study was of high concern in index test.[32] (Figure S1).

In addition to the information obtained using the QUADAS-2, additional information related to the quality of the study design was also extracted. No studies were registered in the WHO International

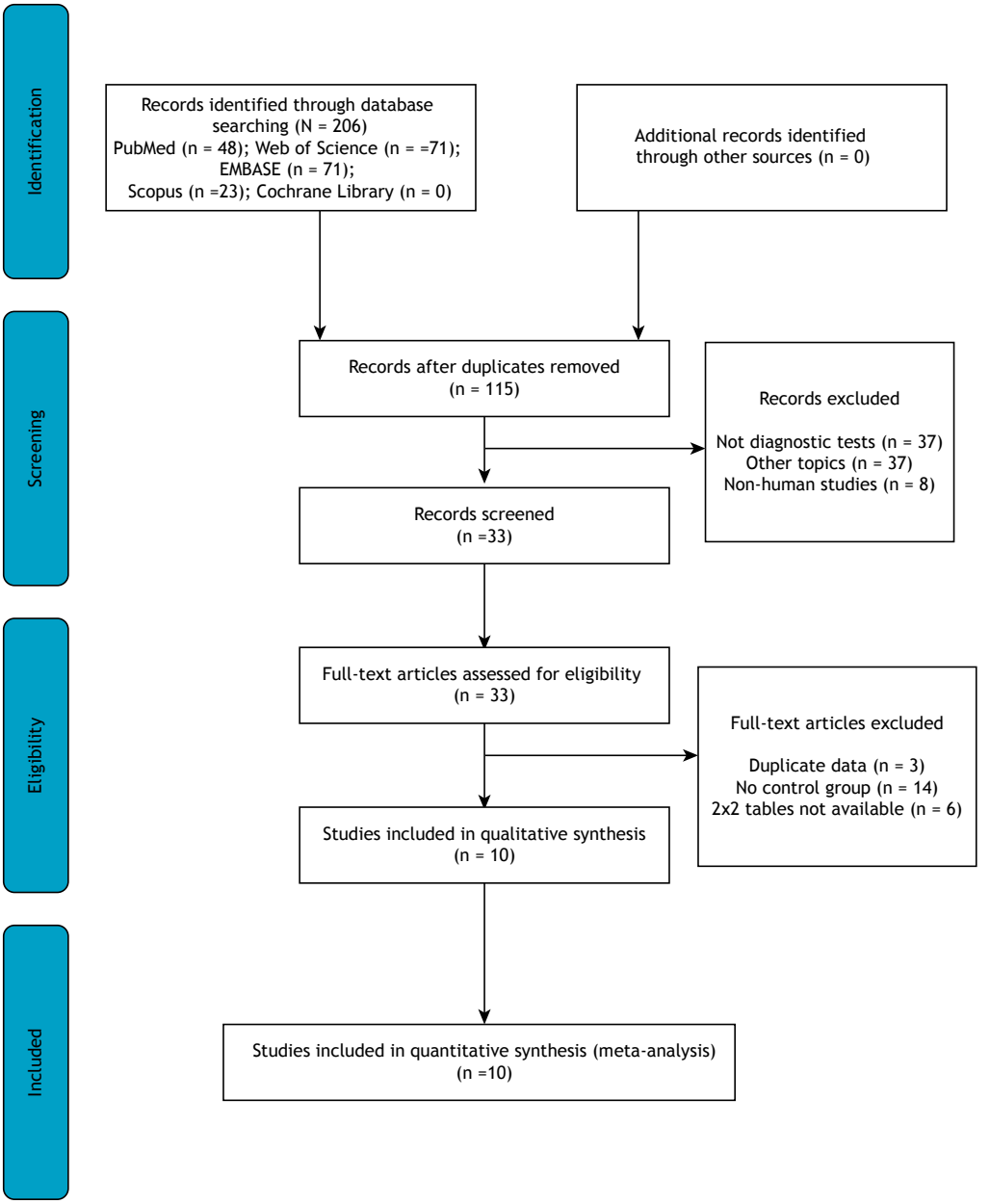

Figure 1. Flow diagram of study selection.

Clinical Trials Registry Platform, European Union Clinical Trials Register, or ClinicalTrials.gov. In the sample as a whole, 7 studies were approved by an institutional review board.[15,16,29,30,34-36] Two studies had a prospective design.[29,32] Inclusion/exclusion criteria were stringent in 2 studies.[29,36] Potential conflicts of interest may exist in 2 studies.[29,34] More detailed information is provided in Table S1.

Diagnostic accuracy

Figure 2 shows that the pooled sensitivity and specificity were 0.82 (95% CI, 0.71-0.90) and 0.98 (95% CI, 0.94-0.99), respectively. The positive likelihood ratio was 35.5 (95% CI, 14.4-87.6), and the negative likelihood ratio was 0.18 (95% CI, 0.11-0.30). The overall diagnostic OR was 197 (95% CI, 66-587), and the AUC was 0.98 (95% CI, 0.97-0.99).

The HSROC model showed that the β-value was −0.31 ($p = 0.678$) and the λ-value was 5.69, suggesting that the HSROC curve was symmetric and the overall diagnostic value was excellent (Figure 3).

We used Fagan's nomogram to support decision making and evaluate the clinical utility (Figure S2). For instance, in an average-risk population with a pretest probability of 20%, the VEGF-D test would increase the probability of diagnosing LAM to 90% when the test result is positive and would decrease that probability to 4% when the test result is negative.

Table 1. Characteristics of the included studies on VEGF-D levels in relation to the diagnosis of lymphangioleiomyomatosis.[a]

Author	Country	P/C, n	Mean age, years (P/C)	Smoking, n (%)	Assay method	VEGF-D test manufacturer	Prespecified cutoff value	Cutoff value, pg/mL	LAM+TSC, n (%)	mTOR inhibitor therapy, n (%)	Lymphatic involvement, n (%)	Diagnostic standard	Controls	TP	FP	FN	TN
Glasgow et al.[16]	USA	106/40	51.0/49.6	UN	ELISA	R&D Systems	No	1,239	0 (0)	UN	77 (73)	Definite LAM	Healthy	61	1	45	39
Young et al.[29]	USA	15/18	UN	UN	ELISA	R&D Systems	Yes	800	0 (0)	UN	UN	Definite LAM	OPLD	12	0	3	18
Cottin et al.[32]	France	45/42	48/?	UN	UN	UN	Yes	800	UC	6(13%)	UN	Definite LAM	OPLD+ Healthy	34	1	11	41
Chang et al.[30]	USA	45/32	46/36	1 (2.2%)	ELISA	R&D Systems	No	440	2 (4.4)	UN	UN	Definite LAM	Healthy	41	1	4	31
Radzikowska et al.[31]	Poland	29/46	41.0/37.6	UN	ELISA	R&D Systems	No	468	7 (24)	UN	UN	Definite LAM	OPLD	25	5	4	41
Xu et al.[15]	China	50/40	40.8/41.4	UN	ELISA	R&D Systems	No	850.7	2 (4%)	7 (14%)	UN	Definite LAM	Healthy	48	0	2	40
Daccord et al.[33]	Switzerland	15/21	UN	UN	ELISA	UN	No	520	UC	3 (20%)	UN	Definite+ Probable LAM	OPLD+ Healthy	12	1	3	20
Amaral et al.[36]	Brazil	104/40	43/43	UN	ELISA	R&D Systems	Yes	800	21 (20)	0 (0%)	20 (24)	Definite LAM	Healthy	52	0	52	40
Hirose et al.[34]	Japan	108/65	UN	UN	ELISA	R&D Systems	No	645	16 (14.8)	35 (32%)	UN	Definite+ Probable LAM	OPLD+ Healthy	90	2	18	63
Mou et al.[35]	China	50/34	39.3/46.9	UN	ELISA	R&D Systems	No	901	3 (6)	UN	UN	Definite LAM	OPLD	47	0	3	34

P/C: patient/control; LAM: lymphangioleiomyomatosis; TSC: tuberous sclerosis complex; mTOR: mammalian target of rapamycin; TP: true positive; FP: false positive; FN: false negative; TN: true negative; UN: unknown; OPLD: other polycystic lung disease; and UC: unclear. [a]All of the studies were conducted at tertiary hospitals, and VEGF-D levels were determined from serum samples.

Subgroup analysis

The I^2 values for the pooled sensitivity and specificity were 92.70% and 57.81%, respectively, indicating significant heterogeneity among the included studies. We first searched for the presence of a threshold effect, a source of heterogeneity unique to the diagnostic meta-analysis. No threshold effect was detected (Spearman's correlation coefficient = 0.097; p = 0.789). We further investigated the potential factors that may affect the overall results of the meta-analysis. As shown in Table 2, the AUC was not significantly affected by the composition of the control group (p = 0.115), prespecified cutoff value (p = 0.839), country of origin, or different cutoff values; this indicated that these covariates did not substantially affect the diagnostic accuracy of VEGF-D for LAM in our study (p = 0.889).

Sensitivity analysis

Not all the patients with LAM met the diagnostic standard for definite LAM in the 2 primary studies,[33,34] and 2 studies were abstracts.[32,33] We performed a sensitivity analysis to explore the effects of these studies on the overall results of the meta-analysis. The results indicated that the overall AUC was not materially altered after excluding the 2 primary studies that included the patients with probable LAM and the 2 abstracts, suggesting the robustness of our study (Table 3).

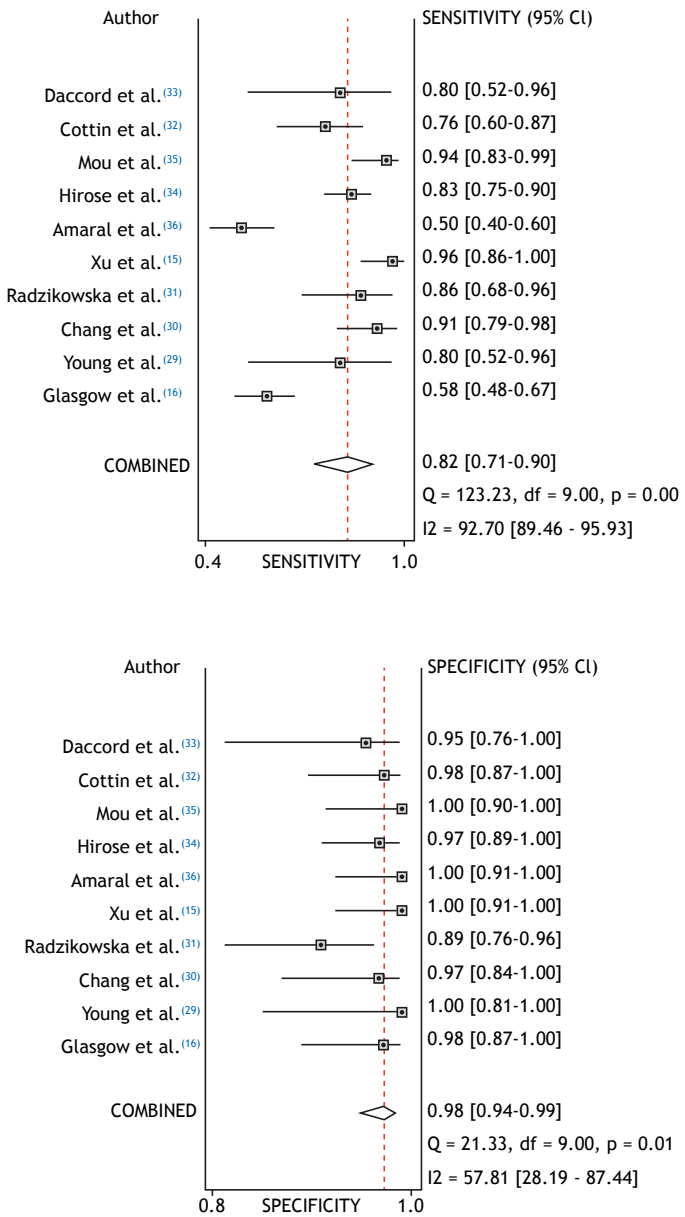

Figure 2. Forest plots of the sensitivity and specificity of VEGF-D levels for the diagnosis of lymphangioleiomyomatosis. The sensitivity and specificity point estimates from each study are shown using solid squares. Error bars indicate the 95% CIs. df: degrees of freedom.

Publication bias

Publication bias was explored using Deeks' funnel asymmetry plot test. The results showed a non-significant value (p = 0.92). The shape of the funnel plots did not reveal any evidence of asymmetry (Figure S3), indicating a low likelihood of publication bias.

Quality of evidence according to the GRADE system

The GRADE system was applied to rate the quality of evidence and to indicate the strength of the recommendations. In our study, the quality of the pooled results was downgraded for the risk of bias (based on the results of the QUADAS-2), inconsistency ($I^2 > 0.5$ and $p < 0.1$), and imprecision (95% CI width > 10%; Table S2). As a result, the quality of evidence was classified as low based on the GRADE summaries.

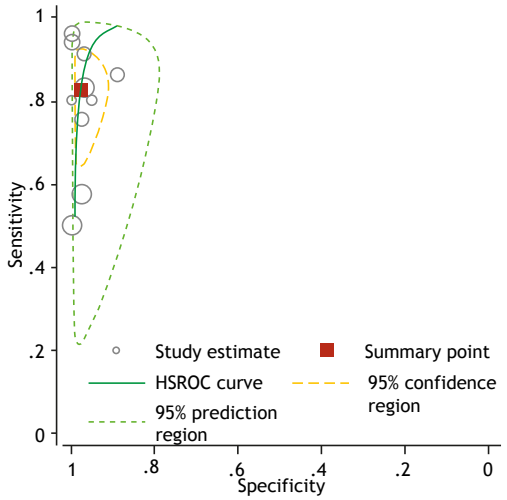

Figure 3. Hierarchical summary ROC (HSROC) curve plot of sensitivity vs. specificity of VEGF-D levels for the diagnosis of lymphangioleiomyomatosis.

DISCUSSION

To the best of our knowledge, this is the first study to systematically explore the diagnostic performance of VEGF-D for LAM. The analysis showed that the overall diagnostic accuracy of VEGF-D determination for LAM was excellent based on the 10 studies with a high risk of bias assessed using the QUADAS-2; the VEGF-D level also exhibited suboptimal sensitivity and high specificity. Subgroup and sensitivity analyses revealed that the overall performance was not substantially affected by the composition of the control group, prespecified cutoff value, country of origin, or different cutoff values. A strong recommendation for serum VEGF-D testing to aid in the diagnosis of LAM in clinical practice was made according to the GRADE system.

In accordance with the ATS/JRS guidelines,[6] the VEGF-D test is recommended before diagnostic lung biopsy for patients with suspected LAM who present with cystic abnormalities on CT but without confirmatory clinical or extrapulmonary radiological features. However, the guidelines only quoted 7 studies. The studies were mainly conducted in the USA and Europe.[14-16,29-31,37] Data from the rest of the world are limited. In addition, the overall sensitivity or specificity of VEGF-D levels was not provided. After the publication of the guidelines, more clinical studies have been reported, and we performed the meta-analysis by including more studies conducted in other parts of the world, which reinforces the use of the VEGF-D test in a broader population.

Table 2. Subgroup analysis of the included studies on the VEGF-D in relation to the diagnosis of lymphangioleiomyomatosis.

Covariate	Study, n	AUC	SE (AUC)	Z	p
Composition of the control group					
Not healthy	6	0.96	0.02	1.576	0.115
Healthy	4	0.99	0.01		
Prespecified cutoff value					
Yes	3	0.98	0.04	0.203	0.839
No	7	0.97	0.02		
Country of origin					
Asian countries	3	0.99	0.00	0.139	0.889
Non-Asian countries	7	0.96	0.02		
Cutoff values					
≤ 600 pg/mL	3	0.94	0.04	1.558[a]	0.119[a]
> 800 pg/mL	3	0.99	0.00	0.739[a]	0.460[a]
600-800 pg/mL	4	0.98	0.02	Ref	Ref

[a]Compared with the cutoff values (> 600 to ≤ 800 pg/mL).

Table 3. Summary of overall analysis and sensitivity analysis.

Variable	Study, n	AUC	SE (AUC)	Z	p
Overall results of the meta-analysis	10	0.98	0.005		
Excluding abstracts	8	0.97	0.015	0.632[a]	0.527[a]
Excluding two studies with probable LAM patients	8	0.9813	0.01116	0.106[a]	0.915[a]

[a]Compared with the overall results of the meta-analysis.

In our study, the specificity of VEGF-D was excellent; but the sensitivity was moderate, which indicates that a positive result can be considered as LAM, whereas a negative result does not exclude LAM. In fact, a high specificity seems to be more acceptable in clinical practice, because an incorrect diagnosis of LAM may lead to missed opportunities to treat the real disease, avoiding adverse effects and unnecessary expenses due to inappropriate treatment.[6] However, if a patient with LAM has a false negative result, the likely consequence is that the patient will proceed to the next diagnostic test for obtaining the final diagnosis—pulmonary biopsy, which reduces the undesirable effects of false negative to a large extent.[6] Therefore, the determination of VEGF-D levels has a potential clinical impact on the LAM diagnosis algorithm. For patients who presented with pulmonary cystic abnormalities but lack confirmatory features of LAM, VEGF-D levels should be considered before proceeding to lung biopsy. It was estimated that 90% of probable LAM cases, in accordance with the ERS guidelines,[9] could be upgraded to definite LAM if the VEGF-D test result is added to the diagnostic criteria.[38] Therefore, many invasive diagnostic procedures can be avoided, which will substantially reduce patient risk and medical burden.

In our study, we found 7 studies that identified their optimal cutoff values using the Youden index.[15,16,30-32,34,35] Data-driven selection of optimal cutoff values for a test of a continuous variable may lead to overoptimistic estimates of diagnostic accuracy, especially in studies with small sample sizes.[39] Using a prespecified cutoff value is an efficient approach to reduce the problem, but it is often difficult to achieve. In the early phases of a test evaluation, there is usually limited information available on the likely value of the optimal cutoff value, especially for a rare disease. In our study, we found that the test performance reported in the studies with data-driven selection of cutoff values was not better than that reported in the studies with prespecified cutoff values.

Although the ATS recommends a VEGF-D threshold value of 800 pg/mL,[6] the cutoff values in the included studies were varied, ranging from 440 pg/mL to 1,239 pg/mL. This is reasonable because VEGF-D levels can be affected by many factors. Several studies have reported that VEGF-D levels were higher in LAM patients with lymphatic involvement than in those without lymphatic involvement.[29] In addition, the severity of the disease,[36] sirolimus treatment status,[5] and whether there is accompanying tuberous sclerosis complex may also affect VEGF-D levels.[40,41] Additionally, differences in sample handling, standard preparation, or other aspects of assay conduct may lead to discrepancies in VEGF-D levels across different studies.[31,34] Therefore, the cutoff value is likely to vary with the severity of disease, equipment, and treatment history. On the one hand, a cutoff value of 800 pg/mL as a diagnostically specific threshold for LAM can provide a good diagnostic value for overall patients with LAM, and a uniform standard for the VEGF-D level is needed if its use is to become a standard practice for diagnosing LAM. On the other hand, investigators should also be open to the possibility that different cutoff values may be needed for patients with different disease statuses.

Our study has some limitations that need to be addressed. First, the number of studies on LAM, since it is a rare disease, was relatively small, although we performed a comprehensive literature search. Second, not all of the LAM patients in this meta-analysis met the diagnostic criteria of definite LAM.[33,34] Nevertheless, our sensitivity analysis indicated that the studies involved did not materially alter the pooled results. Lastly, the possible selection bias should not be ignored, given that all of the included studies were conducted in tertiary hospitals. Multicenter studies conducted in hospitals at different levels are needed to further validate our findings.

In conclusion, this study demonstrated that VEGF-D determination is highly specific and moderately sensitive for the diagnosis of LAM. Given that the effects of VEGF-D for LAM outweigh the undesirable effects, a strong recommendation for serum VEGF-D determination to aid in the diagnosis of LAM in clinical practice was made according to the GRADE system; however, multicenter studies conducted in hospitals at different levels are needed to further validate these findings.

AUTHOR CONTRIBUTIONS

ML, WYZ, and GW: conception and design. GW: administrative support. ML and WYZ: provision of study materials and patients. JW: collection and assembly of data. ML and JW: data analysis and interpretation. All authors: manuscript writing and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210489
https://dx.doi.org/10.36416/1806-3756/e20210489

Potential years of life lost by COVID-19 in the state of Espírito Santo and proportional mortality by age.

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TO THE EDITOR,

Since the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern (PHEIC) and categorized the situation as a severe pandemic,[1] the cumulative number of deaths worldwide up to November 23, 2021, reached 5,158,211.[1]

Premature mortality is understood as the expression of the social value of death. When death occurs at a stage when life is potentially productive, it affects not only the individual and the group where they are inserted, but also collectivity as a whole since they are deprived of their economic and intellectual potential and the future they would have had in society.[2]

Potential years of life lost (PYLL) is an indicator used to estimate how long a person would have lived if they had not died prematurely. The measure of potential years of life lost emphasizes the specific causes of death that affect younger age groups, resulting in a different ordering of such causes.

The present data analysis used the information available in the COVID-19 public dashboard of the state of Espírito Santo[3] with the purpose of calculating the PYLL due to COVID-19. All deaths that occurred in the state of Espírito Santo up to July 22, 2021 in people under 79 years of age were analyzed, totaling 9,073 deaths, considering the average life expectancy of 79.1 years for the state of Espírito Santo in 2019.[4]

The absolute value of PYLL in each age group was calculated by multiplying the number of the remaining years of life by the number of deaths in the same age group; the total PYLL was obtained by the sum of the PYLL in each age group according to the following formula: $PYLL = \Sigma\ a_i \times d_i$, where: a_i represents the difference between the age limit and the age midpoint in each age group, assuming a uniform distribution of deaths in each group, and d_i is equal to the number of COVID-19-related deaths within the same age group.

In order to calculate the mean number of PYLL per 1,000 inhabitants, we used the ratio obtained by the sum of the PYLL per age group divided by the total number of inhabitants of the same age group multiplied by 1,000.

The first case of COVID-19 recorded in the state of Espírito Santo was on March 5th, 2020. More than 530,000 cases and 11,786 deaths were confirmed up to July 22nd, 2021, denoting a 2.2% lethality rate. Regarding age, more than 60% of the deaths occurred in individuals aged 60 years or older.

The number of PYLL by age group is shown in Table 1. Due to the nature of this estimate, deaths in younger people resulted in a higher number of PYLL compared to older age groups. Deaths occurring in the 0–4-year age group had a number of PYLL equal to 77.1 years; however, since COVID-19-related deaths are infrequent in younger age groups (0.15% of deaths up to 79 years), they have little impact on the global PYLL estimate. The lowest number of PYLL per 1,000 inhabitants was observed in the 5–9-year age group, with a loss of life of 1.1 years, while the highest impact on PYLL was observed in the 60–69-year age group, with a loss of 121 years of life per 1,000 inhabitants.

Overall, the 11,786 COVID-19-related deaths in the state of Espírito Santo totaled 154,843.3 years of life lost, with a mean of 38.5 years of life lost per 1,000 inhabitants and a mean of 17.06 PYLL per deceased individual.

Our results were consistent with those found in a study in Colombia, which reported 19,364 COVID-19-related deaths, totaling 346,148 PYLL by August 30, 2020. On average, each of the deceased men lost 17.4 years, while each woman lost 18.7 years.[5]

Meanwhile, in the United Kingdom, the number of PYLL was estimated at 14 for men and 12 for women. Such discrepancy in the number of PYLL for women may be due to the fact that in the UK, the affected population is older, whereas in Brazil, the general population is younger and presents comorbidities and chronic diseases, characteristics that are more similar to those in Colombia and other low and middle-income countries.[6]

PYLL data on COVID-19-related deaths, along with other indicators, reveal a decrease in life expectancy and losses regarding the economically active population. In addition to the reduction in birth rates, such scenario may impose an economic crisis that will require ample assistance from international organizations to developing countries after the pandemic. Should this not take place, we will have to deal with several illnesses, given the social determination of the health-disease process.[7]

Despite the low impact of the number of PYLL on the death of the elderly, in everyday life, many Brazilian families depend entirely on elderly pension income to survive. Although several families received emergency financial assistance provided by the government, many

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Table 1. Potential years of life lost (PYLL) by age group and per 1,000 inhabitants in the state of Espírito Santo, 2021.

Age Group	No. of deaths	PYLL*	Total PYLL**	PYLL/1,000	Percentage distribution of deaths by COVID-19 by age group
0-4	14	77.1	1,079.4	4.2	0.15
5-9	4	72.1	288.4	1.1	0.04
10-19	24	64.1	1,538.4	2.5	0.26
20-29	121	54.1	6,546.1	9.8	1.33
30-39	432	44.1	19,051.2	27.6	4.76
40-49	944	34.1	32,190.4	55.1	10.40
50-59	1,710	24.1	41,211	86.7	18.85
60-69	2,906	14.1	40,974.6	121.0	32.03
70-79	2,918	4.1	11,963.8	74.6	32.16
Total	9,073	17.06***	154,843.3	38.5	100.00

*Per individual. **Per age group. ***Mean per person.

of them lost revenue due to the reduction in informal service activities, which contributed to a decline in household income.[8,9]

Considering birth rate, instead of the expected "baby boom", the concern regarding the future spread of the new coronavirus has caused a "baby bust", *i.e.*, a significant drop in birth rates almost everywhere. In parallel, the worldwide mortality rate has increased significantly, and the combination of several factors has made 2020/2021 a demographically atypical year, which will have intangible economic and social impacts.[10]

It is well known that the death of large numbers of people during a pandemic brings severe social, emotional, and economic consequences to the population and, therefore, should not be underestimated. In addition, urgent measures addressed to contain the spread of the disease must be quickly implemented, such as the rapid vaccination of the population, assessments concerning the need for booster vaccinations, and social protection in vulnerable groups, thus preventing further increases in this large number of deaths in the future.

AUTHOR CONTRIBUTIONS

KCM: study design and planning, data analyses, writing of the manuscript, and approval of the final version. PSSF, HJSM, ACBCV, and ELNM: study design and planning, writing of the manuscript, and approval of the final version.

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J Bras Pneumol. 2022;48(1):e20210297
https://dx.doi.org/10.36416/1806-3756/e20210297

Management of infantile subglottic hemangioma with T-tube placement and propranolol

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TO THE EDITOR,

Subglottic hemangioma (SGH) is a rare benign vascular tumor that accounts for 1.5% of all congenital laryngeal lesions. Usually, the onset of respiratory symptoms occurs soon after birth, during the proliferative phase of the disease.[1] Since most lesions undergo regression during early childhood,[2] treatment focuses on the prevention of long-term complications.

SGH can lead to airway obstruction when left untreated, with mortality rates approaching 50%.[3] In this scenario, tracheostomy is considered a life-saving procedure, although it may cause life-threatening complications, particularly related to the risk of airway obstruction and decannulation during postoperative care. Because of the scarcity of reports, there are no treatment guidelines proposed for SGH. An alternative approach by means of silicone T-tube placement has been used in order to achieve and maintain airway patency. The following case reports describe the management and postoperative outcome in three infants with SGH. Propranolol has become an accepted first-line treatment for SGH, with its benefits outweighing its risks.[4]

A 7-month-old male infant with recurrent respiratory infection and stridor for five months had a history of intubation and tracheostomy at three months during an episode of airway obstruction at another hospital. He presented with inspiratory stridor, and the remaining physical examination was uneventful. A contrast-enhanced neck and chest computed tomography (CT) showed a faint lateral enhancement at the vocal fold (VF) level, suggestive of SGH. A suspension laryngoscopy under general anesthesia confirmed a left-sided laryngotracheal vascular tumor causing obstruction of the larynx and subglottis. Endoscopic findings were consistent with hemangioma. While still under anesthesia, an 8 mm silicone T-tube was placed supraglottically through the tracheostomy. The patient had mild transient dysphagia with aspiration, requiring nasogastric tube feeding, with complete resolution within five days postoperatively, enabling him to resume oral intake. Propranolol (1 mg/kg/day, *per os*) was initiated and, within 3 postoperative weeks, the daily dose was increased to 3 mg/kg/day, with good tolerance. The patient was discharged from the hospital one week after the procedure with no symptoms or signs of aspiration. Currently, he remains on propranolol with a favorable outcome, and treatment is scheduled for two years.

A 6-month-old female infant was referred to our institution with recurrent respiratory infections and stridor since birth. She developed respiratory failure twice, requiring intubation. CT showed a faint enhancement suggestive of airway obstruction due to SGH (Figure 1B). A suspension laryngoscopy was performed, revealing an SGH right below the VF, causing obstruction of the larynx and subglottis (Figure 1A). In the postoperative course, the patient presented with sustained dyspnea and stridor, which ultimately evolved to respiratory failure and intubation, followed by a tracheostomy after 10 days. One year later, the tracheostomy cannula was withdrawn, and an 8 mm silicone T-tube was placed with its upper end in the supraglottis (Figure 1C), without signs of aspiration. Propranolol (1 mg/kg/day) was then started and increased to 3 mg/kg/day within 14 days and continued for two years. Sixteen months later, the T-tube was removed, and the patient underwent closure of a persistent tracheostomy orifice when she was nine years old.

A 6-month-old female infant was admitted to the emergency department with respiratory failure. She was born at 34 weeks and evolved with gastroesophageal reflux and recurrent respiratory infections. Aside from stridor, physical examination was unremarkable. Neck and chest CT showed a heterogeneous and vascularized mass in the larynx. Rigid bronchoscopy revealed a pulsatile mass causing airway obstruction, suggestive of SGH on the left. Treatment was initiated with propranolol (1 mg/kg/day) and increased in a stepwise progression to 3 mg/kg/day, which was maintained for two years. A rigid bronchoscopy and CT scan at 1 year showed a regression of the SGH. The patient remains on outpatient follow-up without recurrence.

SGH is often diagnosed during the first months of life. The three cases described presented with acute respiratory failure, diagnosed as SGH, and had favorable outcomes. Cases 1 and 2 required tracheostomy and were successfully treated thereon with a T-tube and propranolol, whereas the third was successfully treated with propranolol alone. The patients remained on propranolol for 2 years, monitored by a multidisciplinary team, including a pediatric cardiologist and a thoracic surgeon. During the regular follow-up visits, blood glucose levels, vital signs, and cardiac function were monitored, and the patients had no recurrence.

SGHs are usually found right below the VF, are often unilateral, and may involve both sides. Such tumors

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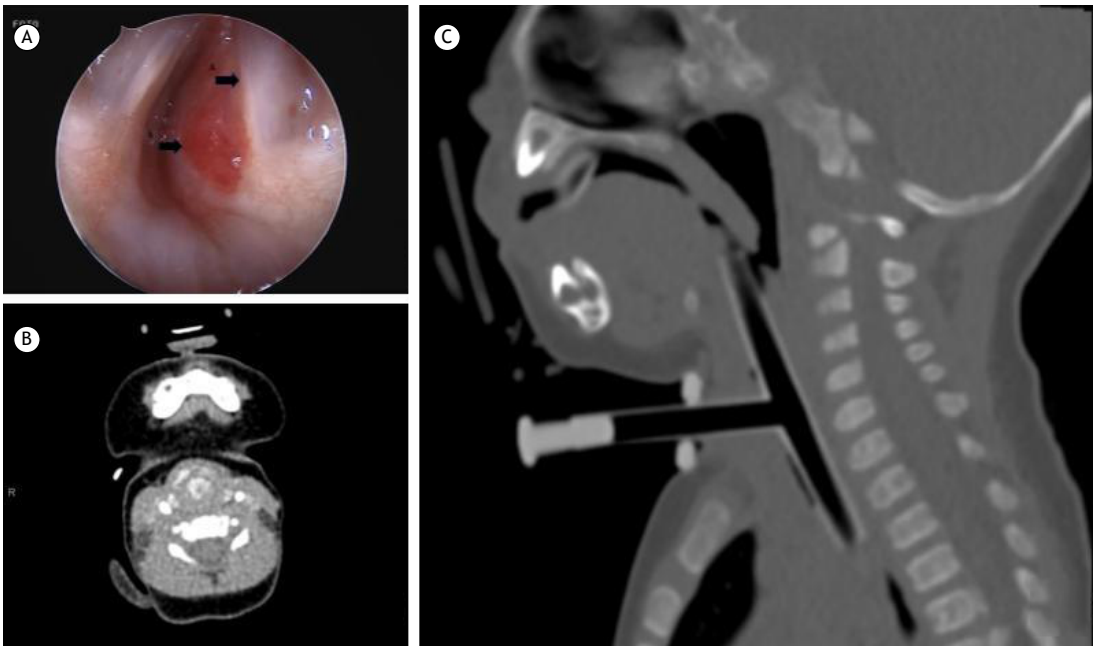

Figure 1. A. Laryngoscopic image showing right subglottic hemangioma (arrows), with airway obstruction. A (arrow): Right vocal cord; B (arrow): Subglottic hemangioma obstructing the upper airway. B. Contrast-enhanced axial CT scan showing obstructive subglottic hemangioma with characteristic intense immediate enhancement after IV contrast injection. C. Sagittal CT scan showing silicone T-tube placement, with the upper end sitting above the vocal folds.

present a surface color varying from pink to blue, are easily compressible, and project into the airway, factors that are necessary for their diagnosis.[5] Cases 1 and 2 progressed to airway obstruction, and tracheostomy was performed before endoscopic evaluation, as recommended.[6] However, a mortality rate of 40% to 60% has been reported due to tracheostomy complications, particularly obstruction or accidental decannulation.[6] The rationale for managing these patients is by stenting with a silicone T-tube and oral propranolol administration.[7] The vertical branch of the T-tube supports the tracheal lumen, while its horizontal branch anchors the tube to the tracheostomy stoma, preventing T-tube displacement.[8] The main purpose of both the tracheostomy and the T-tube is to maintain airway patency while awaiting the resolution of the SGH.

In 2008, the treatment of SGH received a new medical approach with the use of propranolol,[4] reducing the number of tracheostomies performed in these patients in 2012 compared to 2003.[9] An initial dose of 1 mg/kg/day orally is recommended and, if well tolerated, can be increased to 2 or 3 mg/kg/day. It is unknown how long children with SGH should remain on propranolol, but studies suggest its maintenance until the proliferative phase is completed.[10] During treatment with propranolol, insofar, we have not yet observed either cardiac arrhythmias or other side effects of the drug.

It can be concluded that obstructive SGH in children can be managed safely and effectively by long-term oral propranolol and airway stenting by means of a silicone T-tube when a tracheostomy is required.

AUTHOR CONTRIBUTIONS

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

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J Bras Pneumol. 2022;48(1):e20210387
https://dx.doi.org/10.36416/1806-3756/e20210387

Flexible bronchoscopy: the first-choice method of removing foreign bodies from the airways of children

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DEAR EDITOR:

Foreign body aspiration into the airway is an important cause of death in children worldwide.[1,2] Before the advent of bronchoscopy, the only treatment for that was palliative tracheostomy and the death rate was as high as 50%. The first bronchoscopy was performed by Gustav Killian in 1897 to extract an airway foreign body (AFB) from the trachea of a child (a pig bone). Since then, bronchoscopy has been extensively used for the evaluation and treatment of AFBs, reducing the mortality rate to less than 1%.[3]

The incidence of AFBs is higher in children aged 1-2 years, because of inherent developmental characteristics: immature coordination of swallowing, easiness of distraction, oral exploration, and incomplete dentition.[4] The presentation and severity depend on the degree of airway obstruction—total or subtotal obstruction of the proximal airway may lead to life-threatening asphyxia. Prompt recognition is essential, because delayed diagnosis can lead to a chronic condition (e.g., recurrent pneumonias, lung abscess, bronchiectasis, pneumothorax, or asthma-like symptoms—cough, wheezing).[4] The radiological findings are usually nonspecific or even absent, so, if there is a consistent clinical history, a bronchoscopic evaluation is needed.[5]

Bronchoscopic removal of AFBs in children is a complex and demanding procedure with a high potential for complications (e.g., hemoptysis, laryngeal/pulmonary edema, pneumonia, atelectasis, fever, respiratory failure, tracheoesophageal fistula, pneumothorax).[3] Historically, rigid bronchoscopy has been the gold standard for the treatment of foreign body inhalation in children; however, flexible bronchoscopy (FB) has been increasingly used, and several authors have described FB as a diagnostic and therapeutic method for AFBs.[6-10]

Rigid bronchoscopy has some advantages—rigid bronchoscopes are larger in diameter, ensuring safe ventilation, and provide a better operative view, being useful in cases of massive bleeding or central airway obstruction by large or sharp foreign bodies—but it requires general anesthesia and is more invasive.[5,8]

FB is more accessible, with greater availability of trained professionals, and relatively easier and safer to perform, requiring mostly only sedation and local anesthesia in older children and adolescents. When general anesthesia is opted for, FB allows ventilation in a closed system and the safe use of inhaled anesthetics. Another advantage is that FB is less traumatic to the airways, can reach bronchi that are more distal, and can be used in patients with cervical, jaw, or skull fractures.[8]

We present our experience using therapeutic FB as the first-choice method of removing AFBs in children.

We performed a retrospective study of pediatric patients (under 18 years of age) who underwent bronchoscopy for AFB removal at the Respiratory Endoscopy Department of the University of São Paulo School of Medicine *Hospital das Clínicas* Heart Institute, located in the city of São Paulo, Brazil, between January of 2014 and June of 2020. We reviewed medical and bronchoscopy records and collected information about the equipment used, foreign body location/nature, age, sex, success rate, and complications.

All patients underwent FB to locate the AFB in the tracheobronchial tree, evaluate the degree of inflammation or suppuration of the tracheobronchial mucosa, and choose the equipment that was necessary for therapeutic measures. Rigid bronchoscopy was available for immediate use in case of FB failure.

The procedures were performed in the operating room under sedation or general anesthesia. One percent lidocaine without a vasoconstrictor was used as a topical anesthetic on the airways, with the maximum dose being 4 mg/kg. All patients were monitored with oximetry, cardiac monitoring, and noninvasive arterial pressure measurement.

The following equipment was used: a flexible bronchoscope (Pentax FB-10X, Asahi Optical Co., Tokyo, Japan) with an external diameter of 3.2 mm and a working channel of 1.2 mm in children younger than 10 years of age; and a flexible bronchoscope (P30; Olympus BF, New Hyde Park, NY, USA) with an external diameter of 4.9 mm and a working channel of 2.0 mm in children 10 years of age or older. A rigid bronchoscope (Karl Storz GMBH, Tuttlingen, Germany) with an external diameter of 3.5 or 5.5 mm, a telescopic optical system, a suspension laryngoscope, or a combination of methods was used in specific cases when FB failed.

After the procedure, a complete reexamination of the tracheobronchial tree was carried out to exclude the presence of other AFBs, fragments of the removed AFB, or structural alterations. The patients were sent to the recovery room, being monitored and allowed to recover from anesthesia/sedation.

The project was approved by the institutional review board via the Brazilian Research Database, *Certificado*

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ISSN 1806-3756

Table 1. Demographic data of the patients, location/nature of the airway foreign body, and procedure used.

Variable	Patient, n (%)
Male gender	22 (55)
Age, years	
< 1	1 (2.5)
1 to < 2	15 (37.5)
2 to < 3	5 (12.5)
3 to < 4	2 (5.0)
4 to < 5	2 (5.0)
5 to < 6	3 (7.5)
6 to < 7	2 (5.0)
7 to < 8	2 (5.0)
8 to < 9	1 (2.5)
9 to < 15	4 (10.0)
15 to < 18	3 (7.5)
Location of the airway foreign body	
Larynx	3 (7.5)
Trachea	7 (17.5)
Right main bronchus	14 (35.0)
Left main bronchus	12 (30.0)
Bronchus intermedius	3 (7.5)
Left lower lobe	1 (2.5)
Nature of the airway foreign body	
Organic	16 (40)
Inorganic	22 (55)
Unknown	2 (5)
Anesthesia	
General	36 (90)
Sedation	4 (10)
Procedure	
Flexible bronchoscopy	35 (87.5)
Rigid bronchoscopy	3 (7.5)
Flexible + rigid bronchoscopy	1 (2.5)
Laryngoscopy	1 (2.5)
Ancillary material	
Basket	19 (47.5)
Rat tooth forceps	14 (35.0)
Forceps	1 (2.5)
Rigid forceps	4 (10.0)
Unknown	2 (5.0)

de Apresentação para Apreciação Ética (CAAE, Presentation Certificate for Ethical Appreciation; no. 17877919.0.0000.006).

A total of 40 pediatric patients were treated, 22 (55%) of whom were boys. Children under 3 years of age accounted for 52.5% of cases, with a peak incidence occurring among those aged 1 year to less than 2 years (37.5% of cases; Table 1).

Thirty-five percent of the AFBs were lodged in the right main bronchus, 30% were lodged in the left main bronchus, and 17.5% were lodged in the trachea. The majority was inorganic (55%) and was removed by FB (87.5%) under general anesthesia (90%), using either a basket (47.5%) or rat tooth forceps (35%; Table 1).

The overall success rate of AFB removal was 100%. In 35 cases (87.5%), the AFB was removed using FB. In 3 cases (7.5%), there was a need for rigid bronchoscopy—in one of those cases, rigid bronchoscopy was the attending physician's first choice; in another, an unsuccessful attempt at removal by FB had been made at another institution; and, in the third case, there was a subglottic stenosis impeding the passage of the flexible bronchoscope. In 1 case (2.5%), both methods were used (Table 1).

Complications occurred in 3 cases (7.5%). One of them was a minor complication—right main bronchus laceration during removal. There were 2 cases of major complications: 1 of respiratory failure and 1 of cardiac arrest (both cases required orotracheal intubation). No deaths were reported.

Our study has some limitations: it is single center, retrospective, and small sample sized. We also did not have access to the clinical data collected on admission to the emergency room.

In conclusion, based on our series and on results from previous reports, we believe that rigid bronchoscopy is not mandatory in all cases of AFB and that FB can be the first therapeutic option. Some factors contribute to the success rate of FB with minimal complications: an experienced team and ready availability of equipment. Knowledge of the different bronchoscopic techniques minimizes therapeutic failures by facilitating the removal of unexpected objects, especially in infants.

CONFLICT OF INTEREST

None declared.

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J Bras Pneumol. 2022;48(1):e20210128
https://dx.doi.org/10.36416/1806-3756/e20210128

Frequency of spontaneous detection of pulmonary arterial thrombi in unenhanced chest computed tomography in patients diagnosed with pulmonary embolism

Pedro Paulo Teixeira e Silva Torres[1], Marcelo Fouad Rabahi[2], Alexandre Dias Mançano[3], Silvia Helena Rabelo dos Santos[2], Edson Marchiori[4]

TO THE EDITOR,

Pulmonary embolism (PE) is the third most frequent cardiovascular disease, and can be lethal in the acute phase or cause significant late repercussions, such as chronic hypertensive pulmonary embolism. From a clinical point of view, the symptoms of acute PE are extensive, including asymptomatic presentation, dyspnea at rest, chest pain, and episodes of syncope.[1] Given the variability of manifestations of acute presentation, even in face of clinical suspicion, alternative diagnoses can be obtained after angiography by multidetector computed tomography (CT angiography or CTA). CTA is considered the method of choice for the imaging diagnosis of PE, being identified as a safe method for excluding PE in tests with satisfactory technical quality, reaching a negative predictive value of 95%.[1-3] Considering the limitations of the clinical diagnosis of PE and possible contraindications regarding the injection of iodized contrast medium, unenhanced chest CT scans are often performed to assess patients with non-specific acute cardiopulmonary symptoms, making the detection of indirect signs of PE crucial to raise the need for complementary tests that confirm the diagnosis in a timely manner.

The aim of the present study was to evaluate the frequency and characteristics of thrombi visualized in unenhanced chest CT scans in patients with PE confirmed by CTA.

A retrospective, cross-sectional, observational study was carried out using chest CT angiographies performed using a protocol for PE between January 2010 and December 2014 in a tertiary care hospital in Brazil. The tests that were carried out included an unenhanced phase, as part of the institution's protocol, followed by a contrast-enhanced phase, using an intravenous infusion of low-osmolarity non-ionic iodinated contrast. Initially, two examiners (with 19 and 10 years of experience, respectively) independently assessed the angiographies for pulmonary embolism, with positive results being selected for analysis. Afterward, two different examiners (with 2 and 10 years of experience, respectively) were given access to the selected PE-positive tests and were asked to search for signs of thrombi in the unenhanced CT. In this stage, the examiners evaluated the unenhanced CTs blindly in relation to the location of the thrombi, seeking their identification in the unenhanced scans. The presence of images compatible with infarction in the lung parenchyma was also assessed.

A total of 993 consecutive CT angiographies were selected, with positive scans for PE being found in 164 patients (16.5%). Of these, 64 were excluded for various reasons (inadequate protocol or data loss), leaving 100 patients with positive angiographies for PE, which constituted the sample for this evaluation. Among the 100 participating patients, 72 were female, and the mean age was 51.4 years. Thrombi in central branches (pulmonary trunk, main pulmonary arteries, or descending interlobar branches) were characterized in 44 patients.

In 17 patients (17%), it was possible to detect the presence of images compatible with thrombi (TSC+) in the unenhanced assessment; the remaining patients (TSC-) were used as a control group for statistical analysis purposes. In 13 patients (76.5%), the thrombi were hyperattenuating, while in 4 patients (23.5%), they were hypoattenuating. Among these patients, in the unenhanced phase, exclusively central thrombi were observed in 15 individuals (88.2%); in 1 patient (5.9%), it was possible to observe central and segmental branch thrombi, and in 1 patient (5.9%), an isolated segmental branch thrombus was identified. Regarding the location of the thrombi observed in the unenhanced scans, the most affected vessels were the right descending interlobar artery (13 patients), followed by the homolateral main pulmonary artery (7 patients), and the left descending interlobar branch (4 patients); it is noteworthy that, eventually, the same patient had thrombi that could be detected in more than one site. Density measurement was possible in all these patients, and, on average, the spontaneously hyperattenuating thrombi had a density of 71.1 HU (Min 58 HU / Max 87 HU), while the hypoattenuating thrombi presented a mean density of 26.7 HU (Min 11 HU / Max 36 HU).

In the multivariate analysis, when comparing groups TSC+ and TSC-, a significant association was found between the spontaneous visualization of thrombi in the pulmonary arterial system and the presence of a central thrombus (OR: 30.81; CI: 3.80-249.69).

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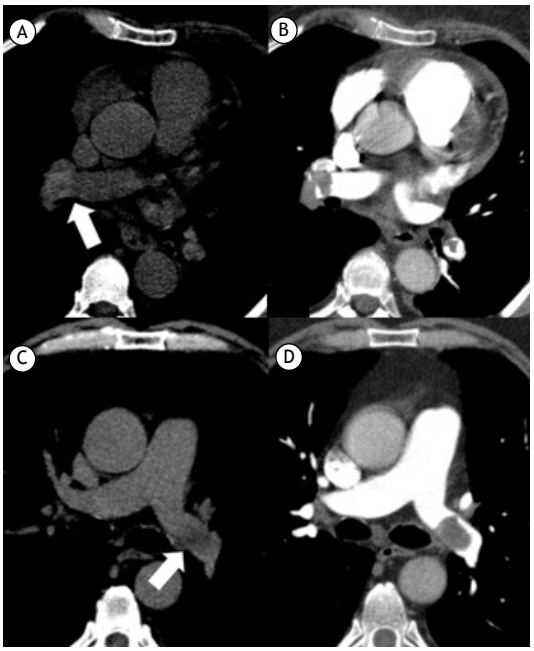

Figure 1. (A and B) Axial chest images in an adapted mediastinal window [window center (WL) = 93; window width (WW) = 284)] without administration of contrast medium in A, and CT angiography in B. Hyperattenuating image in the right descending interlobar artery, with a density of 80 HU (arrow in A), confirmed as a thrombus in the CT angiography in B. (C and D) Axial chest images in an adapted mediastinal window without administration of contrast medium in C (WL = 67; WW = 211), and CT angiography in D. Hypoattenuating image in the left pulmonary artery, with a density of 11 HU (arrow in C), confirmed as a thrombus in the CT angiography in D.

It was noteworthy that, among the patients in the TSC+ group, approximately half (47%) had no images attributable to infarction in the lung parenchyma. It is important to highlight that, occasionally, spontaneous thrombus perception may be the only indirect sign for suspected pulmonary embolism in unenhanced chest CT scans.

The present study included the largest series of CTAs positive for pulmonary embolism among those using similar methodologies to which we had access. It was possible to identify thrombi in unenhanced CTs in 17% of the scans, most of which were centrally located. A statistically significant association was observed between the visualization of thrombi in the unenhanced scans and the presence of central thrombi, corroborating previous studies.[4-8] Although recent studies show that the presence of a central embolism does not represent an independent risk factor for increased mortality, the central location has been related to right ventricular dysfunction, recurrence of venous embolism after anticoagulation withdrawal, and unfavorable clinical evolution, thus emphasizing the importance of recognizing this condition.[9-10]

In the TSC+ group, hyper- and hypoattenuating thrombi were observed in relation to regional blood density. Comparing the frequency of the findings described in the present study and in Cobelli et al.,[5] the frequency of hyperattenuating thrombi was greater herein (76% *vs*. 47%), whereas the frequency of hypoattenuating thrombi was similar (23% in both). The mean attenuation of the hyperattenuating and hypoattenuating thrombi was quite similar between the current study and the one conducted by Cobelli et al.[5] (71.1 HU *vs*. 74.2 HU for hyperattenuating thrombi and 26.7 HU *vs*. 27.7 HU for hypoattenuating thrombi, respectively).

Our study had some limitations. The interobserver variation in the identification of thrombi in the unenhanced scans was not measured since it was not part of the objective. Among the tests excluded due to data loss, most were positive for embolism according to the reports, an aspect that, in addition to reducing the sample, limited the assessment of the accuracy of thrombus identification in the unenhanced CT scans for detection of pulmonary embolism.

AUTHOR CONTRIBUTIONS

PPTST, MFR, ADM, SHRS, and EM: study design and planning; interpretation of findings; writing and/or revision of the preliminary and definitive versions, and approval of the final version.

Study carried out at the Department of Radiology, RA *Radiologia* - Sabin *Medicina Diagnóstica*, Taguatinga (DF), Brazil and at the Federal University of Rio de Janeiro, Rio de Janeiro (RJ), Brazil.

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J Bras Pneumol. 2022;48(1):e20210321
https://dx.doi.org/10.36416/1806-3756/e20210321

Adults with asthma treated with add-on omalizumab report less limitation in activities of daily living

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TO THE EDITOR,

Patients with severe asthma have worse anxiety and depression symptoms, functional capacity, physical activity levels, and quality of life compared to people without the disease.[1] In addition, this population often reports limitations when performing activities of daily living (ADL), such as doing chores, climbing stairs, going outdoors, or undertaking professional activities.[2] Studies have shown positive effects of add-on omalizumab therapy in patients with severe asthma, including improvements in asthma control, quality of life, and physical activity, while reducing the number of exacerbations and hospitalizations.[3] However, the impact of add-on omalizumab on ADL in patients with severe asthma has not yet been studied. We hypothesized that adults with severe stable asthma treated with add-on omalizumab therapy would report less limitation in ADL due to dyspnea. Thus, the aim of the present study was to compare the ADL limitations in subjects with severe asthma with and without add-on omalizumab therapy.

This real-life cross-sectional study included a convenience sample of patients diagnosed with severe asthma, according to the Global Strategy for Asthma Management and Prevention (GINA 2019),[4] with 18 years or more of age, under medical treatment for at least 6 months, clinical stability for at least 30 days (*i.e.*, no symptom exacerbations, need for an oral corticosteroid course, or increment in asthma medication), and absence of limiting cardiovascular and/or musculoskeletal diseases. Subjects were excluded if they had a diagnosis of other pulmonary disease(s) aside from asthma. Recruitment took place by inviting patients followed up at the outpatient clinic of the University Hospital of Londrina (Brazil) to take part in a secondary study aiming to assess functional capacity in patients with asthma.[5] Data collection was carried out between April 2018 and June 2019. The study was approved by the Pitágoras-Unopar University Ethics Committee (protocol No. 3.060.314), and all participants signed an informed consent form.

The patients were assessed regarding sociodemographic data, the number of comorbidities, anxiety and depression symptoms,[6] exacerbations in the previous year, and use and dose of asthma medication. Anthropometric data, biomarkers (eosinophil and total Immunoglobulin E), the 7-item Asthma Control Questionnaire (ACQ - uncontrolled asthma if >1.50 points),[7] and lung function (Spirometer MicroLab 3500, Care Fusion®, Ireland)[8] were also assessed. The limitation to perform ADL was analyzed using the London Chest Activity of Daily Living (LCADL) scale,[9] which has four domains (personal care, domestic, physical activity, and leisure) distributed into 15 items of ADL, each scored from 0 to 5. The total score can vary from 0 to 75 points (sum of each item's score), and the higher the score, the worse the limitation due to dyspnea in ADL.

In the statistical analysis, data distribution was verified by the Shapiro-Wilk test. Student's T-test and the Mann-Whitney and Chi-squared tests were used to compare the two groups, according to the data distribution. Analysis of covariance (ANCOVA) was performed to adjust the LCADL score for sex due to cultural differences regarding ADL between men and women.[10] Spearman's correlation coefficient was used to verify the correlation between the ACQ activity limitations question and the LCADL scores. The statistical software used was SPSS 22.0 (SPSS Inc., USA).

Forty-one patients met the inclusion criteria; however, four were excluded due to other pulmonary diseases aside from asthma, leaving 37 patients in the analysis. Most of the participants were middle-aged and overweight, and 21 (57%) presented uncontrolled asthma.[7] Fourteen patients (38%) had been receiving add-on omalizumab therapy for 30 (9-60) months. Most patients in the conventional therapy group seemed eligible for omalizumab since they had asthma symptoms that were inadequately controlled by inhaled corticosteroids (ICS) and total Immunoglobulin E levels between 30 and 1,500 IU/mL (Table 1).

Both groups were similar regarding sex, age, body mass index, anxiety and depression, biomarkers, asthma control, exacerbations, and pulmonary function ($p \geq 0.08$ overall). There were also no differences in the number of patients who were employed or lived alone within the two groups ($p = 0.790$ and 0.135, respectively). The patients in the add-on omalizumab group used lower doses of ICS ($p = 0.021$) and had, on average, 2 more comorbidities than those in the conventional therapy group. Only one patient (omalizumab group) was in use of a long-acting muscarinic antagonist and oral corticosteroids as controller medication. The characteristics and comparisons of both groups are shown in Table 1.

The domestic domain and total LCADL were lower in the add-on omalizumab group, whereas the other domains

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ISSN 1806-3756

Table 1. Characteristics of subjects with severe asthma on conventional therapy and on add-on therapy with omalizumab.

	Conventional therapy (n = 23)	Add-on omalizumab therapy (n = 14)	P-value
Sex, female	17 (74%)	7 (50%)	0.171
Age, years	50±15	51±13	0.724
Body mass index, kg/m^2	29±6	28±5	0.554
Comorbidities, n	3±2	5±3	0.062
Anxiety symptoms, score[a]	9 [7-12]	6 [3-9]	0.077
Depression symptoms, score[a]	7 [3-9]	7 [1-7]	0.252
Inhaled corticosteroid dose, mcg-d[b]	490 [490-643]	429 [125-490]	0.021
LABA dose, mcg-d	24 [12-24]	24 [20-24]	0.216
Eosinophil, cells/mcL	315 [189-417]	306 [134-524]	0.885
Total Immunoglobulin E, IU/mL	339 [72-610]	174 [126-271]	0.478
Asthma Control Questionnaire (ACQ), score	1.66±0.73	1.57±0.98	0.750
Exacerbation in the previous year, n of patients	15 (65%)	9 (64%)	0.954
Number of exacerbations in the previous year, n	3 [1-5]	3 [2-8]	0.379
FEV_1, L	2.08±0.63	2.05±0.69	0.902
FEV_1, % predicted	73±15	66±17	0.170
FVC, L	2.95±0.83	3.13±0.98	0.561
FVC, % predicted	85±13	82±17	0.553
FEV_1/FVC, %	70±10	66±11	0.221
PEF, L/min	5.15±1.74	5.19±0.06	0.955
LCADL personal care, score	5.32±1.58	5.08±1.44	0.613
LCADL domestic, score	9.64±3.85	7.00±2.98	0.048
LCADL physical activity, score	3.96±1.33	3.08±1.24	0.071
LCADL leisure, score	3.73±1.03	3.42±0.90	0.340
LCADL total, score	23±6	18±5	0.026

ACQ: Asthma Control Questionnaire; FEV_1: forced expiratory volume in the first second; FVC: forced vital capacity; LABA: long-acting B2 agonist; LCADL: London Chest Activity of Daily Living scale; PEF: peak expiratory flow. [a] Points scored on the Hospital Anxiety and Depression Scale.[6] [b] Inhaled corticosteroid doses were equivalent for beclomethasone (*i.e.,* beclomethasone dipropionate [HFA] >400 mcg classified as a high dose[11]). Data expressed as absolute and relative frequency, mean ± standard deviation (SD), or median [interquartile range 25-75%].

were not significantly different between groups (Table 1). However, after the adjustment for sex (ANCOVA), which may be considered a confounder, the physical activity domain was also significantly lower in patients with add-on omalizumab therapy (mean [CI 95%] 4.02 [3.45-4.60] *vs*. 2.96 [2.16-3.76]; p = 0.041). The other domains were not significantly different in the ANCOVA (p≥0.134). The ACQ activity limitations question correlated with the personal care and leisure LCADL domains and with the total LCADL (r = 0.37, 0.48, and 0.40, respectively; p<0.030 overall).

To the best of our knowledge, this is the first study to compare the limitation due to dyspnea in ADL in patients with severe asthma undergoing conventional pharmacological therapy *versus* patients with add-on omalizumab therapy. The results showed that adults with severe asthma who received omalizumab therapy had less limitation in ADL reflected in the LCADL domestic and physical activity domains, as well as in the total score, despite having a higher number of comorbidities than the conventional therapy group (borderline statistical significance [p = 0.06] but clinically relevant).[12]

Omalizumab reduces the release of inflammatory mediators that trigger the downstream inflammatory cascade in allergic asthma and has been shown to enable a reduction in ICS dose.[3] This might have occurred in this study since patients in the omalizumab group were using lower ICS doses than patients in the conventional therapy group; however, we cannot establish cause and effect due to the study design. Omalizumab was the first biological therapy approved for asthma treatment and, at the end of 2019, it was included in the public health system in Brazil. Then, at the 97th CONITEC meeting, which occurred in May 2021, it was decided that another biological therapy would be incorporated for use in the country, mepolizumab. Therefore, further studies investigating the effects of different biological therapies on ADL are warranted, especially interventional studies under controlled conditions such as randomized controlled trials.

Limitations of this study include the small number of subjects enrolled in both groups and the cross-sectional design, which does not allow us to infer cause and effect. However, the application of the LCADL was blinded regarding the subjects' treatment, and both the patients and pulmonologists were blinded concerning the study objectives. Additionally, we did not include patients who had exacerbations or increments in asthma medication in the last 30 days and excluded patients

who had other pulmonary diseases aside from asthma, which could confound the results. Furthermore, our results corroborate previous studies that found positive effects with this add-on therapy in several health aspects of these patients and reflect real-life therapy.

In conclusion, adults with severe asthma undergoing add-on omalizumab therapy reported less limitation in activities of daily living than those who did not use this treatment, despite presenting more comorbidities. A randomized controlled trial may confirm the results of this real-life study.

AUTHOR CONTRIBUTIONS

JMO: literature search, study design, data collection and analysis, manuscript preparation and review. ACN, FMCS, and FP: study design, review of manuscript. KCF: literature search, study design, data analysis, manuscript preparation and review.

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POEMS Syndrome: an uncommon cause of pleural effusion

Clarissa Canella[1,2], Bruno Schau[3], Edson Marchiori[4]

A 38-year-old man presented with dyspnea, progressively worsening back pain, and numbness and weakness in his feet and hands. Physical examination revealed hepatosplenomegaly and diffuse skin thickening with generalized hyperpigmentation. Laboratory analysis showed hypothyroidism and hyperprolactinemia. Computed tomography revealed left pleural effusion, hepatosplenomegaly, and multiple sclerotic lesions involving the axial skeleton (Figure 1). The final diagnosis was POEMS syndrome.

POEMS syndrome is a multisystemic disease occurring secondary to plasma cell dyscrasia. The acronym stands for a range of distinct features: polyneuropathy (P), organomegaly (O), endocrinopathy (E), monoclonal plasma-cell proliferative disorder (M), and skin changes (S). Many other clinical signs, such as sclerotic bone lesions, papilledema, ascites, pleural effusion (related to extravascular volume overload), pericardial effusion, pulmonary hypertension, Castleman disease, thrombocytosis and erythrocytosis, and an increased serum vascular endothelial growth factor level, may be present. POEMS syndrome is diagnosed based on the presence of polyradiculoneuropathy, clonal plasma cell disorder, and at least one additional major criterion and one minor criterion. The disease is potentially fatal, and the patients' quality of life deteriorates due to progressive neuropathy, massive peripheral edema, pleural effusion, and ascites.[1,2] Clinicians who encounter pleural effusion and some of these other signs should be aware of the possibility of POEMS syndrome.

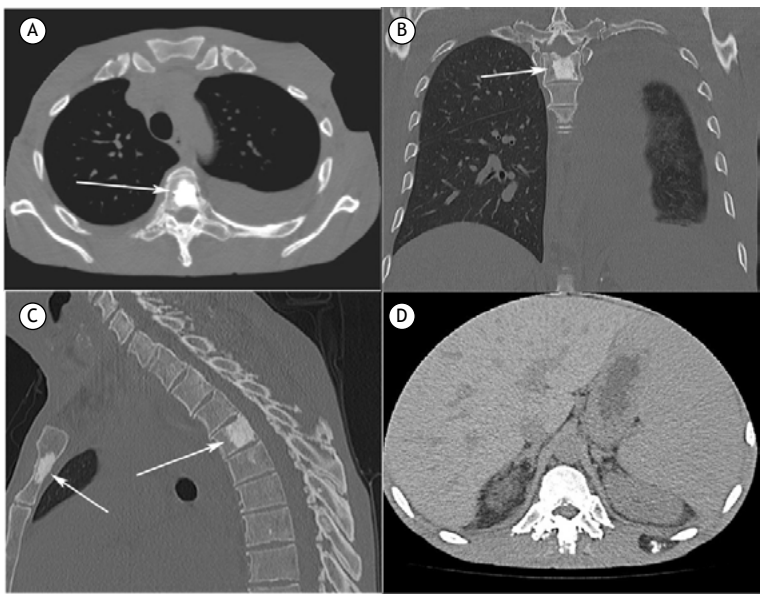

Figure 1. Computed tomography performed with mediastinal window settings and axial (A), coronal (B), and sagittal (C) reconstruction showing left pleural effusion. Note also the presence of multiple sclerotic lesions in the vertebral bodies and sternum (arrows). (D) Axial view of the upper abdomen demonstrating hepatosplenomegaly.

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

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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**

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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.

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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. 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Egurinel® é um medicamento. Durante seu uso, não dirija veículos ou opere máquinas, pois sua agilidade e atenção podem estar prejudicadas.

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