ISSN (ON-LINE): 1806-3756

JBP
Jornal Brasileiro de **Pneumologia**

PUBLICAÇÃO OFICIAL DA SOCIEDADE BRASILEIRA DE PNEUMOLOGIA E TISIOLOGIA

Volume 49, Number 6
November | December
2023

Volume 49, Number 6 November | December 2023

HIGHLIGHT

Detection of subsolid nodules on chest CT scans during the COVID-19 pandemic

ELMO CPAP: an innovative type of ventilatory support for COVID-19-related SARS

The role of polymorphisms in the IL10 and IL17 genes in the treatment of severe childhood asthma

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

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

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

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

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

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

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

COVIS PHARMA

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

moksha8

ISSN (ON-LINE): 1806-3756

JBP Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 49, n. 6, November/December 2023

EDITOR-IN-CHIEF
Marcia Margaret Menezes Pizzichini - Universidade Federal de Santa Catarina, Florianópolis - SC

DEPUTY EDITOR
Bruno Guedes Baldi - Universidade de São Paulo, São Paulo - SP

ASSOCIATE EDITORS
André Prato Schimidt - Universidade Federal do Rio Grande do Sul, Porto Alegre, RS | **Area:** Critical Care and Mechanical Ventilation
Bruno do Valle Pinheiro - Universidade Federal de Juiz de Fora, Juiz de Fora - MG | **Area:** Terapia intensiva/ Ventilação mecânica
Carlos Gustavo Verrastro - Universidade Federal de São Paulo, São Paulo - SP | **Area:** Imagem
Danilo Cortozi Berton - Universidade Federal do Rio Grande do Sul, Porto Alegre - RS | **Area:** Respiratory Physiological
Denise Rossato Silva - Universidade Federal do Rio Grande do Sul, Porto Alegre - RS | **Area:** Tuberculosis and Respiratory Infections
Edson Marchiori - Universidade Federal Fluminense, Niterói - RJ | **Area:** Image
Fernanda Carvalho de Queiroz Mello - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ | **Area:** Tuberculosis and Respiratory Infections
Gilberto Castro Junior - Instituto Brasileiro de Controle do Câncer - São Paulo - SP | **Area:** Oncology
Giovanni Battista Migliori - Director WHO Collaborating Centre for TB and Lung Diseases, Fondazione S. Maugeri, Care and Research Institute, Tradate, Italy | **Area:** Tuberculosis and Respiratory Infections
Ian Pavord - Respiratory Medicine - University of Oxford | **Area:** Asthma
Jaqueline Sonoe Ota Arakaki - Universidade Federal de São Paulo, São Paulo - SP | **Area:** Pulmonary Circulation/ Pulmonary Hypertension
Klaus Irion - School of Biological Sciences, The University of Manchester, United Kingdom | **Area:** Image
Leonardo Araújo Pinto - Pontifícia Universidade Católica do Grande do Sul, Porto Alegre - RS | **Area:** Pneumopediatrics
Paul Jones - Respiratory Medicine at St George's, University of London | **Area:** COPD
Paulo Manuel Pêgo Fernandes - Universidade de São Paulo, São Paulo - SP | **Area:** Thoracic surgery
Pedro Rodrigues Genta - Universidade de São Paulo, São Paulo - SP | **Area:** Sleep
Regina Maria de Carvalho-Pinto - Universidade de São Paulo, São Paulo, SP | **Area:** Asthma/Other Chronic Respiratory Diseases
Rodrigo Silva Cavallazzi- Respiratory Medicine at St George's, University of London University of Louisville - Kentucky - USA | **Area:** UTI e Infecções Respiratórias
Rosemeri Maurici da Silva - Universidade Federal de Santa Catarina, Florianópolis - SC | **Area:** Infections and bronchiectasis
Simone Dal Corso - Universidade Nove de Julho, São Paulo (SP), Brasil. | **Area:** Respiratory physiotherapy/Exercise
Suzana Erico Tanni - Universidade Estadual Paulista "Julio de Mesquita Filho" - Botucatu - SP | **Area:** COPD and Epidemiology
Ubiratan de Paula Santos - Universidade de São Paulo - São Paulo - SP | **Area:** Smoking/Environmental and occupational respiratory diseases
Zafeiris Louvaris - University Hospitals Leuven, Leuven, Belgium | **Area:** Respiratory physiology

EDITORIAL COUNCIL
Alberto Cukier - Universidade de São Paulo, São Paulo - SP
Álvaro A. Cruz - Universidade Federal da Bahia, Salvador - BA
Ana C. Krieger - Weill Cornell Medical College - New York - USA
Ana Luiza Godoy Fernandes - Universidade Federal de São Paulo, São Paulo - SP
Antonio Segorbe Luis - Universidade de Coimbra, Coimbra - Portugal
Ascedio Jose Rodrigues - Universidade de São Paulo - São Paulo - SP
Brent Winston - University of Calgary, Calgary - Canada
Carlos Alberto de Assis Viegas - Universidade de Brasília, Brasília - DF
Carlos Alberto de Castro Pereira - Universidade Federal de São Paulo, São Paulo - SP
Carlos M. Luna - Hospital de Clinicas, Universidad de Buenos Aires, Buenos Aires - Argentina
Carmen Silvia Valente Barbas - Universidade de São Paulo, São Paulo - SP
Celso Ricardo Fernandes de Carvalho - Universidade de São Paulo, São Paulo - SP
Dany Jasinowodolinski - Universidade de São Paulo, São Paulo - SP
Denis Martinez - Universidade Federal do Rio Grande do Sul, Porto Alegre - RS
Douglas Bradley - University of Toronto, Toronto, ON - Canadá
Emílio Pizzichini - Universidade Federal de Santa Catarina, Florianópolis - SC
Fábio Biscegli Jatene - Universidade de São Paulo, São Paulo - SP
Frank McCormack - University of Cincinnati School of Medicine, Cincinnati, OH - USA
Geraldo Lorenzi Filho - Universidade de São Paulo, São Paulo - SP
Gilberto de Castro Junior - Universidade de São Paulo, São Paulo - SP
Gustavo Javier Rodrigo - Hospital Central de las Fuerzas Armadas, Montevidéu - Uruguay
Ilma Aparecida Paschoal - Universidade de Campinas, Campinas - SP
C. Isabela Silva Müller - Vancouver General Hospital, Vancouver, BC - Canadá
J. Randall Curtis - University of Washington, Seattle, Wa - USA
John J. Godleski - Harvard Medical School, Boston, MA - USA
José Alberto Neder - Queen's University - Ontario, Canada
José Antonio Baddini Martinez - Universidade de São Paulo, Ribeirão Preto - SP
José Dirceu Ribeiro - Universidade de Campinas, Campinas - SP
José Miguel Chatkin - Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre - RS
José Roberto de Brito Jardim - Universidade Federal de São Paulo, São Paulo - SP
José Roberto Lapa e Silva - Universidade Federal do Rio de Janeiro, Rio de Janeiro - RJ
Kevin Leslie - Mayo Clinic College of Medicine, Rochester, MN - USA
Luiz Eduardo Nery - Universidade Federal de São Paulo, São Paulo - SP
Marc Miravitlles - University Hospital Vall d'Hebron - Barcelona, Catalonia - Spain
Marisa Dolhnikoff - Universidade de São Paulo, São Paulo - SP
Marli Maria Knorst - Universidade Federal do Rio Grande do Sul, Porto Alegre - RS
Mauro Musa Zamboni - Instituto Nacional do Câncer, Rio de Janeiro - RJ
Nestor Muller - Vancouver General Hospital, Vancouver, BC - Canadá
Noé Zamel - University of Toronto, Toronto, ON - Canadá
Oliver Augusto Nascimento - Universidade Federal de São Paulo - São Paulo - SP
Paul Noble - Duke University, Durham, NC - USA
Paulo Francisco Guerreiro Cardoso - Universidade de São Paulo, São Paulo - SP
Paulo Manuel Pêgo Fernandes - Universidade de São Paulo, São Paulo - SP
Peter J. Barnes - National Heart and Lung Institute, Imperial College, London - UK
Renato Sotto Mayor - Hospital Santa Maria, Lisboa - Portugal
Richard W. Light - Vanderbili University, Nashville, TN - USA
Rik Gosselink - University Hospitals Leuven - Bélgica
Robert Skomro - University of Saskatoon, Saskatoon - Canadá
Rubin Tuder - University of Colorado, Denver, CO - USA
Sérgio Saldanha Menna Barreto - Universidade Federal do Rio Grande do Sul, Porto Alegre - RS
Sonia Buist - Oregon Health & Science University, Portland, OR - USA
Talmadge King Jr. - University of California, San Francisco, CA - USA
Thais Helena Abrahão Thomaz Queluz - Universidade Estadual Paulista, Botucatu - SP
Vera Luiza Capelozzi - Universidade de São Paulo, São Paulo - SP

Associação Brasileira de Editores Científicos ABEC

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

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

NATIONAL LIBRARY OF MEDICINE

PMC

ISI Web of Knowledge℠

SCOPUS

SciELO Brazil

INDEX COPERNICUS INTERNATIONAL

latindex

ISSN (ON-LINE): 1806-3756

JBP
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

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

BTS Board of Directors (2023-2024 biennium):
President: Margareth Maria Pretti Dalcolmo - RJ
President Elect (2025/2026 biennium): Ricardo Amorim Corrêa - MG
Secretary-General: Ricardo Luiz de Melo - DF
Director, Defense and Professional Practice: Octávio Messeder - BA
CFO: Maria Enedina Claudino Aquino Scuarcialupi - PB
Scientific Director: Valeria Maria Augusto - MG
Education Director: Clystenes Odyr Soares Silva - SP
Director, Communications: Waldo Luis Leite Dias de Mattos - RS
Editor-in-Chief of the Brazilian Journal of Pulmonology: Marcia Margaret Menezes Pizzichin - SC

AUDIT COMMITTEE (2023-2024 biennium):
Active Members: Elie FISS - SP, Eduardo Felipe Barbosa Silva - DF, Flávio Mendonça Andrade da Silva - MG

Alternates: Marcelo Tadday Rodrigues - RS, Carlos Alberto de Assis Viegas - DF, Fabio José Fabricio de Souza - SC

COORDINATORS, BTS DEPARTMENTS:
Thoracic Surgery: Artur Gomes Neto - AL
Sleep-disordered Breathing: Ricardo Luiz de Menezes Duarte - RJ
Respiratory Endoscopy: Luis Renato Alves - SP
Pulmonary Function: André Luís Pereira de Albuquerque - SP
Imaging: Danny Warszawiak - PR
Lung Diseases: Alexandre Todorovic Fabro - SP
Pediatric Pulmonology: Luiz Vicente Ribeiro Ferreira da Silva Filho - SP

COORDINATORS, BTS SCIENTIFIC COMMITTEES:
Asthma: Lilian Serrasqueiro Ballini Caetano - SP
Lung Cancer: Gustavo Faischew Prado - SP
Pulmonary Circulation: Veronica Moreira Amado - DF
Advanced Lung Disease: Paulo Henrique Ramos Feitosa - DF
Interstitial Diseases: Karin Mueller Storrer - PR
Environmental and Occupational Respiratory Diseases: Eduardo Algranti - SP
COPD: Luiz Fernando Ferreira Pereira - MG
Epidemiology: Suzana Erico Tanni Minamotos - SP
Cystic Fibrosis: Samia Zahi Rached - SP
Respiratory Infections and Mycoses: José Tadeu Colares Monteiro - PA
Pleura: Philppe de Figueiredo Braga Colares - SP
Smoking: Paulo Cesar Rodrigues Pinto Correa - MG
Intensive Care: Arthur Oswaldo de Abreu - RJ
Tuberculosis: Denise Rossato Silva - RS

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.
Editorial Manager: Luana Maria Bernardes Campos.
E-mail: jbp@jbp.org.br | jbp@sbpt.org.br
Distribution: Free to members of the BTS and libraries

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

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 49, n. 6, November/December 2023

Contents

ISSN (ON-LINE): 1806-3756

Jornal Brasileiro de Pneumologia

Continuous and Bimonthly Publication, J Bras Pneumol. v. 49, n. 6, November/December 2023

Contents

J Bras Pneumol. 2023;49(6):e20230360
https://dx.doi.org/10.36416/1806-3756/e20230360

Eosinophils and therapeutic responses to steroids and biologics in COPD: a complex relationship

Parameswaran Nair[1]

The treatment of the inflammatory component of COPD has undergone significant changes over the past two decades. Inhaled corticosteroids were commonly used, just as they were in asthma, until their use was discouraged by large clinical trials such as the European Respiratory Society Study on Chronic Obstructive Pulmonary Disease[1] and the Copenhagen Lung Health Study,[2] which demonstrated modest to no short-term improvements in lung function, with minimal effect on long-term decline associated with ongoing smoking. The trial designated ISOLDE[3] suggested that the benefits are limited to patients with severe airflow obstruction and frequent exacerbations. The use of inhaled steroids was further supported by retrospective and case-control studies that suggested that they reduced mortality from COPD.[4] Seminal observations from Suissa et al.[5] identified "an immortal time bias" in these observational studies that would reduce the benefits attributed to the use of inhaled corticosteroids. With increasing recognition of adverse effects, particularly pneumonias with the use of inhaled corticosteroids,[6] international guidelines, quite correctly, recommended against the regular use of high doses of inhaled steroids in most patients with COPD.[7]

It is therefore clinically important to be able to identify biomarkers or predictors of response to glucocorticosteroids in patients with COPD so that they are used judiciously. Approximately 25-30% of patients with COPD have raised numbers of circulating eosinophils,[8] and 8-10% may have persistently elevated eosinophil numbers in their sputum.[9] Although the correlations between eosinophil numbers in blood and sputum[10] or tissue[11] are poor, both are predictors of exacerbations[12] and of response to corticosteroids (both oral and inhaled).[13-15] Early clinical studies[13] demonstrated that improvement in FEV_1 and symptoms with prednisone use in those with sputum eosinophils greater than 3% is more significant than that demonstrated with any currently approved bronchodilator for COPD. More recent studies have demonstrated that not only are eosinophils (> 2%) in circulation a predictor of response to corticosteroids,[16,17] but the use of corticosteroids in those with lower eosinophil counts show a signal to harm as well.[16]

However, unlike in asthma, eosinophils may not be directly contributing to exacerbations as the results of clinical trials regarding anti-IL-5 monoclonal antibodies in patients with COPD and raised circulating eosinophil numbers of > 150 or 300 cells/μL have been disappointing. Clinical trials using mepolizumab demonstrated modest non-statistically significant reduction in exacerbations,[18] while larger trials using benralizumab did not meet the primary endpoint of exacerbation reduction.[19] In the METREX (ClinicalTrials.gov number NCT02105948) clinical trial (n = 230 in the eosinophilic arm, and n = 604 in the non-eosinophilic + placebo arms) 100 mg s.c. mepolizumab was associated with an 18% reduction in exacerbations (p = 0.04). However, in the replicate METREO (ClinicalTrials.gov number NCT02105961) trial, the same dose of mepolizumab (n = 223 in the eosinophilic arm, and n = 226 in the non-eosinophilic + placebo arms) was associated with a non-statistically significant 20% reduction in exacerbation frequency (p = 0.07). Paradoxically, the 14% reduction in exacerbations observed with the higher dose of 300 mg s.c. mepolizumab was not statistically significant (p = 0.14). In the much larger clinical trials with benralizumab—GALATHEA and TERRANOVA (ClinicalTrials.gov numbers NCT02138916 and NCT02155660, respectively)—neither the lower dose of 30 mg s.c. nor the higher dose of 100 mg s.c. were associated with statistically significant reductions in exacerbations, although higher blood eosinophil numbers were associated with greater reduction in exacerbation frequency. While these large anti-eosinophil clinical trials failed to show a significant clinical benefit, a relatively small Canadian study in which 147 patients discharged from an ER were randomly assigned to daily doses of prednisone 40 mg or placebo demonstrated significant reductions in relapse, as well as improvements in FEV_1 and in symptoms.[20] Indeed, we had demonstrated, in 20 patients with severe COPD and CT-confirmed emphysema, a > 300 mL improvement in FEV_1 with a short five-day course of prednisone, but no improvement in FEV_1 after six months of treatment with mepolizumab 750 mg i.v. monthly.[21]

Despite observations that small studies of 20-150 patients have demonstrated a benefit of steroids use in those with increased blood or sputum eosinophils, large studies with 600-4,000 patients could not demonstrate benefits from powerful anti-eosinophil biologics, suggesting that steroids might be acting on some other cells or pathways that are upregulated along with eosinophils. Eosinophils may not directly be contributing to exacerbations but work as a biomarker for another process that is being targeted by steroids. We are not currently certain what these cellular or other immunological processes might be. Steroid withdrawal studies such as that carried out by the GLUCOLD study group[22] provide us some evidence that CD8+ cells or mast cells may increase with steroid dose reduction and are associated with worsening of symptoms. Indeed, there is evidence of an association of mast cells with alveolar septae in patients with centrilobular and paraseptal emphysema.[23] Mast cells, eosinophils,[24] and basophils[25] may be activated by IL-33

1. Firestone Institute for Respiratory Health, St Joseph's Healthcare & McMaster University, Hamilton (ON) Canada.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

to secrete IL-13 that can stimulate mucus secretion or directly stimulate macrophages to release matrix metalloproteinase-12. The recent demonstration that, unlike anti-IL-5 biologics, anti-IL-4R biologic dupilumab could reduce exacerbations by a third in patients with COPD,[26] eosinophilia, and history of bronchitis would suggest that this strategy might be effective in those patients with raised IL-13 activity in the airway[24] and consequent mucus secretion contributing to symptoms and exacerbations.

Other strategies such as targeting IL-33 signalling[27,28] have suggested modest improvements in former smokers and those with low blood eosinophils. There is also speculation that the benefits of IL-33 blockade might be influenced by a complex interacting network involving the microbiome and airway inflammation.[29] Eosinophilia observed in blood (or even in sputum) may not always be a pathological process but could also be a reflection of airway microbial dysbiosis[30] that could also be modulated by inhaled or oral corticosteroids. The association between airway eosinophilia in COPD and mixed viral and bacterial infections was demonstrated almost two decades ago,[31] and this may not be critically dependent on IL-5.[32]

In summary, epithelial alarmin activation by multiple stimuli including cigarette smoke, pollutants, and certain microbes could recruit eosinophils into the airway in patients with COPD. While increased eosinophils in blood and COPD are predictors of exacerbations and response to corticosteroids, these effects may not be directly modulated by eosinophils. Therefore eosinophil-specific therapies may not have much clinical effect unless the patients have concomitant asthma. However, targeting the IL-13 pathway, particularly in those with eosinophilia, might lead to clinical benefits by possibly reducing airway mucus secretion. This needs to be proven. Additionally, targeting this pathway or the IL-33 pathway might decrease the rate of decline of FEV_1 (or increase in airspace) by reducing airway metalloproteinase activity. The beneficial effects might be modulated by airway microbial dysbiosis. It is indeed a complex interplay of pathological processes.

CONFLICTS OF INTEREST

The author has received financial support from AstraZeneca, Sanofi Regeneron, GSK, Roche, Genentech, and Arrowhead for participating in scientific advisory boards and giving academic lectures. St Joseph's Healthcare & McMaster University have received grants from AstraZeneca, Sanofi Regeneron, Teva, Roche, Methapharm, and Cyclomedica.

REFERENCES

1. Pauwels RA, Löfdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med. 1999;340(25):1948-1953. https://doi.org/10.1056/NEJM199906243402503
2. Vestbo J, Sørensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet. 1999;353(9167):1819-1823. https://doi.org/10.1016/S0140-6736(98)10019-3
3. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ. 2000;320(7245):1297-1303. https://doi.org/10.1136/bmj.320.7245.1297
4. Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001;164(4):580-584. https://doi.org/10.1164/ajrccm.164.4.2009033
5. Suissa S. Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. Eur Respir J. 2004;23(3):391-395. https://doi.org/10.1183/09031936.04.00062504
6. Suissa S, Patenaude V, Lapi F, Ernst P. Inhaled corticosteroids in COPD and the risk of serious pneumonia. Thorax. 2013;68(11):1029-1036. https://doi.org/10.1136/thoraxjnl-2012-202872
7. Bourbeau J, Bhutani M, Hernandez P, Aaron SD, Beauchesne MF, Kermelly SB, et al. 2023 Canadian Thoracic Society Guideline on Pharmacotherapy in Patients With Stable COPD [published online ahead of print, 2023 Sep 6]. Chest. 2023;S0012-3692(23)05275-3. https://doi.org/10.1016/j.chest.2023.08.014
8. David B, Bafadhel M, Koenderman L, De Soyza A. Eosinophilic inflammation in COPD: from an inflammatory marker to a treatable trait. Thorax. 2021;76(2):188-195. https://doi.org/10.1136/thoraxjnl-2020-215167
9. D'silva L, Hassan N, Wang HY, Kjarsgaard M, Efthimiadis A, Hargreave FE, et al. Heterogeneity of bronchitis in airway diseases in tertiary care clinical practice. Can Respir J. 2011;18(3):144-148. https://doi.org/10.1155/2011/430317
10. Hastie AT, Martinez FJ, Curtis JL, Doerschuk CM, Hansel NN, Christenson S, et al. Association of sputum and blood eosinophil concentrations with clinical measures of COPD severity: an analysis of the SPIROMICS cohort. Lancet Respir Med. 2017;5(12):956-967. https://doi.org/10.1016/S2213-2600(17)30432-0
11. Turato G, Semenzato U, Bazzan E, Biondini D, Tinè M, Torrecilla N, et al. Blood Eosinophilia Neither Reflects Tissue Eosinophils nor Worsens Clinical Outcomes in Chronic Obstructive Pulmonary Disease. Am J Respir Crit Care Med. 2018;197(9):1216-1219. https://doi.org/10.1164/rccm.201708-1684LE
12. Yun JH, Lamb A, Chase R, Singh D, Parker MM, Saferali A, et al. Blood eosinophil count thresholds and exacerbations in patients with chronic obstructive pulmonary disease. J Allergy Clin Immunol. 2018;141(6):2037-2047.e10. https://doi.org/10.1016/j.jaci.2018.04.010
13. Pizzichini E, Pizzichini MM, Gibson P, Parameswaran K, Gleich GJ, Berman L, et al. Sputum eosinophilia predicts benefit from prednisone in smokers with chronic obstructive bronchitis. Am J Respir Crit Care Med. 1998;158(5 Pt 1):1511-1517. https://doi.org/10.1164/ajrccm.158.5.9804028
14. Leigh R, Pizzichini MM, Morris MM, Maltais F, Hargreave FE, Pizzichini E. Stable COPD: predicting benefit from high-dose inhaled corticosteroid treatment. Eur Respir J. 2006;27(5):964-971. https://doi.org/10.1183/09031936.06.00072105
15. Bafadhel M, Peterson S, De Blas MA, Calverley PM, Rennard SI, Richter K, Fagerås M. Predictors of exacerbation risk and response to budesonide in patients with chronic obstructive pulmonary disease: a post-hoc analysis of three randomised trials. Lancet Respir Med. 2018;6(2):117-126. https://doi.org/10.1016/S2213-2600(18)30006-7
16. Bafadhel M, McKenna S, Terry S, Mistry V, Pancholi M, Venge P, et al. Blood eosinophils to direct corticosteroid treatment of exacerbations of chronic obstructive pulmonary disease: a randomized placebo-controlled trial. Am J Respir Crit Care Med. 2012;186(1):48-55. https://doi.org/10.1164/rccm.201108-1553OC
17. Ramakrishnan S, Jeffers H, Langford-Wiley B, Davies J, Thulborn SJ, Mahdi M, et al. Blood eosinophil-guided oral prednisolone for COPD exacerbations in primary care in the UK (STARR2): a non-inferiority,

multicentre, double-blind, placebo-controlled, randomised controlled trial [published online ahead of print, 2023 Nov 1]. Lancet Respir Med. 2023;S2213-2600(23)00298-9. https://doi.org/10.1016/S2213-2600(23)00298-9

18. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017;377(17):1613-1629. https://doi.org/10.1056/NEJMoa1708208
19. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, et al. Benralizumab for the Prevention of COPD Exacerbations. N Engl J Med. 2019;381(11):1023-1034. https://doi.org/10.1056/NEJMoa1905248
20. Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, et al. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med. 2003;348(26):2618-2625. https://doi.org/10.1056/NEJMoa023161
21. Dasgupta A, Kjarsgaard M, Capaldi D, Radford K, Aleman F, Boylan C, et al. A pilot randomised clinical trial of mepolizumab in COPD with eosinophilic bronchitis. Eur Respir J. 2017;49(3):1602486. https://doi.org/10.1183/13993003.02486-2016
22. Kunz LIZ, Ten Hacken NH, Lapperre TS, Timens W, Kerstjens HAM, van Schadewijk A, et al. Airway inflammation in COPD after long-term withdrawal of inhaled corticosteroids. Eur Respir J. 2017;49(6):1700848. https://doi.org/10.1183/13993003.00848-2017
23. Ballarin A, Bazzan E, Zenteno RH, Turato G, Baraldo S, Zanovello D, et al. Mast cell infiltration discriminates between histopathological phenotypes of chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2012;186(3):233-239. https://doi.org/10.1164/rccm.201112-2142OC
24. Doyle AD, Mukherjee M, LeSuer WE, Bittner TB, Pasha SM, Frere JJ, et al. Eosinophil-derived IL-13 promotes emphysema. Eur Respir J. 2019;53(5):1801291. https://doi.org/10.1183/13993003.01291-2018
25. Shibata S, Miyake K, Tateishi T, Yoshikawa S, Yamanishi Y, Miyazaki Y, et al. Basophils trigger emphysema development in a murine model of COPD through IL-4-mediated generation of MMP-12-producing macrophages. Proc Natl Acad Sci U S A. 2018;115(51):13057-13062. https://doi.org/10.1073/pnas.1813927115
26. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389(3):205-214. https://doi.org/10.1056/NEJMoa2303951
27. Yousuf AJ, Mohammed S, Carr L, Yavari Ramsheh M, Micieli C, Mistry V, et al. Astegolimab, an anti-ST2, in chronic obstructive pulmonary disease (COPD-ST2OP): a phase 2a, placebo-controlled trial. Lancet Respir Med. 2022;10(5):469-477. https://doi.org/10.1016/S2213-2600(21)00556-7
28. Rabe KF, Celli BR, Wechsler ME, Abdulai RM, Luo X, Boomsma MM, et al. Safety and efficacy of itepekimab in patients with moderate-to-severe COPD: a genetic association study and randomised, double-blind, phase 2a trial. Lancet Respir Med. 2021;9(11):1288-1298. https://doi.org/10.1016/S2213-2600(21)00167-3
29. Lea S, Higham A, Beech A, Singh D. How inhaled corticosteroids target inflammation in COPD. Eur Respir Rev. 2023;32(170):230084. https://doi.org/10.1183/16000617.0084-2023
30. Wang Z, Locantore N, Haldar K, Ramsheh MY, Beech AS, Ma W, et al. Inflammatory Endotype-associated Airway Microbiome in Chronic Obstructive Pulmonary Disease Clinical Stability and Exacerbations: A Multicohort Longitudinal Analysis. Am J Respir Crit Care Med. 2021;203(12):1488-1502. https://doi.org/10.1164/rccm.202009-3448OC
31. Papi A, Bellettato CM, Braccioni F, Romagnoli M, Casolari P, Caramori G, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. Am J Respir Crit Care Med. 2006;173(10):1114-1121. https://doi.org/10.1164/rccm.200506-859OC
32. Saetta M, Di Stefano A, Maestrelli P, Turato G, Mapp CE, Pieno M, et al. Airway eosinophilia and expression of interleukin-5 protein in asthma and in exacerbations of chronic bronchitis. Clin Exp Allergy. 1996;26(7):766-774. https://doi.org/10.1111/j.1365-2222.1996.tb00606.x

J Bras Pneumol. 2023;49(6):e20230369
https://dx.doi.org/10.36416/1806-3756/e20230369

GOLD 2024: a brief overview of key changes

Alvar Agusti[1], Claus F. Vogelmeier[2]

Since 2001 (more than twenty years ago) the Global Initiative for Obstructive Lung Disease (GOLD) publishes and updates every year a document that recommends how to best diagnose and manage chronic obstructive pulmonary disease (COPD).[1] This is an enormous and continued team effort, so we want to start by acknowledging the dedication and hard work of all GOLD members through the years (www.goldcopd.org). The GOLD 2024 document has just been released and is available for free download in the GOLD website, together with a pocket guide and a teaching slide set.[2] Here we present a brief overview of what we think are the most relevant changes (or lack of) introduced in this 2024 edition of the GOLD recommendations.

To begin with, it is worth mentioning that, to avoid potential duplications and improve readability of the document, Chapter 3 (Evidence supporting prevention and maintenance therapy) and Chapter 4 (Management of stable COPD) in the GOLD 2023 document have now been merged into a single chapter (new Chapter 3 in GOLD 2024: Prevention and Management of COPD). Besides, the GOLD Science Committee identified a number of topics that, although already discussed in GOLD 2023, required and deserved further discussion. Accordingly, the following aspects about the diagnosis or management of COPD have been expanded and updated in GOLD 2024.

DIAGNOSIS

Spirometry

GOLD 2024 continues to propose that *a post-bronchodilator $FEV_1/FVC<0.7$, in the appropriate clinical context, is mandatory to establish the diagnosis of COPD.*[2] However, we also recognize that there is an ongoing, and not yet resolved, debate on two key aspects of this proposal. First, whether the use of the lower limit of normal (LLN) of the FEV_1/FVC ratio would be better or worse than the use of the currently recommended fixed ratio <0.7.[3] As already discussed in GOLD 2023, and now expanded in GOLD 2024, both options have pros and cons.[2] For instance, subjects classified as normal using LLN criteria but obstructed or restricted using the fixed ratio have a higher risk of mortality.[4] Further, as we know that COPD can occur in young subjects,[5] and that, in them, a fixed ratio may underdiagnose patients who may need treatment.[6,7] Besides, whether the diagnosis of COPD has to be based on pre- or post-bronchodilator spirometric values is also controversial. In this context, it is worth noting the results of a recent analysis in the SPIROMIC cohort that shows that the presence of reversible obstruction is associated with an increased incidence of COPD over time.[8] The GOLD Science Committee will continue discussing these pro- and con- arguments in relation to this key key diagnostic tool for COPD with the goal of providing a more informed proposal in GOLD 2025.

Preserved Ratio Impaired Spirometry (PRISm)

PRISm is a spirometric pattern characterized by $FEV_1/FVC \geq 0.70$ and post-BD $FEV_1 < 80\%$ pred.[9] The pathogenesis of PRISm is still unclear but potential causes may include cardiac disease (i.e., lung edema), initial stages of obstructive or restrictive lung disease, gas trapping and/or incomplete inspiration or expiration (insufficient cooperation).[9,10] Importantly, although PRISm may not be stable over time, it seems associated with an increased cardiovascular risk.[11] Clearly, as discussed in GOLD 2024, PRISm requires research to better understand its pathogenesis and to determine the best management alternatives.[2]

Lung hyperinflation

This is one of the main mechanisms, if not the leading one, of dyspnea in patients with COPD. Hyperinflation can be static (at rest) or dynamic (during exercise) and has prognostic value.[12] Bronchodilator treatment benefits are likely related to pharmacological lung "deflation". This is further discussed in detail in GOLD 2024

Interstitial lung abnormalities (ILA)

ILA are often found in patients with COPD. A new analysis in the COPDGene cohort showed that they are not always detrimental but that those ILAs associated with suspected interstitial lung disease have worse prognosis.[13]

ADDRESSING UNDERDIAGNOSIS: SCREENING AND CASE FINDING

Recent data shows that 57% of 986 individuals screened for lung cancer with low dose CT in whom forced spirometry was also measured had COPD and that, importantly, 67% of them were undiagnosed (hence untreated).

MANAGEMENT OF STABLE PATIENT

Smoking cessation

The section on smoking cessation has been revised, and a new section on pharmacotherapies for smoking cessation has been added. Further, the possibility that e-cigarettes may help as a bridge for smoking cessation was revised and, based on the available evidence and the lack of knowledge about the long-term effects of

1. Respiratory Institute, Clinic Barcelona, University of Barcelona, IDIBAPS, CIBERES, Spain
2. Department of Medicine, Pulmonary and Critical Care Medicine, University of Marburg, German Center for Lung Research (DZL), Marburg, Germany

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

e-cigarettes on respiratory health,[14] GOLD 2024 does not recommend this intervention for smoking cessation in patients with COPD.

Inhaled pharmacologic therapy

Inhaled therapy is the corner stone of pharmacologic treatment in patients with COPD. GOLD 2024 expands the discussion on how to choose the best inhaler device for a particular patient considering her/his ability to use the delivery system correctly. GOLD 2024 also discusses the potential environmental impact of different inhalers and recommend to use, whenever possible, green inhalers.[15]

On the other hand, GOLD 2023 made a practical recommendation to consider *initial* treatment with triple therapy in E patients with more than 300 Eos/mL. Now, a recent retrospective analysis of a large, real-world database (the Clinical Practice Research Datalink) in the UK provides support for this recommendation although it has to be mentioned that this analysis was not based on randomized individuals.[16]

Biologics

Previous studies of mepolizumab[17] and benralizumab[18,19] in COPD yielded inconclusive results. By contrast, the BOREAS study showed clear clinical effects of dupilumab in a selected subgroup of COPD patients (those with more than 300 eosinophils/mL who, despite the use of triple therapy, continue to suffer exacerbations and have symptoms of chronic bronchitis).[20] GOLD 2024 acknowledges these results pending confirmation studies.[2] If confirmed, this would finally open the possibility of using biologic therapy in patients with COPD.[21]

VACCINATION

The term *immunosenescence* refers to the gradual deterioration of the immune system caused by advancing age.[22] It is associated with a reduced ability to respond to infections and develop long-term immune memory.[22] It plays a key role in the development of respiratory infections in the elderly,[22] particularly in patients with COPD.[23] Refraining from smoking, limiting alcohol consumption, regular exercise, appropriate diet and establishing a proper vaccination program can slow down the process of immunosenescence (*immune fitness*).[22] Figure 1 presents the vaccination recommendations for people with COPD, which has been *updated* in line with current guidance by the U.S. Centers for Disease Control (CDC). In particular, GOLD 2024 now recommends the vaccination of COPD patients with the new respiratory syncytial virus (RSV) vaccines, which are highly efficient both in the general population[24] and in older patients with cardio-respiratory comorbidities,[25] on top of those vaccines already recommended in GOLD 2023 (flu, pneumococcus, COVID-19, pertussis and shingles).

EXACERBATIONS

Traditionally the severity of exacerbations has been determined *post-hoc* based on the type and site of treatment received*:* mild if ambulatory with minimal therapeutic changes, moderate if antibiotics and/or systemic steroids were prescribed, and severe if the patient was hospitalized. This classification have been extensively used in many clinical trials as well as to classify *stable* patients in the A, B, or E groups to guide their *initial* pharmacologic treatment.[2] It is useless, however, to guide treatment at the point of care during an actual episode of exacerbation. Because of this, GOLD 2023 adopted the Rome proposal for the definition and assessment of severity of the episodes of exacerbation of COPD at the point of care based on a number of physiological biomarkers independently of the type or site of treatment.[26] GOLD 2024 continues to propose the use of the Rome classification to guide the treatment of the actual exacerbation episode but discusses (and hopefully clarifies) several aspects that

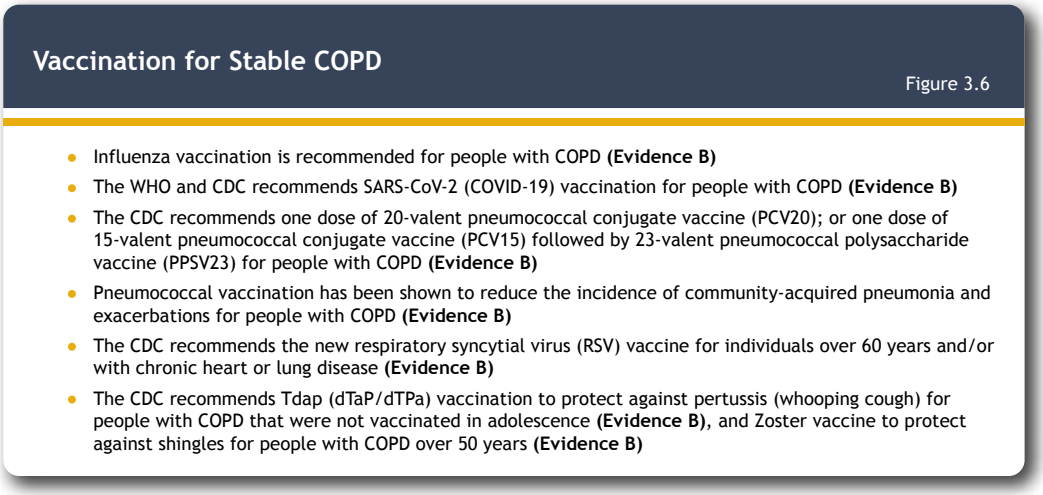


Figure 1. Vaccination for stable COPD. Reproduced from GOLD 2024 with permission.[2]

deserve consideration: 1. it is necessary to separate the physiological classification of exacerbations (Rome proposal), intended to guide treatment at the point of care, from the site of care (outpatient, inpatient), which may be dictated by the clinical severity of the exacerbation but also by the structure of different health systems, availability of resources and/or personal/social conditions (e.g., living alone, comorbidities). In fact, GOLD 2024 now discusses several retrospective studies that confirm the validity of the Rome proposal to predict mortality but also showed that a substantial proportion of hospitalized patients had, according to Rome, mild exacerbations[27,28]; 2. the classification of the stable patient in the A, B or E groups to guide initial pharmacologic treatment must still rely (by necessity) on the history recall of *previous* exacerbations which will have to be classified as moderate or severe by the site and type of treatment received.

CONCLUSIONS

As discussed above, the GOLD 2024 document discusses relevant aspects for the diagnosis, prevention, and management of COPD. Like GOLD has done over the last two decades,[1] it will continue to provide the different stakeholders interested in COPD, including patients, practicing clinicians and other health care professionals, basic science investigators, epidemiologists, pharma industry and payers, with the most updated and critically reviewed evidence on a yearly basis in order to improve the care for COPD patients and the distant goal of eventually eliminate COPD.[29]

ACKNOWLEDGMENTS

The authors acknowledge the work of Katie Lagerfeld (GOLD program Director) and Ruth Hadfield (medical writer) for their continued work to make possible the publication of the GOLD document every year.

CONFLICTS OF INTEREST

Dr. Alvar Agusti is the Chair of the Board of Directors of GOLD. Dr. Claus Vogelmeier is the Chair of the Scientific Committee of GOLD.

REFERENCES

1. Rodriguez-Roisin R, Rabe KF, Vestbo J, Vogelmeier C, Agustí A; all previous and current members of the Science Committee and the Board of Directors of GOLD (goldcopd.org/committees/). Global Initiative for Chronic Obstructive Lung Disease (GOLD) 20th Anniversary: a brief history of time. Eur Respir J. 2017;50(1):1700671. https://doi.org/10.1183/13993003.00671-2017
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2023 Nov 17]. Global Strategy for Prevention, Diagnosis and Management of COPD: 2024 Report. Available from: Available from: https://goldcopd.org/2024-gold-report/
3. Mannino DM, Sonia Buist A, Vollmer WM. Chronic obstructive pulmonary disease in the older adult: what defines abnormal lung function?. Thorax. 2007;62(3):237-241. https://doi.org/10.1136/thx.2006.068379
4. Mannino DM, Diaz-Guzman E. Interpreting lung function data using 80% predicted and fixed thresholds identifies patients at increased risk of mortality. Chest. 2012;141(1):73-80. https://doi.org/10.1378/chest.11-0797
5. Martinez FJ, Agusti A, Celli BR, Han MK, Allinson JP, Bhatt SP, et al. Treatment Trials in Young Patients with Chronic Obstructive Pulmonary Disease and Pre-Chronic Obstructive Pulmonary Disease Patients: Time to Move Forward. Am J Respir Crit Care Med. 2022;205(3):275-287. https://doi.org/10.1164/rccm.202107-1663SO
6. Miller MR, Quanjer PH, Swanney MP, Ruppel G, Enright PL. Interpreting lung function data using 80% predicted and fixed thresholds misclassifies more than 20% of patients [published correction appears in Chest. 2011 Mar;139(3):733]. Chest. 2011;139(1):52-59. https://doi.org/10.1378/chest.10-0189
7. Bhatt SP, Sieren JC, Dransfield MT, Washko GR, Newell JD Jr, Stinson DS, et al. Comparison of spirometric thresholds in diagnosing smoking-related airflow obstruction. Thorax. 2014;69(5):409-414. https://doi.org/10.1136/thoraxjnl-2012-202810
8. Buhr RG, Barjaktarevic IZ, Quibrera PM, Bateman LA, Bleecker ER, Couper DJ, et al. Reversible Airflow Obstruction Predicts Future Chronic Obstructive Pulmonary Disease Development in the SPIROMICS Cohort: An Observational Cohort Study. Am J Respir Crit Care Med. 2022;206(5):554-562. https://doi.org/10.1164/rccm.202201-0094OC
9. Wan ES. The Clinical Spectrum of PRISm. Am J Respir Crit Care Med. 2022;206(5):524-525. https://doi.org/10.1164/rccm.202205-0965ED
10. Perez-Padilla R, Montes de Oca M, Thirion-Romero I, Wehrmeister FC, Lopez MV, Valdivia G, et al. Trajectories of Spirometric Patterns, Obstructive and PRISm, in a Population-Based Cohort in Latin America. Int J Chron Obstruct Pulmon Dis. 2023;18:1277-1285. https://doi.org/10.2147/COPD.S406208
11. Wan ES, Balte P, Schwartz JE, Bhatt SP, Cassano PA, Couper D, et al. Association Between Preserved Ratio Impaired Spirometry and Clinical Outcomes in US Adults [published correction appears in JAMA. 2022 Jan 18;327(3):286]. JAMA. 2021;326(22):2287-2298. https://doi.org/10.1001/jama.2021.20939
12. Casanova C, Cote C, de Torres JP, Aguirre-Jaime A, Marin JM, Pinto-Plata V, et al. Inspiratory-to-total lung capacity ratio predicts mortality in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2005;171(6):591-597. https://doi.org/10.1164/rccm.200407-867OC
13. Rose JA, Menon AA, Hino T, Hata A, Nishino M, Lynch DA, et al. Suspected Interstitial Lung Disease in COPDGene Study. Am J Respir Crit Care Med. 2023;207(1):60-68. https://doi.org/10.1164/rccm.202203-0550OC
14. Xie W, Kathuria H, Galiatsatos P, Blaha MJ, Hamburg NM, Robertson RM, et al. Association of Electronic Cigarette Use With Incident Respiratory Conditions Among US Adults From 2013 to 2018. JAMA Netw Open. 2020;3(11):e2020816. https://doi.org/10.1001/jamanetworkopen.2020.20816
15. Pernigotti D, Stonham C, Panigone S, Sandri F, Ferri R, Unal Y, et al. Reducing carbon footprint of inhalers: analysis of climate and clinical implications of different scenarios in five European countries. BMJ Open Respir Res. 2021;8(1):e001071. https://doi.org/10.1136/bmjresp-2021-001071
16. Suissa S. Single-inhaler triple versus dual bronchodilator therapy for GOLD group E and other exacerbating patients with COPD: real-world comparative effectiveness and safety. Eur Respir J. 2023;62(3):2300883. https://doi.org/10.1183/13993003.00883-2023
17. Pavord ID, Chanez P, Criner GJ, Kerstjens HAM, Korn S, Lugogo N, et al. Mepolizumab for Eosinophilic Chronic Obstructive Pulmonary Disease. N Engl J Med. 2017;377(17):1613-1629. https://doi.org/10.1056/NEJMoa1708208
18. Brightling CE, Bleecker ER, Panettieri RA Jr, Bafadhel M, She D, Ward CK, et al. Benralizumab for chronic obstructive pulmonary disease and sputum eosinophilia: a randomised, double-blind, placebo-controlled, phase 2a study. Lancet Respir Med. 2014;2(11):891-901. https://doi.org/10.1016/S2213-2600(14)70187-0
19. Criner GJ, Celli BR, Brightling CE, Agusti A, Papi A, Singh D, et al. Benralizumab for the Prevention of COPD Exacerbations. N

Engl J Med. 2019;381(11):1023-1034. https://doi.org/10.1056/NEJMoa1905248

20. Bhatt SP, Rabe KF, Hanania NA, Vogelmeier CF, Cole J, Bafadhel M, et al. Dupilumab for COPD with Type 2 Inflammation Indicated by Eosinophil Counts. N Engl J Med. 2023;389(3):205-214. https://doi.org/10.1056/NEJMoa2303951
21. Agusti A. Biologics for COPD - Finally Here. N Engl J Med. 2023;389(3):274-275. https://doi.org/10.1056/NEJMe2305752
22. Villar-Álvarez F, de la Rosa-Carrillo D, Fariñas-Guerrero F, Jiménez-Ruiz CA. Immunosenescence, Immune Fitness and Vaccination Schedule in the Adult Respiratory Patient. Open Respir Arch. 2022;4(3):100181. https://doi.org/10.1016/j.opresp.2022.100181
23. Faner R, Cruz T, Agusti A. Immune response in chronic obstructive pulmonary disease. Expert Rev Clin Immunol. 2013;9(9):821-833. https://doi.org/10.1586/1744666X.2013.828875
24. Papi A, Ison MG, Langley JM, Lee DG, Leroux-Roels I, Martinon-Torres F, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine in Older Adults. N Engl J Med. 2023;388(7):595-608. https://doi.org/10.1056/NEJMoa2209604
25. Feldman RG, Antonelli-Incalzi R, Steenackers K, Lee DG, Papi A, Ison MG, et al. Respiratory Syncytial Virus Prefusion F Protein Vaccine Is Efficacious in Older Adults With Underlying Medical Conditions [published online ahead of print, 2023 Sep 12]. Clin Infect Dis. 2023;ciad471. https://doi.org/10.1093/cid/ciad471
26. Celli BR, Fabbri LM, Aaron SD, Agusti A, Brook R, Criner GJ, et al. An Updated Definition and Severity Classification of Chronic Obstructive Pulmonary Disease Exacerbations: The Rome Proposal. Am J Respir Crit Care Med. 2021;204(11):1251-1258. https://doi.org/10.1164/rccm.202108-1819PP
27. Crisafulli E, Sartori G, Huerta A, Gabarrús A, Fantin A, Soler N, et al. Association Between Rome Classification Among Hospitalized Patients With COPD Exacerbations and Short-Term and Intermediate-Term Outcomes [published online ahead of print, 2023 Jul 27]. Chest. 2023;S0012-3692(23)01056-5. https://doi.org/10.1016/j.chest.2023.07.021
28. Reumkens C, Endres A, Simons SO, Savelkoul PHM, Sprooten RTM, Franssen FME. Application of the Rome severity classification of COPD exacerbations in a real-world cohort of hospitalised patients. ERJ Open Res. 2023;9(3):00569-2022. https://doi.org/10.1183/23120541.00569-2022
29. Stolz D, Mkorombindo T, Schumann DM, Agusti A, Ash SY, Bafadhel M, et al. Towards the elimination of chronic obstructive pulmonary disease: a Lancet Commission. Lancet. 2022;400(10356):921-972. https://doi.org/10.1016/S0140-6736(22)01273-9

J Bras Pneumol. 2023;49(6):e20230384
https://dx.doi.org/10.36416/1806-3756/e20230384

Increasing patient access to spirometry in the Unified Health System in Brazil: no longer a dream but a near reality

Ricardo Amorim Corrêa[1,2], Eliane Viana Mancuzo[1,2], Camila Farnese Rezende[2], Antônio Luiz Pinho Ribeiro[1,3]

Spirometry is a test that measures the volume and flow of air that an individual expires through a maximal effort after a full inspiration in a sealed system.[1] It was developed by John Hutchinson and his fellow, Charles Thackrah, in 1831, who later published a paper about the five measurements of modern spirometry.[2] Afterwards, spirometers evolved from simple mechanical devices to sophisticated computational systems. Later on, population-based studies established reference spirometric values, and publication of guidelines with requirements and standards assured reliability and quality control of the test.[1,3]

The indications of spirometry have been increasing in parallel with the refinement of other methods for diagnosis of prevalent respiratory diseases such asthma, COPD, and bronchiectasis, as well as of occupational, interstitial, and vascular pulmonary diseases. Spirometry is essential not only in monitoring disease progression and responsiveness to therapy, but also in clinical practice and in research, improving the quality and precision of health care.[4]

COPD is the third leading cause of death worldwide and the fourth in low- and middle-income countries. According to the PLATINO study,[5] 87.5% of individuals had never been diagnosed with the disease, and 82.3% had never received any pharmacological treatment in the city of São Paulo, Brazil. This picture is similar in other countries. Data derived from four epidemiological studies revealed that only 26.4% of participants reported undergoing a previous lung function test ever, and only 5.0% had received a diagnosis of COPD, resulting in a proportion of 81.4% of underdiagnosed individuals.[6]

Asthma causes significant morbidity to individuals of all ages and affects a large portion of the global population, and, in spite of the modern therapies available, the disease is still underdiagnosed and uncontrolled, resulting in significant morbidity, absenteeism, and a high risk of exacerbations, emergency department visits, and hospitalizations. In Latin America, only 51% and 38% of adults and children with asthma, respectively, had ever undergone spirometry, and two-thirds of them reported undergoing the test in the previous year.[7] These data depict spirometry underuse and a high rate of underdiagnosis of respiratory diseases in Brazil as well as in other low- and middle-income countries, owing to physicians' and patients' misperception on the diagnosis and monitoring of these diseases, as well as the poor availability of spirometry in the region. Making matters worse, the COVID-19 pandemic has led to an increased demand for respiratory care and use of health resources, including the use of spirometry and other tests.[8]

Considering the continental dimension of Brazil and the heterogeneity of the primary care health system, increasing access to spirometry is demanding. How could it be addressed? One of the possibilities would be to use electronics to cover large geographic areas throughout the country. Telehealth systems (TS) have been important tools in this context. The most important predictor for using digital technologies is their usability, while the main barriers are technological issues, poor connectivity, computational illiteracy, inability to perform physical examinations, among others. In general, availability of web-based remote support for primary health care units (PHCUs) involving technicians and specialists generates a positive impact on the quality of spirometry.[9]

In the city of Belo Horizonte, Brazil, the *Centro de Telessaúde* (Telehealth Center) of the *Hospital das Clínicas* of the Federal University of Minas Gerais has joined with the Brazilian Ministry of Health to implement the Telespirometry System Brazil (TS-BR) to a number of PHCUs in low-to-medium human development index cities in Brazil to support PHCU physicians in their routine practice through a reliable and easy-to-access tool.[10] The project has included several stages: composition of the team for the selection of municipalities, development of virtual and face-to-face training on spirometry, acquisition of spirometers, creation and validation of software for test transmission, selection of pulmonologists for interpretation of results, in-person training of PHCU staff, periodic re-training of technicians, and evaluation of quality of tests and reports. The municipalities were selected based on their participation in the Brazilian family health care strategy, availability of electronic medical records, burden of asthma and COPD, and high mortality from COVID-19. The municipalities had to select technicians to be trained, to guarantee the purchase of spirometer mouthpieces and filters, and to maintain a regular offer of spirometric tests. The TS-BR provided training to medical specialists selected for interpretation and report of spirometry results as well for asynchronous teleconsultation.

Implementation of TS-BR took place between January of 2022 and June of 2023. By the time this manuscript was submitted, 147 municipalities had the TS-BR program active, and more than 14,500 tests were carried out to that date (November of 2023). The quality of the tests was remotely addressed and it improved as the number of tests increased (currently, 80.62% are at A/B categories).

1. Departamento de Clínica Médica, Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
2. Serviço de Pneumologia e Cirurgia Torácica, Hospital das Clínicas, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
3. Centro de Telessaúde, Hospital das Clínicas, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

A cost-effectiveness analysis of TS use has shown it to be 23% more expensive but 46% more effective, costs tending to decrease as the number of tests carried out increases.[11] However, as the quality of the TS may decrease over time, centralized quality control and a re-training program are mandatory.[12]

In conclusion, there is high demand for pulmonary function testing in PHCUs worldwide, and that has been aggravated after the outbreak of the COVID-19 pandemic in Brazil. The TS-BR has shown that it is possible to achieve a large-scale increase in the supply of spirometric tests in the country by means of a structured, agile, and well-monitored remote system using appropriate electronic resources.

FINANCIAL SUPPORT

Antônio Luiz Pinho Ribeiro receives partial financial support from the *Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Grants no. 310790/2021-2 and 465518/2014-1) and from the Fundação de Amparo à Pesquisa de Minas Gerais (FAPEMIG, Foundation for the Support of Research in the State of Minas Gerais; Grants PPM-00428-17 and RED-00081-16).

AUTHOR CONTRIBUTIONS

RAC contributed to the conception. and RAC, EVM, CFR, and ALPR equally contributed to the writing and revision of the final version of the manuscript. All the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. https://doi.org/10.1164/rccm.201908-1590ST
2. Hutchinson J. On the capacity of the lungs, and on the respiratory functions, with a view of establishing a precise and easy method of detecting disease by the spirometer. Med Chir Trans. 1846;29:137-252. https://doi.org/10.1177/095952874602900113
3. Pereira CAC, Soares MR, Gimenez A. The importance of appropriate reference values in patients suspected of having obstructive lung disease. J Bras Pneumol. 2019;45(6):e20190299. https://doi.org/10.1590/1806-3713/e20190299
4. Kouri A, Dandurand RJ, Usmani OS, Chow CW. Exploring the 175-year history of spirometry and the vital lessons it can teach us today. Eur Respir Rev. 2021;30(162):210081. https://doi.org/10.1183/16000617.0081-2021
5. Nascimento OA, Camelier A, Rosa FW, Menezes AM, Pérez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease is underdiagnosed and undertreated in São Paulo (Brazil): results of the PLATINO study. Braz J Med Biol Res. 2007;40(7):887-895. https://doi.org/10.1590/S0100-879X2006005000133
6. Lamprecht B, Soriano JB, Studnicka M, Kaiser B, Vanfleteren LE, Gnatiuc L, et al. Determinants of underdiagnosis of COPD in national and international surveys. Chest. 2015;148(4):971-985. https://doi.org/10.1378/chest.14-2535
7. Neffen H, Fritscher C, Schacht FC, Levy G, Chiarella P, Soriano JB, et al. Asthma control in Latin America: The Asthma Insights and Reality in Latin America (AIRLA) survey. Rev Panam Salud Publica. 2005;17(3):1917. https://doi.org/10.1590/S1020-49892005000300007
8. Burgos Rincón F, Martínez Llorens J, Cordovilla Pérez R. Impact of the COVID-19 Pandemic on Lung Function Laboratories: Considerations for "Today" and the "Day After". Arch Bronconeumol (Engl Ed). 2020;56(10):611-612. https://doi.org/10.1016/j.arbr.2020.07.009
9. Burgos F, Disdier C, de Santamaria EL, Galdiz B, Roger N, Rivera ML, et al; Telemedicine enhances quality of forced spirometry in primary care. Eur Respir J. 2012;39(6):1313-1318. https://doi.org/10.1183/09031936.00168010
10. Alkmim MB, Figueira RM, Marcolino MS, Cardoso CS, Pena de Abreu M, Cunha LR, et al. Improving patient access to specialized health care: the Telehealth Network of Minas Gerais, Brazil. Bull World Health Organ. 2012;90(5):373-378. https://doi.org/10.2471/BLT.11.099408
11. Marina N, Bayón JC, López de Santa María E, Gutiérrez A, Inchausti M, Bustamante V, et al. Economic Assessment and Budgetary Impact of a Telemedicine Procedure and Spirometry Quality Control in the Primary Care Setting. Arch Bronconeumol. 2016;52(1):24-28. https://doi.org/10.1016/j.arbr.2015.11.002
12. Pérez-Padilla R, Vázquez-García JC, Márquez MN, Menezes AM; PLATINO Group. Spirometry quality-control strategies in a multinational study of the prevalence of chronic obstructive pulmonary disease. Respir Care. 2008;53(8):1019-1026. PMID: 18655739.

J Bras Pneumol. 2023;49(6):e20230392
https://dx.doi.org/10.36416/1806-3756/e20230392

Subsolid nodules, adenocarcinomas, and COVID-19: looking for needles in a haystack

Pedro Paulo Teixeira e Silva Torres[1], Edson Marchiori[2]

By November 2023, the World Health Organization had counted over 770 million confirmed cases of COVID-19.[1] Given that chest CT played a relevant role in the management of these patients during the pandemic, we can at best assume that tens of millions of CT scans were performed during that period. Even if the reasons were unrelated from the perspective of oncological imaging, that might have been the largest opportunistic screening of lung neoplasms to date.

In this sense, the study by Zanardo et al.[2] sheds light on a relevant issue that involves the differential diagnosis of subsolid lung nodules (SLNs) and the current knowledge about the morphology/evolution of adenocarcinomas on CT. Although not statistically significant, a tendency toward a reduction in the diagnosis of SLNs was demonstrated in the sample collected during the COVID-19 pandemic when interpreted by a thoracic radiologist. This fact is explained by the morphological similarity between persistent lesions that present as SLNs and transient lesions related to SARS-CoV-2 on CT, highlighting the possibility of neoplastic changes, especially lesions in the spectrum of adenocarcinomas. If we imagine a real-life scenario during the pandemic, some factors might have potentially complicated the underdiagnosis of persistent SLNs. First, during that period, radiologists were exposed to a disproportionate number of chest CT scans for evaluation, with demands for rapid responses to be included in medical reports, which certainly reduced interpretation time and might have influenced the detailing of some of these lesions.[3] Second, with the increased demand, radiologists with different levels of experience in thoracic imaging (and therefore familiarity with SLN interpretation) were called upon to interpret these exams.

Important studies on the morphological diagnosis of lung adenocarcinomas were published in the 1990s, notably the one by Noguchi et al.,[4] correlating the morphological (histopathological) appearance and prognosis of small lung adenocarcinomas. Knowledge on the morphology and evolution of these tumors on CT derived from those studies, and persistent SLNs (semisolid or purely ground glass) began to be recognized for their neoplastic potential.[5] It is worth emphasizing that the differential diagnosis of SLNs is broad in transient lesions, including inflammatory and infectious changes (including COVID-19) and focal hemorrhage, whereas it encompasses interstitial fibrosis, organizing pneumonia, endometriosis, and neoplasms (including changes in the spectrum of adenocarcinomas, lymphoproliferative disorders, and, less commonly, secondary neoplastic implants) in persistent lesions.[6]

Although the morphological semiology of SLNs on CT is limited in differentiating between benign lesions and neoplasms (especially adenocarcinomas), persistent lesions presenting specific findings such as spiculations, internal lucencies, vascular convergence, coarse interface but well-defined with the adjacent parenchyma, and pleural retraction should suggest malignancy.[7] Current protocols for the diagnostic management of SLNs by the Fleischner society[8] recommend that morphological elements (purely ground-glass or semi-solid lesions), their size, and multiplicity should be combined for follow-up suggestions, and such lesions should often be monitored for long periods of time to evaluate their behavior.

The female population deserves special attention, and in the study by Zanardo et al.[2] they more often detected SLN in women regardless of COVID-19 status. A trend toward an increase in the frequency of lung neoplasms in the female population has been demonstrated in several countries, and mortality from lung neoplasms is expected to exceed mortality from breast neoplasms in the future.[9] Furthermore, some screening studies have shown a greater benefit in the reduction in lung neoplasm mortality in women, with an emphasis on a study in which the reduction in specific lung cancer mortality was 24% in men and 33% in women.[9,10]

We thus return to the point of the countless chest CT studies carried out around the world during the challenging period of the COVID-19 pandemic. We need to reflect that, given the morphological similarity between lung changes caused by SARS-CoV-2 and lesions in the spectrum of adenocarcinomas, some of the latter might not have been readily recognized. Prospectively, it is worth reinforcing to the radiological community the importance of careful comparative analysis of current chest CT scans with any previous exams during that period for retrospective diagnosis and adequate management of those lesions.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this editorial.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. World Health Organization [homepage on the internet]. Geneva: WHO; c2023 [cited 2023 Dec 2]. Coronavirus (COVID-19) Dashboard. Available from: https://covid19.who.int/
2. Zanardo AP, Brentano VB, Grando RD, Rambo RR, Hertz FT, Anflor Júnior

1. Hospital Israelita Albert Einstein, Goiânia (GO) Brasil.
2. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

LC, et al. Detection of subsolid nodules on chest CT scans during the COVID-19 pandemic. J Bras Pneumol. 2023;49(6):20230300.

3. Alaref A, Elnayal A, Kulkarni A, Alabousi A, Van Der Pol C. Burnout Exacerbation due to COVID-19 Pandemic. Can Assoc Radiol J. 2022;73(1):272. https://doi.org/10.1177/08465371211022291
4. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung. Histologic characteristics and prognosis. Cancer. 1995;75(12):2844-2852. https://doi.org/10.1002/1097-0142(19950615)75:12<2844::AID-CNCR2820751209>3.0.CO;2-
5. Travis WD, Brambilla E, Noguchi M, Nicholson AG, Geisinger KR, Yatabe Y, et al. International association for the study of lung cancer/american thoracic society/european respiratory society international multidisciplinary classification of lung adenocarcinoma. J Thorac Oncol. 2011;6(2):244-285. https://doi.org/10.1097/JTO.0b013e318206a221
6. Carter BW, Walker CM, Hobbs SB, Chung JH. A Subsolid Pulmonary Lesion. Diagnostic Considerations and Management Options. Ann Am Thorac Soc. 2016;13(7):1180-1182. https://doi.org/10.1513/AnnalsATS.201601-086CC
7. Fan L, Liu SY, Li QC, Yu H, Xiao XS. Multidetector CT features of pulmonary focal ground-glass opacity: differences between benign and malignant. Br J Radiol. 2012;85(1015):897-904. https://doi.org/10.1259/bjr/33150223
8. MacMahon H, Naidich DP, Goo JM, Lee KS, Leung ANC, Mayo JR, et al. Guidelines for Management of Incidental Pulmonary Nodules Detected on CT Images: From the Fleischner Society 2017. Radiology. 2017;284(1):228-243. https://doi.org/10.1148/radiol.2017161659
9. Revel MP, Chassagnon G. Ten reasons to screen women at risk of lung cancer [published correction appears in Insights Imaging. 2023 Nov 22;14(1):198]. Insights Imaging. 2023;14(1):176. https://doi.org/10.1186/s13244-023-01512-8
10. de Koning HJ, van der Aalst CM, de Jong PA, Scholten ET, Nackaerts K, Heuvelmans MA, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med. 2020;382(6):503-513. https://doi.org/10.1056/NEJMoa1911793

Paraseptal emphysema

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

A 35-year-old man presented with a two-year history of dry cough and progressive dyspnea that had recently worsened. He had been using marijuana since he was 11 years old. Chest CT revealed a single layer of multiple subpleural cystic spaces (Figure 1).

Basically, subpleural cystic spaces have two differential diagnoses: honeycombing and paraseptal emphysema. Honeycombing is a CT pattern that consists of multiple contiguous cysts that occur in layers and are located in the subpleural region. Histologically, honeycombing consists of lung cysts resulting from the destruction of distal air spaces due to fibrosis of the lung parenchyma, accompanied by loss of acinar and bronchiolar architecture. In summary, the finding of lung honeycombing means the presence of fibrosis and is an important criterion for the diagnosis of usual interstitial pneumonia.[1]

Emphysema is pathologically characterized by abnormal, permanent enlargement of air spaces distal to the terminal bronchiole, accompanied by destruction of alveolar walls. The classification of emphysema is traditionally based on the disease distribution in the secondary pulmonary lobules. The principal types are centriacinar or centrilobular emphysema, paraseptal or distal acinar emphysema, and panacinar or panlobular emphysema. CT findings consist of areas of low attenuation, typically without visible walls. In paraseptal emphysema, there is permanent enlargement of the distal region of the secondary pulmonary lobule, accompanied by destruction of alveolar ducts and sacs and by dilated alveoli that are located subpleurally adjacent to the interlobular septa. Less severe forms of paraseptal emphysema are difficult to detect on chest x-rays. On CT, subpleural cystic spaces are seen, possibly separated by intact interlobular septa. Paraseptal emphysema is characteristically bounded by pleural surface or interlobular septa. The anterior and posterior portions of the upper lobes and the posterior portions of the lower lobes are most often affected. This form of emphysema may be accompanied by bullae. If it occurs alone or is the predominant type, paraseptal emphysema tends not to cause any respiratory symptoms, and therefore it is often underrecognized clinically.[2]

Paraseptal emphysema is more common in marijuana smokers than in tobacco-only smokers. It appears that certain maneuvers performed by marijuana smokers, such as inhalation with the Valsalva maneuver, can lead to barotrauma and formation of apical bullae. Paraseptal emphysema is the predominant pattern seen in marijuana smokers, while centrilobular emphysema is more often seen in tobacco-only smokers. This may represent an earlier stage of apical bulla formation reported in marijuana smokers. Our patient was a heavy marijuana smoker who developed paraseptal emphysema.[3]

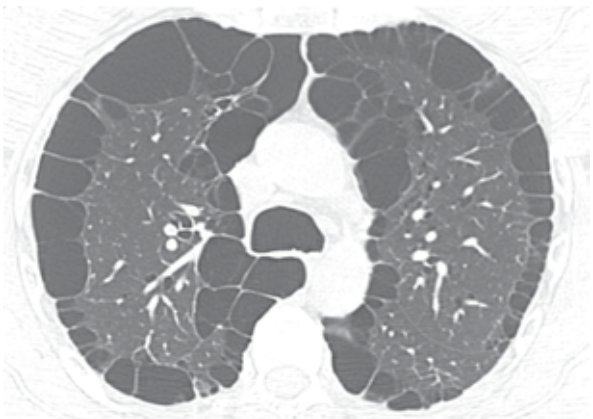


Figure 1. An axial CT scan at the level of the upper lobes shows a single layer of subpleural cystic spaces consistent with paraseptal emphysema.

REFERENCES

1. Marchiori E, Hochhegger B, Zanetti G. Honeycombing. https://doi.org/10.1590/S1806-37562017000000232
2. Hochhegger B, Marchiori E, Rodrigues R, Mançano A, Jasinowodolinski D, Chate RC, et al. Consensus statement on thoracic radiology terminology in Portuguese used in Brazil and in Portugal [published correction appears in J Bras Pneumol. 2022 Jan 10;47(6):e20200595errata]. J Bras Pneumol. 2021;47(5):e20200595. https://doi.org/10.36416/1806-3756/e20200595
3. Murtha L, Sathiadoss P, Salameh JP, Mcinnes MDF, Revah G. Chest CT Findings in Marijuana Smokers. Radiology. 2023;307(1):e212611. https://doi.org/10.1148/radiol.212611

1. Universidade Federal do Rio de Janeiro, Rio de Janeiro (RJ) Brasil.
2. University of Florida, Gainesville (FL) USA.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

Crafting a research protocol: a stepwise comprehensive approach

Ricardo Gassmann Figueiredo[1,2], Cecilia María Patino[2,3], Juliana Carvalho Ferreira [2,4]

PRACTICAL SCENARIO

A group of researchers plan to conduct a cross-sectional study to estimate the prevalence of frailty in elderly patients with moderate to severe asthma and to report a measure of association between asthma control and frailty.[1] The research protocol outlines the complex interactions of asthma control in frail patients and motivation to address this research question. Study design, objectives, methods, ethical issues, risks, and impact were also detailed in the protocol.

WHAT IS A RESEARCH PROTOCOL?

A well-structured research protocol guides researchers through the intricate process of conducting rigorous research. A research protocol is designed to be concise and self-contained, and to summarize the core aspects of the study. Self-discipline is vital in this process, as it requires the investigator to structure the central concepts of the study and reveal particular issues that demand attention.[2] The research protocol often serves as the foundation for the development of manual of operating procedures, which includes comprehensive information on the organization and policies of the study, as well as an operational approach to the procedures outlined in the study protocol; therefore, both documents complement each other.

ELEMENTS OF A RESEARCH PROTOCOL

The research protocol framework (outlined in Chart 1) usually includes a title, rationale, background information, objectives, methodology, data management, statistical plan, quality control, ethics, budget, developing plan, timeline, references, and appendices, although the sections included vary depending on institutional templates.

The title should be concise, descriptive, and engage readers, effectively reflecting the core of the research.[3] The background section outlines the driving factors and motivation for conducting the research. It should provide a broad context, elucidate the problem, address specific knowledge gaps, and establish the rationale for the study. In our practical example, the authors provided background information about how the multidimensional aspects of

Chart 1. Research protocol stepwise approach.

Step	Description
Title	Concise, reflecting study main ideas, and attracting reader's attention
Background and rationale	What is the problem? Why is it important? What is known about it?
Objectives	Specific, measurable, and established prior to carrying out the study
Relevance and study design	Contributions of the study to the field, aligned with rationale and objectives
Methods	Participants, exposures/intervention, outcomes, study setting, eligibility criteria, participant timeline, sample size, recruitment, and blinding Detailed script: How will the study be conducted? Why was the described design chosen?
Data collection, access, and management	Methods for data storage, security, privacy, and treatment of missing data
Statistical plan	Descriptive statistics, hypothesis testing, sample size, and power calculation
Quality control	Credibility of the research: instruments, data collection, data acquisition
Ethics	Ethical dilemmas, application to ethics research committees, Informed consent form
Roles and responsibilities	Affiliations, roles, and responsibilities of protocol contributors[3]
Budget	Detailed expenses: personnel, equipment, consumables, logistics
Funding	Sources of financial support
Dissemination plan	Effective communication of research findings
Timeline	Be realistic about project management throughout the research
References	Check publishers' guidelines, consider using reference manager software
Appendices	Extensive descriptions of procedures, questionnaires, and informed consent forms
Protocol version	Indicator of version and date of the protocol

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

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

frailty are imbricated into proper asthma management in patients with advanced age. This section should align with the objectives, highlighting the potential impact of the study. Research objectives should be clear, measurable, precise, and set before conducting the study.[2] After the statement of the primary objective, secondary aims might be appropriate. The objectives will guide the study design and methodology, directing attention toward the intended research outcomes.

The methods section is a detailed blueprint of the research project and the basis for the manual of operating procedures. It should detail the study design, participant selection (eligibility, sampling, and recruitment), variables, data acquisition, data management (storage, security, privacy, and treatment of missing data), statistical plan, and sample size calculation. The scientific robustness of the study relies on its methodology, ensuring validity and replicability. The statistical plan should clearly outline the analysis methods, software used, and criteria for determining statistical significance. Quality control mechanisms uphold the internal validity of the study. This segment should describe measures to minimize bias and ensure data quality.[2] Steps might include regular data verification, calibration and certification of instruments, as well as research personnel training.

Ethical considerations are paramount in research. This section should document the issues that are likely to raise ethical concerns, including informed consent forms, confidentiality, data protection, and potential ethical dilemmas.[3] Moreover, it should also mention approvals obtained from institutional review boards. The budget section details the financial requirements of the research. It includes costs with personnel, equipment, materials, logistics, consumables, and contingencies. A realistic and well-planned timeline is crucial for successful project management.

Deficiencies in effectively disseminating and transferring research-based knowledge into clinical practice can impair the potential benefits of the research project. Therefore, most health research funding agencies expect commitment from investigators to disseminate the study findings actively. Integrating a dissemination plan in the research protocol will facilitate effective communication of research outcomes to the scientific community and those who can apply the knowledge in real-world situations.

KEY MESSAGES

1. A comprehensive research protocol not only provides a roadmap for the implementation of the study but also ensures that the research question is addressed according to high-quality research standards.
2. Quality control is essential to improve internal validity of the study.
3. A structured approach to conducting research reduces the likelihood of misleading conclusions and biases, ensuring validity and reproducibility of the study.

REFERENCES

1. Figueiredo RG, Pinheiro GP, Arata V, Leal MFM, Santana CVN, Tiraboschi TL, et al. Impact of frailty in elderly patients with moderate to severe asthma. PLoS One. 2022;17(7):e0270921. https://doi.org/10.1371/journal.pone.0270921
2. Hulley SB, Cummings SR, Browner WS, Grady DG, Newman TB. Designing Clinical Research. Lippincott Williams & Wilkins; 2011.
3. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gøtzsche PC, Krleža-Jerić K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. Ann Intern Med. 2013;158(3):200-207. https://doi.org/10.7326/0003-4819-158-3-201302050-00583

Pulmonary function laboratory to assist in the management of cardiac disease

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

BACKGROUND

Pulmonary function tests (PFTs) are highly sensitive to derangements in the cardiopulmonary unit. Recognizing the effects of cardiac disease on PFTs is paramount to proper testing interpretation, a task particularly challenging in the presence of coexisting respiratory disorders.

OVERVIEW

A 72-year-old former smoker underwent PFTs due to out-of-proportion dyspnea after treatment optimization for heart failure with reduced ejection fraction (HFrEF). RV and functional residual capacity (FRC) were markedly increased (~160%) despite only a mild and proportional decrease in post-bronchodilator (BD) FEV_1 and FVC with preserved TLC. Given air trapping and smoking history, long-acting BDs were initiated with rapid improvement in dyspnea (case #1). An 81-year-old former smoker admitted to the hospital due to HFrEF decompensation showed "fixed" obstruction with a low DL_{CO} a week after discharge. The patient refused BD treatment for potential COPD. Two months later, all PFTs were within normal range (case #2).

Clinical interpretation of PFTs in cardiac disease associated with lung congestion and/or low cardiac output is full of pitfalls.[1,2] In chronic HFrEF, decrements in lung volumes (low lung compliance, alveolar filling, cardiomegaly) and, in some patients, inspiratory muscle weakness might cause restriction. If severe enough, this may "normalize" spirometry and counterbalance any hyperinflation in coexisting COPD.[3] Air trapping is not commonly seen in stable HFrEF and, in the proper clinical context, might signal underlying airway disease (case #1; Figure 1A). Exaggerated ventilation[4] coupled with poor muscle O_2 delivery on cardiopulmonary exercise testing might suggest that HFrEF contributes to exertional dyspnea in COPD. Overt obstruction with reduced mid-expiratory flows due to peribronchiolar cuffing, mucosal swelling, and vagal reflexes may occur in acute decompensated HFrEF ("cardiac asthma"; Figure 1B). These abnormalities may take weeks to resolve (case #2), frequently accompanied by airway hyperresponsiveness.[5] Although higher capillary blood volume may increase the "vascular" conductance to gas transfer, this is superseded by increases in the "membrane" resistance. Thus, mild-moderate decreases in DL_{CO}—worsening with HFrEF progression—may make it difficult to portion out the contribution of any underlying lung disease (e.g., COPD, interstitial lung disease) to a low DL_{CO} (Figure 1B).

In contrast with HFrEF, mild decrement in FEV_1/(F)VC and increases in RV are frequently seen in patients with stable moderate-to-severe mitral valve disease, likely because of the congested vessels in alveolar walls impeding their complete deflation. Congenital heart disease associated with left (L)-to-right (R) shunt and increased capillary blood volume may increase DL_{CO} and carbon monoxide transfer coefficient (K_{CO}). Mild hypoxemia and an increased alveolar-arterial O_2 gradient may occur due to ventilation/perfusion mismatch. Severe hypoxemia is the hallmark of patients with R-to-L shunt (e.g., tetralogy of Fallot, Eisenmenger syndrome), the shunted fraction being estimated by the 100% O_2 inhalation test.[6]

CLINICAL MESSAGE

Given that respiratory and cardiac disease often coexist and given the overlapping consequences to lung function, the pulmonologist should recognize the "shades of gray" when interpreting PFTs in these patients. Frequently, little is known about the pre-test likelihood of disease or disease severity/stability in patients with known cardiac disease. Thus, the report should cautiously state that testing results should be analyzed considering the individual's clinical context.

AUTHOR CONTRIBUTIONS

All authors contributed to conceptualization, writing, reviewing, and editing.

CONFLICTS OF INTEREST

None declared.

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

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

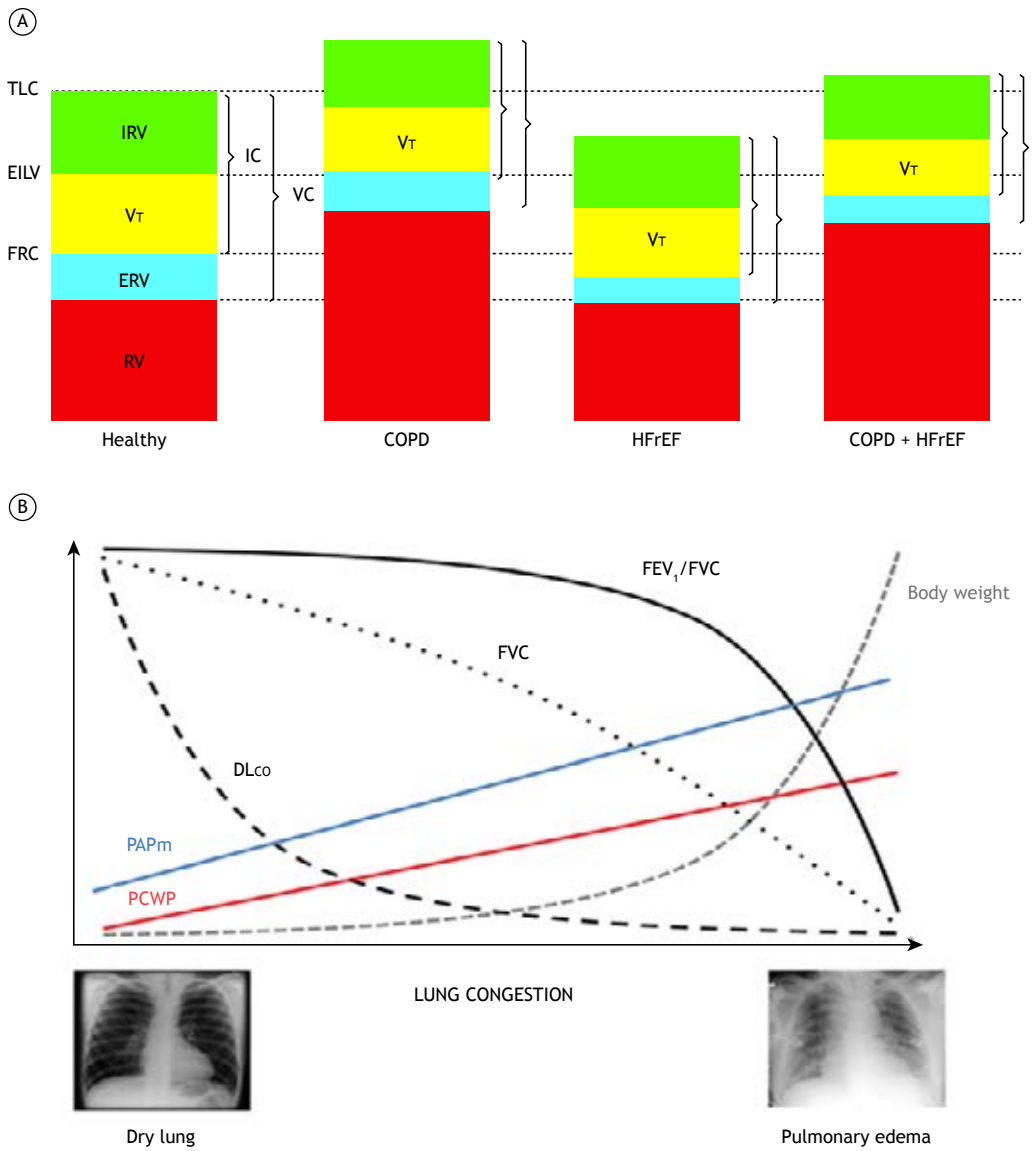


Figure 1. Respiratory functional consequences of heart failure with reduced ejection fraction (HFrEF) with the highest potential to influence the interpretation of pulmonary function tests. Panel A depicts the effects of COPD, HFrEF, and their combination on resting lung volumes and capacities in a non-obese subject. Variable degrees of thoracic hyperinflation (⇑ TLC), lung hyperinflation (⇑ FRC), and gas trapping (⇑ RV) result in low volume available (⇓ IC) for tidal volume (V_T) expansion in patients with moderate-to-severe COPD. This latter consequence is also observed in moderate-to-severe HFrEF in which the most consistent mechanical effect is a reduction in TLC that is also more pronounced than those found in FRC. In contrast to COPD, the IC decrement in HFrEF occurs predominantly due to a lower "ceiling" (TLC) rather than a higher "floor" (FRC). Lung volume measurements (e.g. body plethysmography) are particularly useful to suggest coexistent HF and COPD. HF may 'normalize' TLC in a COPD patient with previous thoracic hyperinflation. Conversely, high RV and RV/TLC may indicate the presence of COPD-related gas trapping as RV is more "resistant" than TLC to decrease secondary to coexistent HFrEF. Panel B provides a schematic representation of potential trajectories of lung function, hemodynamics, and body weight with progressing lung (and peripheral) congestion. As left ventricular filling pressure increases (⇑ pulmonary capillary wedge pressure; PCWP), lung congestion and interstitial edema develop, causing reductions in FVC and DL_{CO}, while FEV_1/FVC remains normal. Therefore, FVC and particularly DL_{CO} may decline with even moderate congestion, whereas an obstructive-like pattern (low FEV_1/FVC) may emerge with advanced congestion due to thickening of bronchial wall by edema and increased vascular volume, peribronchial edema, and vascular engorgement, as well as low radial distending forces on the bronchial wall due to low lung volumes and increased airway smooth muscle contractility elicited by neuro-humoral mechanisms. EILV: end-inspiratory lung volume; FRC: functional residual capacity; IRV: inspiratory reserve volume; ERV: expiratory reserve volume; IC: inspiratory capacity; and PAPm: mean pulmonary arterial pressure. Panel B reproduced with permission of the publisher.[1]

REFERENCES

1. Magnussen H, Canepa M, Zambito PE, Brusasco V, Meinertz T, Rosenkranz S. What can we learn from pulmonary function testing in heart failure?. Eur J Heart Fail. 2017;19(10):1222-1229. https://doi.org/10.1002/ejhf.946
2. Neder JA, Rocha A, Alencar MCN, Arbex F, Berton DC, Oliveira MF, et al. Current challenges in managing comorbid heart failure and COPD. Expert Rev Cardiovasc Ther. 2018;16(9):653-673. https://doi.org/10.1080/14779072.2018.1510319
3. Souza AS, Sperandio PA, Mazzuco A, Alencar MC, Arbex FF, Oliveira MF, et al. Influence of heart failure on resting lung volumes in patients with COPD. J Bras Pneumol. 2016;42(4):273-278. https://doi.org/10.1590/S1806-37562015000000290
4. Arbex FF, Alencar MC, Souza A, Mazzuco A, Sperandio PA, Rocha A, et al. Exercise Ventilation in COPD: Influence of Systolic Heart Failure. COPD. 2016;13(6):693-699. https://doi.org/10.1080/15412555.2016.1174985
5. Tanabe T, Rozycki HJ, Kanoh S, Rubin BK. Cardiac asthma: new insights into an old disease. Expert Rev Respir Med. 2012;6(6):705-714. https://doi.org/10.1586/ers.12.67
6. Neder JA, Berton DC, O'Donnell DE. Integrating measurements of pulmonary gas exchange to answer clinically relevant questions. J Bras Pneumol. 2020;46(1):e20200019. https://doi.org/10.1590/1806-3713/e20200019

Management of pneumonia and pleural effusion in children

Laura Menestrino Prestes[1], Miguel Ângelo Uflacker Lutz de Castro[1], Gabriela de Azevedo Bastian de Souza[1], Laura Gomes Boabaid de Barros[1], Marcelo Comerlato Scotta[2,3], Leonardo Araujo Pinto[2,3]

INTRODUCTION

Childhood pneumonia is a public health concern due to its high incidence and potential severity. It is one of the three most common causes of death in children younger than 5 years of age. This acute lung infection, caused mainly by viruses and bacteria, requires an understanding of its manifestations, treatment, and preventive measures. This article aims to review the criteria for diagnosis, hospitalization, and clinical approach, focusing on bacterial pneumonia and common complications.[1] Symptoms include fever, cough, tachypnea, thoracic retractions, crackles, and chest pain. It is difficult to distinguish clinically between bacterial and viral etiologies. One should consider bacterial pneumonia in children presenting with persistent or recurrent fever ≥ 38.5°C over the preceding 48 h with chest wall recession and tachypnea.[2] Differentiating pneumonia from conditions such as asthma and acute bronchiolitis is often a challenge in infants and preschoolers, with the presence of wheezing being a key differential indicator. Wheezing is not often associated with bacterial pneumonia. Common etiologic agents are also *Streptococcus pneumoniae* and *Staphylococcus aureus*.[1]

DIAGNOSIS AND SEVERITY MARKERS

The diagnosis of community-acquired pneumonia (CAP) may be based on clinical presentation. Therefore, chest radiography should not be routinely performed in outpatient settings. Radiography is often indicated in the presence of severity markers, need for hospitalization, or lack of improvement after 48-72 h of treatment.[1] Blood cultures are recommended for hospitalized CAP patients to identify the etiological agent along with swabs for viral detection. Additionally, nonspecific tests such as C-reactive protein levels, procalcitonin, and leukocyte count may suggest bacterial infection when values are extremely high, but have limited value in presuming the etiology of CAP. Finally, polymerase chain reaction can also be used in diagnosing etiological agents.[2]

Inability to drink/eat, incoercible vomiting, convulsions, central cyanosis, lethargy, and oxygen saturation < 90% are predictors of death and should be used as indicators for hospitalization. Moderate and large pleural effusions and multilobar infiltrates are also associated with severe disease.

RECOMMENDED MANAGEMENT

All children require pulse oximetry. In secondary care, children with oxygen saturation < 92% in room air require supplemental oxygen to maintain > 94% saturation. Oxygen can be administered via nasal cannulae. Intravenous fluid replacement may be required if hydration becomes compromised. Clinical trials have shown no benefit from physiotherapy.[3]

Oral antibiotics are safe and effective for children with CAP. Use of intravenous antibiotics in children is recommended if children are unable to tolerate oral fluids (because of vomiting) or have signs of septicemia or complicated pneumonia.

Amoxicillin is the first-line therapy for outpatients. Macrolides can be added at any age if there is no response to first-line therapy. Macrolides should be used if *Mycoplasma pneumoniae* or *Chlamydia pneumoniae* are suspected in atypical presentations or if disease is severe; in this case, an association with another agent is always needed. The first line of intravenous antibiotic therapy is ampicillin or penicillin G. Ampicillin-sulbactam or ceftriaxone may be recommended for severe pneumonia (Chart 1). Vancomycin may also be used in cases of suspected methicillin-resistant *Staphylococcus aureus*.

Complicated pneumonia is a severe illness characterized by local complications (parapneumonic effusion, empyema, necrotizing pneumonia, or lung abscess) or systemic complications (bacteremia). Complicated CAP should be suspected in any child with pneumonia not responding to appropriate antibiotic treatment within 48-72 h. Patients have initial imaging with chest radiography, and ultrasound can also be used to identify pleural fluid.

Complicated pneumonia should be treated with a prolonged course of intravenous antibiotics, and then oral antibiotics.[4] The initial choice of antibiotic is guided by local microbiological knowledge and by subsequent positive cultures, including cultures from pleural fluid.

Most patients may be treated by pleural drainage. Information from pleural space imaging and drainage should guide the decision on whether to administer intrapleural fibrinolytic agents. More extensive surgery (video-assisted thoracoscopic surgery) may be indicated in loculated empyemas.[5]

PREVENTION AND PROGNOSIS

Current treatment guidelines suggest several interventions to prevent CAP. These include frequent hand washing, avoiding tobacco smoke, promoting breastfeeding, reducing exposure to other children,

1. Centro Infant, Instituto de Pesquisas Biomédicas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
2. Programa de Pós-Graduação em Medicina – Pediatria, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre (RS) Brasil.
3. Serviço de Pediatria, Hospital Moinhos de Vento – HMV – Porto Alegre (RS) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

Chart 1. Overview of pneumonias: etiologic agents and treatment recommendations.

	Atypical pneumonia	Outpatient pneumonia[a]	Hospitalization due to pneumonia	Complicated pneumonia + pleural effusion[b]	ICU admission due to pneumonia
Possible common etiologic agents	***Mycoplasma pneumoniae***	***Streptococcus pneumoniae***	***Streptococcus pneumoniae*** **MSSA**	***Streptococcus pneumoniae*** **MSSA**	***Streptococcus pneumoniae*** **MRSA**
Antimicrobial treatment options	Azithromycin 10 mg/kg/day single dose for 5 days Clarithromycin 7.5 mg/kg/dose every 12 h for 10 days	<u>Age: from 2 months to 5 years</u> Amoxicillin 50 mg/kg/day every 8 or 12 h for 7 days <u>Age: > 5 years</u> Amoxicillin 50 mg/kg/day every 8 or 12 h for 7 days + Macrolide (erythromycin, clarithromycin, or azithromycin) on suspicion of atypical pneumonia for 7 days	<u>Age: > 2 months</u> Ampicillin or ampicillin-sulbactam 50 mg/kg/dose every 6 h	Cefuroxime i.v. 150 mg/kg divided into 4 doses OR Ceftriaxone i.v. 100 mg/kg divided into 2 doses OR Ampicillin-sulbactam 50 mg/kg/dose every 6 h	Cefuroxime i.v. 150 mg/kg divided into 4 doses OR Ceftriaxone i.v. 100 mg/kg divided into 2 doses OR Ampicillin-sulbactam 50 mg/kg/dose every 6 h MRSA treatment Vancomycin i.v. 15 mg/kg every 6-8 h

MSSA: methicillin-sensitive *Staphylococcus aureus*; and MRSA: methicillin-resistant *Staphylococcus aureus*. [a]Initial treatment is empirical, according to the patient's age group and local epidemiology. Reassessment is recommended within 48-72 h in all cases or earlier if there is clinical worsening. [b]Other interventions are simple drainage and video-assisted thoracoscopic surgery for complicated pleural effusion.

and immunization. Pneumococcal conjugate vaccines have been approved for the prevention of invasive pneumococcal disease in children and are highly effective in reducing disease against the included pneumococcal serotypes.

Several new interventions to prevent respiratory syncytial virus such as long-acting monoclonal antibodies and maternal vaccines potentially have a major impact on the epidemiology of pneumonia.[6] Children should also be vaccinated against other potential causes of pneumonia, including influenza, SARS-CoV-2, *Haemophilus influenzae* type B, pertussis, varicella, and measles.[3]

The clinical course of CAP can be long, especially in patients with necrotizing pneumonia, but complete recovery is the usual outcome.[4,5]

FINANCIAL SUPPORT

Leonardo A. Pinto is the recipient of a Research Productivity Grant from the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq; National Council for Scientific and Technological Development; Grant no. 309074/2022-3).

AUTHOR CONTRIBUTIONS

LMP, MAULC, GABS, and LGBB: literature search and drafting of the manuscript. MCC and LAP: drafting, reviewing, and editing the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Haq IJ, Battersby AC, Eastham K, McKean M. Community acquired pneumonia in children. BMJ. 2017;356:j686. https://doi.org/10.1136/bmj.j686
2. Nascimento-Carvalho CM. Community-acquired pneumonia among children: the latest evidence for an updated management. J Pediatr (Rio J). 2020;96 Suppl 1(Suppl 1):29-38. https://doi.org/10.1016/j.jped.2019.08.003
3. Smith DK, Kuckel DP, Recidoro AM. Community-Acquired Pneumonia in Children: Rapid Evidence Review. Am Fam Physician. 2021;104(6):618-625.
4. de Benedictis FM, Kerem E, Chang AB, Colin AA, Zar HJ, Bush A. Complicated pneumonia in children. Lancet. 2020;396(10253):786-798. https://doi.org/10.1016/S0140-6736(20)31550-6
5. Moral L, Reyes S, Toral T, Ballesta A, Cervantes E. Management of parapneumonic pleural effusion and empyema in children: A tale of two cities. Pediatr Pulmonol. 2022;57(10):2546-2548. https://doi.org/.1002/ppul.26055
6. Scotta MC, Stein RT. Current strategies and perspectives for active and passive immunization against Respiratory Syncytial Virus in childhood. J Pediatr (Rio J). 2023;99 Suppl 1(Suppl 1):S4-S11. https://doi.org/10.1016/j.jped.2022.10.004

J Bras Pneumol. 2023;49(6):e20230092
https://dx.doi.org/10.36416/1806-3756/e20230092

The role of *IL10* and *IL17* gene polymorphisms in treatment response in children and adolescents with severe asthma

Mariana Isadora Ribeiro Vieira[1], Mônica Versiani Nunes Pinheiro de Queiroz[3], Maria Borges Rabelo de Santana[2], Hatilla dos Santos Silva[2], Almirane Oliveira[2], Camila Alexandrina Viana Figueiredo[2], Eduardo Martín Tarazona Santos[4], Ryan dos Santos Costa[2], Laura Maria de Lima Belizário Facury Lasmar[1,2]

1. Programa de Pós-Graduação em Ciências da Saúde, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
2. Departamento de Pediatria, Faculdade de Medicina, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.
3. Programa de Pós-Graduação em Imunologia, Departamento de Biorregulação, Instituto de Ciências da Saúde, Universidade Federal da Bahia, Salvador (BA) Brasil.
4. Departamento de Genética, Ecologia e Evolução, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte (MG) Brasil.

Submitted: 17 April 2023.
Accepted: 18 October 2023.

Study carried out at the Universidade Federal de Minas Gerais, Belo Horizonte (MG) and the Universidade Federal da Bahia, Salvador (BA) Brasil.

ABSTRACT

Objective: To determine whether polymorphisms of the *IL10* and *IL17* genes are associated with severe asthma control and bronchodilator reversibility in children and adolescents with severe asthma. **Methods:** This was a cross-sectional study, nested within a prospective cohort study of patients with severe asthma. Two outcomes were evaluated: asthma control and bronchodilator reversibility. We extracted DNA from peripheral blood and genotyped three single nucleotide polymorphisms: rs3819024 and rs2275913 in the *IL17A* gene; and rs3024498 in the *IL10* gene. For the association analyses, we performed logistic regression in three genetic models (allelic, additive, and dominant). **Results:** The rs3024498 C allele in the *IL10* gene was associated with failure to achieve asthma control despite regular treatment (p = 0.02). However, the G allele of the *IL17A* rs3819024 polymorphism was associated with failure to respond to stimulation with a β_2 agonist. The rs2275913 polymorphism of the *IL17A* gene showed no relationship with asthma control or bronchodilator reversibility. **Conclusions:** In pediatric patients with severe asthma, the *IL10* polymorphism appears to be associated with failure to achieve clinical control, whereas the *IL17A* polymorphism appears to be associated with a worse bronchodilator response. Knowledge of the involvement of these polymorphisms opens future directions for pharmacogenetic studies and for the implementation of individualized therapeutic management of severe asthma in pediatric patients.

Keywords: Polymorphism, genetic; Interleukin-10; Interleukin-17; Asthma.

INTRODUCTION

Although severe asthma affects only approximately 2% of all children with asthma, it is associated with a high rate of morbidity.[1,2] The refractory form of severe asthma is characterized by continued poor control despite maximum doses of asthma controller medications and a focus on modifiable factors such as treatment adherence, exposure to allergens, and exposure to smoking. One major reason for that lack of control is probably the heterogeneous nature of the disease, the pathogenesis of which involves the interaction of environmental factors and individual variability, together with a complex genetic basis.[3]

The heterogeneity of severe asthma can be explained by distinct molecular phenotypes comprising cytokines unrelated to the classical Th2 lymphocyte pathway, such as IL-10 and IL-17.[4] By inhibiting the production of proinflammatory cytokines, IL-10 reduces allergic inflammation; its failure to respond to increasing doses of inhaled steroids in patients with severe asthma is likely related to poor clinical control.[5] In contrast, IL-17 stimulates the production of Th17 inflammatory cytokines, thus promoting airway inflammation.[6]

Polymorphisms in the *IL10* and *IL17* genes were described in a meta-analysis of pediatric patients of different ethnicities, although only the risk of asthma was assessed.[6,7] Polymorphisms of these cytokine genes might explain the difficulty in achieving clinical and functional control in patients with severe asthma. However, to our knowledge, there have been no studies associating genetic variants in *IL10* and *IL17* with clinical control in cases of severe asthma. Given that polymorphisms of these cytokine genes can be useful biomarkers for adjusting treatment regimens, the objective of the present study was to evaluate whether polymorphisms in the *IL10* and *IL17* genes were associated with severe asthma control and bronchodilator responsiveness in a sample of pediatric patients.

Correspondence to:
Mariana Isadora Ribeiro Vieira. Rua dos Aimorés, 1294/304, CEP 30140-071, Belo Horizonte, MG, Brasil.
Tel.: 55 31 98404-4140. E-mail: mirvieira18@gmail.com
Financial support: None.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

METHODS

Study design, study participants, and clinical characteristics

This was a cross-sectional study, nested within a prospective cohort study of patients with severe asthma,[8] carried out between 2021 and 2022 at the Multidisciplinary Center for Difficult-to-Control Asthma and the Institute of Biological Sciences of the Federal University of Minas Gerais, located in the city of Belo Horizonte, Brazil. The study was conducted in collaboration with the Laboratory of Immunopharmacology and Molecular Biology at the Health Sciences Institute of the Federal University of Bahia, located in the city of Salvador, Brazil. We selected patients who had severe asthma (defined as asthma confirmed by an objective measure of lung function), who had good adherence to treatment, and who, despite elimination or minimization of factors associated with poor disease control, required high doses of inhaled corticosteroids (ICS—budesonide ≥ 1,600 µg or equivalent) and a second controller medication—long-acting β_2 agonists (LABAs), long-acting muscarinic antagonists, leukotriene receptor antagonists, or any combination of the three—or oral corticosteroids ≥ 50% of the previous year in order to maintain disease control, as well as those in whom the disease remained uncontrolled because of its intrinsic severity.[9-11] Given that severe refractory asthma is an uncommon phenotype, sampling was convenience-based. We performed a posteriori sample size calculation using the free, Web-based, open-source program OpenEpi, version 3.01, and found that, for a statistical power of 80%, a sample size of 34 per group was required.[12]

Patients who were first-degree relatives (e.g., siblings) were excluded, as were those with other chronic lung diseases. Healthy individuals were not included in the present study.

Clinical characteristics such as age (in years), age at initiation of treatment with ICS (in months), maternal smoking during pregnancy, reported passive smoking, previous ICU admission for asthma, severe exacerbations in the last 12 months, weight (in kg), height (in cm), and BMI (in kg/m^2) were assessed.

The dose of ICS was evaluated in terms of its equivalence with that of budesonide. The ICS adherence rate was considered optimized if it was above 80%. It was calculated as the proportion of the total recommended dose, by checking the dose counter of a pressurized metered-dose inhaler or by counting the capsules that had been used in a dry-powder inhaler.[9] Some patients were using dry-powder inhalers that delivered a combination of budesonide and formoterol (Alenia; *Aché Laboratórios Farmacêuticos S/A*, Guarulhos, Brazil), whereas others were using pressurized metered-dose inhalers that delivered a combination of fluticasone and salmeterol (Seretide; GlaxoSmithKline, Stevenage, United Kingdom) or omalizumab only (Xolair; *Novartis Biociências S/A.*, São Paulo, Brazil). The use of leukotriene receptor antagonists and biologic agents was also evaluated.

The diagnosis of allergic rhinitis was made on the basis of patient clinical history and a nasal symptom questionnaire, as well as a positive skin prick test for aeroallergens.[9] In addition to rhinitis, other comorbidities were considered: atopic dermatitis, mouth breathing, gastroesophageal reflux disease, behavioral disorders, and emotional disorders.[10]

Procedures

The level of asthma control was assessed by applying the GINA criteria.[10] Patients were asked whether in the last four weeks they had experienced symptoms of asthma during the day more than twice a week; woken up at night because of asthma; used a short-acting β_2 agonist (SABA) to relieve asthma symptoms more than twice a week; and had any activity limitations because of asthma. Controlled asthma was defined as a negative answer to all four questions, whereas uncontrolled asthma was defined as an affirmative answer to any one of the four questions. On the basis of their answers, patients were divided into two groups: controlled severe asthma and uncontrolled severe asthma.

Skin prick tests were performed and were considered positive if the wheal was at least 3 mm larger than that of the negative control.[13] We tested the following allergens, all obtained from the same supplier (Imunotec, São Paulo, Brazil): *Dermatophagoides pteronyssinus*; *Dermatophagoides farinae*; *Blomia tropicalis*; dog and cat dander; *Aspergillus* sp.; *Penicillium* sp.; *Periplaneta americana*; and *Cladosporium* sp. Peripheral blood eosinophils were also measured, as were serum cytokine levels. However, the latter were found to be no higher than the lower limit of detection.

All patients underwent pulmonary function tests, which were performed with a KoKo spirometer (KoKo PFT, Longmont, CO, USA) and in accordance with the recommendations of the American Thoracic Society.[14] FEV_1, FVC, and the FEV_1/FVC ratio were evaluated before and after administration of 400 µg of albuterol by pressurized metered-dose inhaler. Significant postbronchodilator variation, or bronchodilator reversibility, was defined as a 200 mL or 12% increase in FEV_1.[15]

Genomic DNA extraction, genotyping, and in silico *analysis*

Peripheral blood samples were collected under vacuum in 10-mL tubes containing the anticoagulant ethylenediaminetetraacetic acid (Vacutainer; Becton Dickinson, Sparks, MD, USA) and were centrifuged in a Kasvi centrifuge (K14-0815A; Kasvi, São José dos Pinhais, Brazil) at 3,000 rpm for 10 min at 4°C. The plasma and buffy coat were separated, after which they were placed in Eppendorf tubes and stored at −30°C. For DNA extraction, we employed a commercial blood kit (Gentra Puregene; QIAGEN, Hilden, Germany). All

genotyped samples were standardized at a concentration of 5 ng/μL and stored at −30°C until use.

On the basis of previous association studies of asthma,[16-19] we selected three genotyped single nucleotide polymorphisms (SNPs) that have been associated with asthma: rs3819024 and rs2275913 in the *IL17A* gene; and rs3024498 in the *IL10* gene. Genotyping was performed with TaqMan probe-based 5'-nuclease assays (Applied Biosystems, Foster City, CA, USA) on the QuantStudio 12K Flex real-time polymerase chain reaction system (Applied Biosystems). In our analysis, we included only SNPs with a call rate of at least 93%. As negative controls, we used blank wells to evaluate nonspecific amplification.

Information regarding the function of each single nucleotide variant was obtained from the U.S. National Center for Biotechnology Information website (www.ncbi.nlm.nih.gov). Additionally, RegulomeDB was used in order to identify potential regulatory and functional variants through computational predictions and manual annotations.[20] The database assigns a score ranging from 1 to 6, where lower scores indicate increasing evidence of a variant being located in a functional region.[20]

HaploReg (Broad Institute, Cambridge, MA, USA) is a tool that allows researchers to explore annotations of the noncoding genome at variants on haplotype blocks. It specifically focuses on identifying candidate regulatory single nucleotide variants at disease-associated loci. HaploReg is designed to assist researchers in developing mechanistic hypotheses regarding the impact of noncoding variants on clinical phenotypes and normal variation.[21]

The U.S. National Institutes of Health Genotype-Tissue Expression (GTEx) Project (www.gtexportal.org) has provided valuable insights into the association between gene expression, genetic variation, and other molecular phenotypes across various human tissues.[22] Through expression quantitative trait loci mapping, we can effectively investigate the genetic factors responsible for changes in gene expression. Using this tool, we extracted information specifically related to the influence of variants within the gene of interest on its expression in whole blood samples.

Statistical analysis

The distribution of continuous variables was analyzed by using the Shapiro-Wilk test. Data are expressed as mean ± standard deviation, as median [interquartile range], or as absolute and relative frequencies, depending on the type of variable. For comparisons between groups (patients vs. controls or genotype vs. genotype), we used the unpaired Student's t-test or the Mann-Whitney test, as appropriate. Values of $p < 0.05$ were considered significant.

Association analyses were performed by logistic regression in three genetic models (allelic, additive, and dominant), adjusted for the covariates sex and age, using PLINK software, version 1.9.[23] To reduce the chance of associations with false-positive values of p,[23] only the SNP associations with values of $p < 0.05$, which were revalidated by permutation procedures, were considered statistically significant.

The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais (Protocol no. 4.048.940). Written informed consent was obtained from all participants or their legal guardians.

RESULTS

Initially, 62 patients with severe asthma were eligible. However, 6 were excluded because they were first-degree relatives of other selected patients. Therefore, the sample comprised 56 patients with severe asthma: 19 in the controlled asthma group and 37 in the uncontrolled asthma group. The demographic, clinical, and functional characteristics of the study population are shown in Table 1.

We observed no significant difference between the two severe asthma groups in terms of functional variables and biological markers, showing that these markers do not discriminate between controlled and uncontrolled asthma. There was no difference between the two groups in terms of the BMI. However, the mean height was lower in the uncontrolled asthma group. Both groups of patients used high doses of ICS in combination with high doses of other controller medications, and there was no significant difference between the two groups regarding doses or treatment adherence.

Table 2 presents the characteristics of the SNPs studied. The minor allele frequency was greater than 10% for all three of the SNPs genotyped. No variants were excluded by the Hardy-Weinberg equilibrium or on the basis of a low call rate. The *IL17A* variants were in an untranslated region 2 kb upstream of the gene, and the *IL10* variant was in the 3'-untranslated region.

As can be seen in Table 3, patients with at least one rs3024498 C allele in the *IL10* gene were found to be at a greater risk of having uncontrolled asthma despite regular treatment. Neither of the two other variants was associated with failure to control severe asthma in any of the genetic models tested.

Severe asthma patients with the AG or GG genotype of rs3819024 had a lower bronchodilator response than did those with the AA genotype (Figure 1). Neither of the two other variants was associated with a lack of bronchodilator reversibility in any of the genetic models tested. The rs2275913 SNP of the *IL17A* gene showed no relationship with disease control or bronchodilator reversibility. Using the GTEx browser we found that the TC and CC genotypes of rs3024498 had higher expression of IL-10 in whole blood samples than did the TT genotype (Figure 2; $p = 0.000053$).

DISCUSSION

In pediatric patients, airway inflammation related to the allergic process is typically eosinophilic and orchestrated by Th2 cells. However, eosinophilia is

Table 1. Demographic, clinical, and functional characteristics of the study participants.[a]

Variable	Group		p
	CSA (n = 19)	USA (n = 37)	
Age, years	14.6 ± 3.74	12.2 ± 5.48	0.06
Male sex	10 (52.6)	18 (48.6)	0.89
Age at initiation of ICS, months (median)	34	24	0.56
Maternal smoking during pregnancy	1 (5.3)	3 (8.1)	0.69
Reported passive smoking	6 (31.6)	17 (45.9)	0.30
Previous ICU admission for asthma	7 (36.8)	9 (24.3)	0.27
Severe exacerbations in the last 12 months	1 (5.3)	6 (16.2)	0.23
Comorbidities			
Allergic rhinitis	9 (47.4)	15 (40.5)	0.69
Rhinitis + ≥ 1 other comorbidity	10 (52.6)	22 (59.5)	0.69
Weight, kg	51.00	42.15	0.027
Height, cm	164.0	147.4	0.003
BMI, kg/m^2	20.8	19.0	0.37
Medications			0.44
ICS dose,[b] µg:	800 [800-1,200]		
associated with an LABA or other controller medication		800 [800-1,600]	
Measured adherence rate > 80%	9 (47.4)	22 (59.5)	0.25
Positive skin prick test	19 (100.0)	18 (81.8)	0.05
Peripheral blood eosinophils, %	8.3 [5.8-12.1]	7.4 [4.0-10.5]	0.41
Baseline spirometry parameters			
Pre-BD FEV_1, mL	2.82 [2.13-3.22]	2.57 [1.74-3.11]	0.68
Pre-BD FEV_1, %	86.0 [79.8-97.5]	89.5 [77.5-101.2]	0.49
FEV_1/FVC ratio	82.0 [76.5-86.5]	82.0 [79.15-88.5]	0.73
Post-BD FEV_1, mL	2.88 [2.35-3.6]	2.74 [1.96-3.26]	0.59
Post-BD FEV_1, %	89.0 [85.5-101.5]	94.0 [84-103.5]	0.49

CSA: controlled severe asthma; USA: uncontrolled severe asthma; LABA: long-acting β_2 agonist; ICS: inhaled corticosteroid(s); and BD: bronchodilator. [a]Values expressed as n (%), mean ± SD, or median [IQR], except where otherwise indicated. [b]Dose equivalent to that of budesonide.

not synonymous with activation of a Th2-mediated response.[4,24] This was demonstrated in a study of pediatric patients with severe asthma that was refractory to treatment, in which no significant levels of IL-4, IL-5, or IL-13 were observed in sputum samples or endobronchial biopsy samples.[25] Therefore, it remains unclear which immune mechanism would explain the conversion of eosinophilia into asthma and the severity phenotype. In the present study, we demonstrated that polymorphisms in the *IL10* and *IL17* genes were associated with failure to achieve asthma control and with the bronchodilator response in patients with severe asthma. Poor asthma control was associated with the presence of at least one C allele of the *IL10* rs3024498 polymorphism in patients under regular treatment with high doses of ICS associated with LABAs or other controller medications. It is known that one of the objectives of asthma treatment is to achieve symptom control with the lowest possible dose of inhaled medication.

On the basis of the data provided by the GTEx Project, individuals with at least one C allele of the *IL10* rs3024498 polymorphism show increased expression of IL-10 in the blood. Although we were unable to measure IL-10 levels in our population, Rogers et al.[26] showed higher IL-10 levels in children with uncontrolled asthma than in those with controlled asthma. The variant form of this gene likely contributes to this disparity.[26]

In view of the fact that high doses of ICS have major adverse effects, the knowledge that a lack of asthma control might be associated with the rs3024498 polymorphism in the *IL10* gene could be used in order to guide medical management, thus minimizing the risks associated with the continuous use of ICS and progressive increases in the dosage.

To our knowledge, there have been no studies associating the *IL10* rs3024498 polymorphism with failure to control pediatric asthma. However, this polymorphism has been reported to be associated with various other clinical conditions accompanied by an exuberant inflammatory process, such as systemic lupus erythematosus, rheumatoid arthritis, and chronic hepatitis.[27,28] In addition, other *IL10* polymorphisms (rs1800896, rs1800871, rs302109, rs1800872, and rs3024491) have been associated with pediatric asthma.[7,29]

In assessing the bronchodilator response, we found that patients with the AA homozygous genotype of rs3819024 (*IL17A*) were more likely to respond to the acute stimulation of an SABA than were those with the AG or GG genotype. Although we evaluated the response to an SABA, it should be borne in mind that

Table 2. Characteristics of the polymorphisms studied.

SNP	Gene	Chromosome	Position	A1/A2[a]	MAF	Functional annotation	RegulomeDB	HaploReg
rs3024498	*IL10*	1	206768184	C/T	0.1429	3'-untranslated variant	1f	Enhancer histone marks/ Dnase
rs3819024	*IL17A*	6	52185988	G/A	0.2987	2-kb upstream variant	1f	Enhancer histone marks
rs2275913	*IL17A*	6	52186235	A/G	0.2208	2-kb upstream variant	1f	Enhancer histone marks

SNP: single nucleotide polymorphism; and MAF: minor allele frequency. [a]The first is the alternative allele, and the second is the reference allele (1/2).

Table 3. Association of *IL10* and *IL17* gene variants with asthma control[a] in children and adolescents with severe asthma.[b]

Variant	Genotype	Group		Model	OR	95% CI	p	PPerm
		CSA (n = 19)	USA (n = 37)					
rs3024498 (*IL10*)	TT	17 (89.5)	26 (70.3)	Allelic	4.2	0.90-19.55	0.08	0.12
	CT	2 (10.5)	8 (21.6)	Additive	5.9	0.95-36.84	0.05	0.03
	CC	0 (0.0)	3 (8.1)	Dominant	6.9	1.003-47.9	0.04	0.02
rs3819024 (*IL17*)	AA	9 (47.4)	18 (48.6)	Allelic	0.8	0.38-1.99	0.83	0.92
	AG	7 (36.8)	15 (40.5)	Additive	0.6	0.27-1.56	0.33	0.70
	GG	3 (15.8)	4 (10.8)	Dominant	0.6	0.18-2.12	0.44	0.57
rs2275913 (*IL17*)	GG	13 (68.4)	18 (48.6)	Allelic	2.4	0.88-6.55	0.11	0.11
	GA	6 (31.6)	15 (40.5)	Additive	2.1	0.74-6.41	0.16	0.20
	AA	0 (0.0)	4 (10.8)	Dominant	2.0	0.60-6.82	0.25	0.29

CSA: controlled severe asthma; USA: uncontrolled severe asthma; and PPerm: permutation p value. [a]In accordance with the GINA criteria. [b]Values expressed as n (%), except where otherwise indicated.

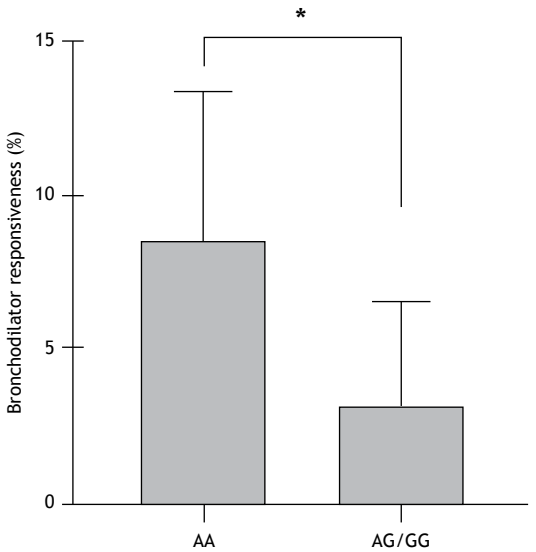


Figure 1. Bronchodilator responsiveness of rs3819024 genotypes. Note: Comparison of median percent change in percent predicted FEV_1 after bronchodilator use, by rs3819024 genotype. Asthma patients with the AG or GG genotype showed less bronchodilator responsiveness than did those with the AA genotype ($p < 0.05$; Mann-Whitney test).

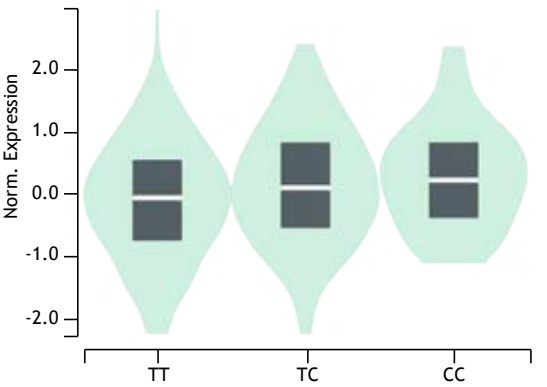


Figure 2. IL-10 expression for rs3024498 in whole blood samples, as assessed by the U.S. National Institutes of Health Genotype-Tissue Expression Project. Note: The TC and CC genotypes of rs3024498 have higher expression of IL-10 in whole blood samples than does the TT genotype ($p = 0.000053$).

formoterol, despite being an LABA and recommended in all severe asthma scenarios, has an onset of action similar to that of albuterol.[10] This is consistent with the findings of studies indicating that IL-17A acts directly on the airway smooth muscle, increasing contractility.[4,30] In clinical practice, blocking *IL17* signaling might be an attractive target for treating asthma with a Th17 phenotype.[4]

Although the specific effect of the rs3819024 polymorphism on IL-17A expression remains unknown, it is plausible that this variant may enhance the production

of this cytokine. This assumption is supported by its 2-kb upstream location with high regulatory potential, as indicated by a score of 1f in the RegulomeDB database, with the potential to impact the interaction with histones in the promoter (H3K4me3) and enhancer (H3K4me1) regions of Th17 lymphocytes, as described in HaploReg.

It is noteworthy that poor symptom control is not always attributable to poor adherence to treatment with ICS and LABAs or other controller medications. In our population, the treatment adherence rate was good in the controlled asthma and uncontrolled asthma groups, with no significant difference between the two groups. However, the phenotypic expression depends on the interaction of environmental factors and the genetic predisposition of an individual, assuming that genes do not operate in isolation but rather within their environment (which includes other genes around them), which can modify and even completely reverse their effects.[3] Therefore, given the high cost for society as a whole, studies that generate evidence from phenotyping, endotyping, and genotyping should be encouraged in order to identify the target patients and expend resources more rationally, as has been done in other chronic diseases.

Our study has some limitations. One is the small sample size, which is attributable to the fact that refractory severe asthma is an uncommon phenotype. The sample size calculation was carried out a posteriori with OpenEpi and showed that, for the study outcomes, with a statistical power of 80%, the minimum sample size would be 34 per group.[12] Our patients were selected from a cohort of patients who had a well-established diagnosis of severe asthma and who were under regular long-term follow-up, in which several methods were used in order to quantify adherence, minimize exposure to allergens, and manage comorbidities, thus limiting our sample size. Therefore, there is a need for studies involving larger samples of patients in order to replicate our findings and identify other genes that may explain the lack of disease control in patients with severe asthma. Future studies should also be carried out with the objective of analyzing the immunological profile, including other cytokines, which will help to understand the complex and heterogeneous pathophysiology of severe asthma. Another limitation of the present study is the lack of quantification of IL-10 and IL-17. This was due to the fact that the samples went through thermal variability, which could have denatured the cytokine proteins.

In conclusion, polymorphisms of the *IL10* and *IL17* genes appear to be involved in complex modulation pathways related to a lack of control and bronchodilator response in treatment-refractory severe asthma in children and adolescents. Functional studies should be carried out to characterize the molecular impact of such variants, which could facilitate the implementation of personalized treatment and management of asthma.

ACKNOWLEDGMENTS

We wish to thank all of the patients who volunteered to participate in this study, as well as their relatives. We also express our special thanks to Diego Menezes, a technician at the Genetics Laboratory of the Federal University of Minas Gerais Institute of Biological Sciences, for his contribution to the initial processing of the samples.

AUTHOR CONTRIBUTIONS

MIRV: investigation, methodology, project administration, and writing of the original draft. LMLBFL and MVNPQ: conceptualization, data curation, formal analysis, investigation, methodology, resources, supervision, writing of the original draft, and reviewing and editing of the manuscript. RSC: conceptualization, formal analysis, investigation, methodology, resources, supervision, writing of the original draft, and reviewing and editing of the manuscript. MBRS, HSS, AO, and CAVF: methodology, formal analysis, writing of the original draft, and reviewing and editing of the manuscript. EMTS: data curation, investigation, methodology, formal analysis, validation, writing of the original draft, and reviewing and editing of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Busse WW. Definition and impact. In: Chung KF, Israel E, Gibson PG. (eds.). Severe asthma (ERS Monograph). Sheffield: European Respiratory Society; 2019; p. 1-15. https://doi.org/10.1183/2312508X.10022418
2. Kuruvilla ME, Lee FE, Lee GB. Understanding Asthma Phenotypes, Endotypes, and Mechanisms of Disease. Clin Rev Allergy Immunol. 2019;56(2):219-233. https://doi.org/10.1007/s12016-018-8712-1
3. Bush A. Genes in their environment: how can we read the riddles?. J Pediatr (Rio J). 2008;84(3):185-188. https://doi.org/10.2223/JPED.1789
4. Ramakrishnan RK, Al Heialy S, Hamid Q. Role of IL-17 in asthma pathogenesis and its implications for the clinic. Expert Rev Respir Med. 2019;13(11):1057-1068. https://doi.org/10.1080/17476348.2019.1666002
5. Gupta A, Dimeloe S, Richards DF, Chambers ES, Black C, Urry Z, et al. Defective IL-10 expression and in vitro steroid-induced IL-17A in paediatric severe therapy-resistant asthma. Thorax. 2014;69(6):508-515. https://doi.org/10.1136/thoraxjnl-2013-203421
6. Wang YH, Wills-Karp M. The potential role of interleukin-17 in severe asthma. Curr Allergy Asthma Rep. 2011;11(5):388-394. https://doi.org/10.1007/s11882-011-0210-y
7. Huang ZY, Cheng BJ, Wan Y, Zhou C. Meta-analysis of the IL-10 promoter polymorphisms and pediatric asthma susceptibility. Genet Mol Res. 2016;15(2):10.4238/gmr.15028320. https://doi.org/10.4238/gmr.15028320
8. Versiani Nunes Pinheiro de Queiroz M, Gonçalves Alvim C, Cruz ÁA, de Lima Belizário Facury Lasmar LM. Lung function in severe pediatric asthma: a longitudinal study in children and adolescents in

Brazil. Clin Transl Allergy. 2017;7:48. https://doi.org/10.1186/s13601-017-0183-6

9. Carvalho-Pinto RM, Cançado JED, Pizzichini MMM, Fiterman J, Rubin AS, Cerci Neto A, et al. 2021 Brazilian Thoracic Association recommendations for the management of severe asthma. J Bras Pneumol. 2021;47(6):e20210273. https://doi.org/10.36416/1806-3756/e20210273
10. Global Initiative for Asthma (GINA) [homepage on the Internet]. Bethesda: GINA; c2022 [cited 2022 May 1]. Global Strategy for Asthma Management and Prevention (Updated 2022). [Adobe Acrobat document, 225p.]. Available from: https://ginasthma.org/wp content/uploads/2022/05/GINA Main Report 2022 FINAL 22 05 03 WMS.pdf
11. Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma [published correction appears in Eur Respir J. 2014 Apr;43(4):1216. Dosage error in article text] [published correction appears in Eur Respir J. 2018 Jul 27;52(1):] [published correction appears in Eur Respir J. 2022 Jun 9;59(6):]. Eur Respir J. 2014;43(2):343-373. https://doi.org/10.1183/09031936.00202013
12. Dean AG, Sullivan KM, Soe MM. OpenEpi: Open Source Epidemiologic Statistics for Public Health, Version. www.OpenEpi.com [updated 2013 Apr 6]. Available from: https://www.openepi.com
13. Bousquet J, Heinzerling L, Bachert C, Papadopoulos NG, Bousquet PJ, Burney PG, et al. Practical guide to skin prick tests in allergy to aeroallergens. Allergy. 2012;67(1):18-24. https://doi.org/10.1111/j.1398-9995.2011.02728.x
14. Beydon N, Davis SD, Lombardi E, Allen JL, Arets HGM, Aurora P, et al. An official American Thoracic Society/European Respiratory Society statement: pulmonary function testing in preschool children. Am J Respir Crit Care Med. 2007;175(12):1304-1345. https://doi.org/10.1164/rccm.200605-642ST
15. Graham BL, Steenbruggen I, Miller MR, Barjaktarevic IZ, Cooper BG, Hall GL, et al. Standardization of Spirometry 2019 Update. An Official American Thoracic Society and European Respiratory Society Technical Statement. Am J Respir Crit Care Med. 2019;200(8):e70-e88. https://doi.org/10.1164/rccm.201908-1590ST
16. Holster A, Teräsjärvi J, Lauhkonen E, Törmänen S, Helminen M, Koponen P, et al. IL-17A gene polymorphism rs2275913 is associated with the development of asthma after bronchiolitis in infancy. Allergol Int. 2018;67(1):109-113. https://doi.org/10.1016/j.alit.2017.05.010
17. Maalmi H, Beraies A, Charad R, Ammar J, Hamzaoui K, Hamzaoui A. IL-17A and IL-17F genes variants and susceptibility to childhood asthma in Tunisia. J Asthma. 2014;51(4):348-354. https://doi.org/10.3109/02770903.2013.876647
18. Chen J, Deng Y, Zhao J, Luo Z, Peng W, Yang J, et al. The polymorphism of IL-17 G-152A was associated with childhood asthma and bacterial colonization of the hypopharynx in bronchiolitis. J Clin Immunol. 2010;30(4):539-545. https://doi.org/10.1007/s10875-010-9391-8
19. Figueiredo CA, Barreto ML, Alcantara-Neves NM, Rodrigues LC, Cooper PJ, Cruz AA, et al. Coassociations between IL10 polymorphisms, IL-10 production, helminth infection, and asthma/wheeze in an urban tropical population in Brazil [published correction appears in J Allergy Clin Immunol. 2013 Oct;132(4):1015]. J Allergy Clin Immunol. 2013;131(6):1683-1690. https://doi.org/10.1016/j.jaci.2012.10.043
20. Boyle AP, Hong EL, Hariharan M, Cheng Y, Schaub MA, Kasowski M, et al. Annotation of functional variation in personal genomes using RegulomeDB. Genome Res. 2012;22(9):1790-1797. https://doi.org/10.1101/gr.137323.112
21. Ward LD, Kellis M. HaploReg: a resource for exploring chromatin states, conservation, and regulatory motif alterations within sets of genetically linked variants. Nucleic Acids Res. 2012;40(Database issue):D930-D934. https://doi.org/10.1093/nar/gkr917
22. GTEx Consortium. The Genotype-Tissue Expression (GTEx) project. Nat Genet. 2013;45(6):580-585. https://doi.org/10.1038/ng.2653
23. Purcell S, Neale B, Todd-Brown K, Thomas L, Ferreira MAR, Bender D, et al. PLINK: a tool set for whole-genome association and population-based linkage analyses. Am J Hum Genet. 2007;81(3):559-575. https://doi.org/10.1086/519795
24. Woodruff PG, Modrek B, Choy DF, Jia G, Abbas AR, Ellwanger A, et al. T-helper type 2-driven inflammation defines major subphenotypes of asthma [published correction appears in Am J Respir Crit Care Med. 2009 Oct 15;180(8):796]. Am J Respir Crit Care Med. 2009;180(5):388-395. https://doi.org/10.1164/rccm.200903-0392OC
25. Bossley CJ, Fleming L, Gupta A, Regamey N, Frith J, Oates T, et al. Pediatric severe asthma is characterized by eosinophilia and remodeling without T(H)2 cytokines. J Allergy Clin Immunol. 2012;129(4):974-82.e13. https://doi.org/10.1016/j.jaci.2012.01.059
26. Rogers VE, Bollinger ME, Tulapurkar ME, Zhu S, Hasday JD, Pereira KD, et al. Inflammation and asthma control in children with comorbid obstructive sleep apnea. Pediatr Pulmonol. 2018;53(9):1200-1207. https://doi.org/10.1002/ppul.24074
27. Lv TT, Wu J, Li J, Zhang TP, Yang XK, Xiang N, et al. Association of interleukin-10 gene single nucleotide polymorphisms with susceptibility to systemic lupus erythematosus in a Chinese population. Gene. 2018;642:549-554. https://doi.org/10.1016/j.gene.2017.11.072
28. Świątek-Kościelna B, Kałużna E, Strauss E, Januszkiewicz-Lewandowska D, Bereszyńska I, Wysocki J, et al. Interleukin 10 gene single nucleotide polymorphisms in Polish patients with chronic hepatitis C: Analysis of association with severity of disease and treatment outcome. Hum Immunol. 2017;78(2):192-200. https://doi.org/10.1016/j.humimm.2016.10.015
29. Mocellin M, de Azeredo Leitão LA, de Araújo PD, Jones MH, Stein RT, Pitrez PM, et al. Association between interleukin-10 polymorphisms and CD4+CD25+FOXP3+ T cells in asthmatic children. J Pediatr (Rio J). 2021;97(5):546-551. https://doi.org/10.1016/j.jped.2020.11.008
30. Kudo M, Melton AC, Chen C, Engler MB, Huang KE, Ren X, et al. IL-17A produced by αβ T cells drives airway hyper-responsiveness in mice and enhances mouse and human airway smooth muscle contraction. Nat Med. 2012;18(4):547-554. https://doi.org/10.1038/nm.2684

J Bras Pneumol. 2023;49(6):e20230300
https://dx.doi.org/10.36416/1806-3756/e20230300

ORIGINAL ARTICLE

Detection of subsolid nodules on chest CT scans during the COVID-19 pandemic

Ana Paula Zanardo[1,2], Vicente Bohrer Brentano[2], Rafael Domingos Grando[1,2], Rafael Ramos Rambo[1,2], Felipe Teixeira Hertz[2], Luís Carlos Anflor Júnior[2,3], Jônatas Fávero Prietto dos Santos[1,2], Gabriela Schneider Galvão[1,2], Cristiano Feijó Andrade[4,5]

1. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.
2. Departamento de Radiologia, Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.
3. Departamento de Medicina Interna, Universidade Federal de Ciências da Saúde de Porto Alegre, Porto Alegre (RS) Brasil.
4. Serviço de Cirurgia Torácica e Pulmonar, Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.
5. Serviço de Cirurgia Torácica e Pulmonar, Hospital de Clínicas de Porto Alegre, Porto Alegre (RS) Brasil.

Submitted: 15 September 2023.
Accepted: 9 October 2023.

Study carried out under the auspices of the Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul, Porto Alegre (RS) Brasil.

ABSTRACT

Objective: To investigate the detection of subsolid nodules (SSNs) on chest CT scans of outpatients before and during the COVID-19 pandemic, as well as to correlate the imaging findings with epidemiological data. We hypothesized that (pre)malignant nonsolid nodules were underdiagnosed during the COVID-19 pandemic because of an overlap of imaging findings between SSNs and COVID-19 pneumonia. **Methods:** This was a retrospective study including all chest CT scans performed in adult outpatients (> 18 years of age) in September of 2019 (i.e., before the COVID-19 pandemic) and in September of 2020 (i.e., during the COVID-19 pandemic). The images were reviewed by a thoracic radiologist, and epidemiological data were collected from patient-filled questionnaires and clinical referrals. Regression models were used in order to control for confounding factors. **Results:** A total of 650 and 760 chest CT scans were reviewed for the 2019 and 2020 samples, respectively. SSNs were found in 10.6% of the patients in the 2019 sample and in 7.9% of those in the 2020 sample ($p = 0.10$). Multiple SSNs were found in 23 and 11 of the patients in the 2019 and 2020 samples, respectively. Women constituted the majority of the study population. The mean age was 62.8 ± 14.8 years in the 2019 sample and 59.5 ± 15.1 years in the 2020 sample ($p < 0.01$). COVID-19 accounted for 24% of all referrals for CT examination in 2020. **Conclusions:** Fewer SSNs were detected on chest CT scans of outpatients during the COVID-19 pandemic than before the pandemic, although the difference was not significant. In addition to COVID-19, the major difference between the 2019 and 2020 samples was the younger age in the 2020 sample. We can assume that fewer SSNs will be detected in a population with a higher proportion of COVID-19 suspicion or diagnosis.

Keywords: Solitary pulmonary nodule; Multiple pulmonary nodules; Lung neoplasms/diagnostic imaging; Tomography, X-ray computed; COVID-19.

INTRODUCTION

Subsolid nodules (SSNs) are common findings in chest CT scans and represent a subset of pulmonary nodules that may have proliferative potential and should be monitored when persistent. They include ground-glass nodules (GGNs) and part-solid nodules (PSNs).[1,2]

In a study of CT screening for lung cancer,[3] persistent SSNs accounted for 19% of all positive results, the malignancy rate being higher for SSNs than for solid nodules of the same size.

In recent years, there has been an increase in the detection of all types of lung nodules as a result of the widespread availability of CT scanners, advances in CT technology, positive results of lung cancer screening programs,[4,5] and increased CT utilization in clinical practice.[6]

Chest CT is a fast, noninvasive method for evaluating respiratory diseases, widely used for the evaluation of pneumonia during the COVID-19 pandemic.[7] Because numerous imaging findings have been reported in association with COVID-19, the Radiological Society of North America published in March of 2020 an expert consensus document stating that COVID-19 pneumonia typically presents with multifocal, rounded ground-glass opacities with or without consolidation and septal thickening.[8]

The objective of the present study was to investigate whether the overlap of imaging findings between SSNs and COVID-19[9] could affect the detection of GGNs and PSNs on chest CT scans.

METHODS

This was a retrospective study including all chest CT scans performed in September of 2019 and in September of 2020 in the radiology department of a tertiary care hospital in southern Brazil. The study was approved by the institutional review board of the hospital (Protocol no. 4.260.736, September 5, 2020), and the requirement for

Correspondence to:
Ana Paula Zanardo. Programa de Pós-Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul, Rua Ramiro Barcelos, 2400, CEP 90035-003, Porto Alegre, RS, Brasil.
Tel.: 55 51 3314-5221. E-mail: zanardoap@gmail.com
Financial support: None.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

written informed consent was waived because of the noninterventional, retrospective nature of the study.

Inclusion criteria were being > 18 years of age and having undergone CT in accordance with a standardized chest CT protocol; exclusion criteria were being < 18 years of age and having undergone CT in accordance with other protocols (e.g., cardiac CT and radiation therapy planning scans). Emergency room patients and inpatients were not included in the evaluation, in order to avoid nosocomial pneumonia and other hospital-acquired complications that could add confounding factors to the study.

All CT images were reviewed by a thoracic radiologist who had 10 years of experience and who had access to the epidemiological data, which were collected from patient-filled questionnaires and clinical referrals. All chest CT scans were obtained with a 16-slice or a 256-slice multidetector scanner (SOMATOM Emotion 16; Siemens Healthineers, Forcheim, Germany and SOMATOM Drive 256; Siemens Healthineers, respectively) at end inspiration, with or without contrast enhancement, with the patients in the supine position. Although most of the CT examinations were standard-dose HRCT scans of the chest, some were contrast-enhanced CT scans, low-dose CT scans, or CT pulmonary angiography scans. Image data sets were reconstructed with 1-mm slice thickness and increments of 0.7 mm and 0.5 mm, with the use of soft-tissue and sharp kernels and standard lung window settings.

All CT images were evaluated for SSNs and their features, including number, size, density (pure GGNs, heterogeneous GGNs, and PSNs), lobar distribution, and number of affected lobes. All nodules were measured at their longest and shortest axes, the lung window being used for the ground-glass component. The solid component was measured when detected in the soft-tissue window. Multiple nodules were included. Subsequently, all CT images were evaluated for the presence and quantification of emphysema with the use of a visual scale.[10]

COVID-19 patients were defined as those referred for CT examination as COVID-19 patients (i.e., not necessarily presenting with a positive RT-PCR result). All other patients were considered non-COVID-19 patients. Although this was an arbitrary choice, our decision was based on the idea that suspicion of SARS-CoV-2 infection can interfere with the interpretation of CT images even without laboratory confirmation. In addition, we chose not to blind the radiologist who evaluated the CT images. Therefore, for COVID-19 patients, CT scans were read as positive for SSNs when lesions were not typical for COVID-19 in accordance with the Radiological Society of North America expert consensus document, including solitary nodules and persistent nodules in patients who had previously undergone imaging. Multiple nodules were not considered positive for SSNs, except in patients who had previously undergone imaging tests, which were reviewed when available, in accordance with best practice recommendations. For non-COVID-19 patients, CT scans were read as positive for SSNs if one or more (persistent or new) GGNs or PSNs were found. For COVID-19 patients, we reviewed all follow-up CT scans available by February of 2022.

Statistical analysis was performed with R software, version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria). Categorical variables are shown as absolute numbers (n) or relative frequencies (%). Continuous variables such as age are shown as mean ± SD. The Shapiro-Wilk test was used in order to verify the normal distribution of variables. Nonparametric data were analyzed with the Mann-Whitney Wilcoxon test and the chi-square test, with a 0.05 significance level. Poisson regression with robust variance was used for regression models.

RESULTS

The baseline characteristics of the patients and a flow chart of the study are shown in Table 1 and Figure 1, respectively.

The number of CT scans was 17% higher in September of 2020 than in September of 2019. At that moment in 2020, Brazil was experiencing a transition between the end of the first and the beginning of the second wave of the COVID-19 pandemic.[11]

Females constituted the majority of the study population. No significant differences were found between the September of 2019 and September of 2020 samples regarding sex ($p = 0.07$). The mean age was 62.8 ± 14.8 years in the 2019 sample and 59.5 ± 15.1 years in the 2020 sample ($p < 0.01$).

The proportion of patients with a history of cancer was 45.7% in 2020 and 50.7% in 2019 ($p = 0.07$). Cancer types included breast, gastrointestinal, rectal, prostate, melanoma, head and neck, and lung, as well as lymphoproliferative disorders, in initial staging or follow-up. Metastatic lung disease was present in 5.1% and 4.6% of the oncologic patients, respectively.

Current smokers and former smokers within 15 years of quitting constituted 24.1% of the 2019 sample and 21.1% of the 2020 sample ($p = 0.3$). Emphysema was found in 22.5% of the patients in the 2019 sample and in 19.7% of those in the 2020 sample.

SSNs were found in 10.6% of the patients in the 2019 sample and in 7.9% of those in the 2020 sample ($p = 0.10$). The detection rates for 2019 and 2020 were 1.34 and 1.23, respectively (95% CI, 0.96-1.86; $p = 0.084$). After Poisson regression with robust variance for age and sex, the difference remained nonsignificant (95% CI, 0.89-1.71; $p = 0.215$).

SSN-positive patients in the 2019 sample (mean age, 66.8 ± 13.3 years) were significantly older than SSN-negative patients ($p = 0,015$). This difference was not significant for the patients in the 2020 sample, although SSN-positive patients were older than SSN-negative patients (61.8 ± 13.7 years; $p = 0.186$).

Table 1. Baseline characteristics of the patients included in the study.

Characteristic		September of 2019	September of 2020	p	COVID-19 September of 2020
Valid exams, n		650	760	-	175
Female sex, %		58.2%	53.6%	0.07	52.8%
Age, years (mean ± SD)		62.8 ± 14.8	59.5 ± 15.1	< 0.01	53.2 ± 13.5
History of cancer		50.7%	45.7%	0.07	-
Current smokers or former smokers within 15 years of quitting, %		24.1%	21.1%	0.3	-
Emphysema	No	77.5%	80.1%		
	Mild	14.3%	14.0%		
	Moderate to severe	8.2%	5.7%		

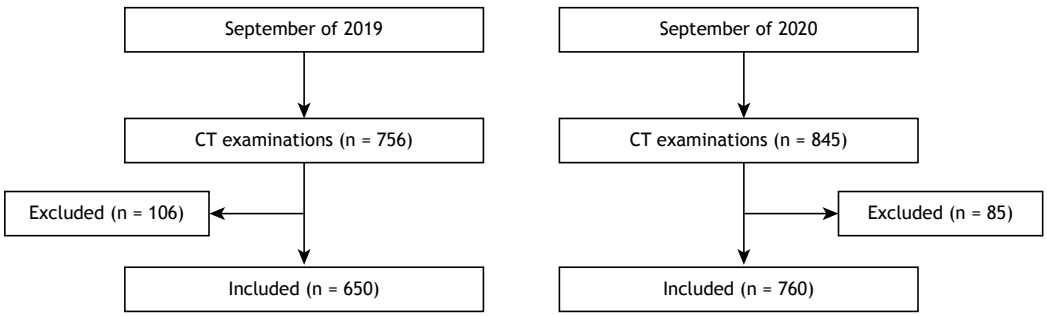


Figure 1. Flow chart of the study.

Multiple SSNs were found in 23 patients in the 2019 sample and in 11 patients in the 2020 sample (10 non-COVID-19 patients and 1 COVID-19 patient with two persistent GGNs).

COVID-19 patients constituted 24% of the 2020 sample (females, 52.8%; mean age, 53.2 ± 13.5 years). If we take into consideration that COVID-19 cases in southern Brazil were first reported in March of 2020, the maximum time interval between infection with SARS-CoV-2 and data collection was 6 months. SSNs were detected in 6.7% of COVID-19 patients (n = 12; solitary nodules, in 11; females, 58%). Of those 12 patients, 8 showed persistent SSNs on subsequent CT scans (resected adenocarcinoma, in 1; Figure 2), 3 did not undergo follow-up imaging, and 1 had a solitary GGN that disappeared within 6 months. Follow-up CT scans were available for 98 of 175 COVID-19 patients.

Non-COVID-19 patients constituted 76% of the 2020 sample, SSNs being detected in 9.3%. Using regression models for age and sex in order to compare SSN-positive patients between the 2020 COVID-19 subpopulation and the 2019 sample, we found a detection rate of 0.79 (95% CI, 0.43-1.44; p = 0.44) for COVID-19 patients. SSNs were more commonly detected in women, independently of the COVID-19 status (p = 0.006), as well as in older patients (p = 0.010). Table 2 shows the characteristics of the SSN-positive subgroups in the 2019 and 2020 samples.

DISCUSSION

SSNs are a cause for concern when persistent, because of their cancer potential.[1-3] However, there is a highly variable rate of inflammatory lesions first detected as SSNs on imaging.

As thoracic radiologists, we experienced reasonable diagnostic uncertainty when reading chest CT scans during the COVID-19 pandemic, especially when ground-glass lesions were few, nonperipheral, or even part solid, because of the overlap between ground-glass lesions and consolidation. Although most lesions were probably inflammatory given the clinical context, some (pre) malignant subsolid lesions could have been missed.

To overview these imaging limitations, our study sought to evaluate SSN detection before and during the COVID-19 pandemic. We chose to investigate outpatients in order to avoid inpatient complications. We chose the month of September because the lockdown in Brazil was over by then, with outpatient visits and tests being partially resumed at the beginning of the second wave of the pandemic.

In our study, almost a quarter of the patients undergoing chest CT as outpatients in September of 2020 had been referred to us as COVID-19 patients. The number of SSNs detected in the 2020 sample was lower than that of SSNs detected in the pre-pandemic (2019) sample, especially in the COVID-19 subpopulation, including multiple lesions. Nevertheless, the difference was not significant.

A confounding factor to consider is that the mean age was lower in the 2020 sample. This could lead us to conclude that we found fewer SSNs because of the younger age in the 2020 sample. However, it is debatable whether that age difference has actual

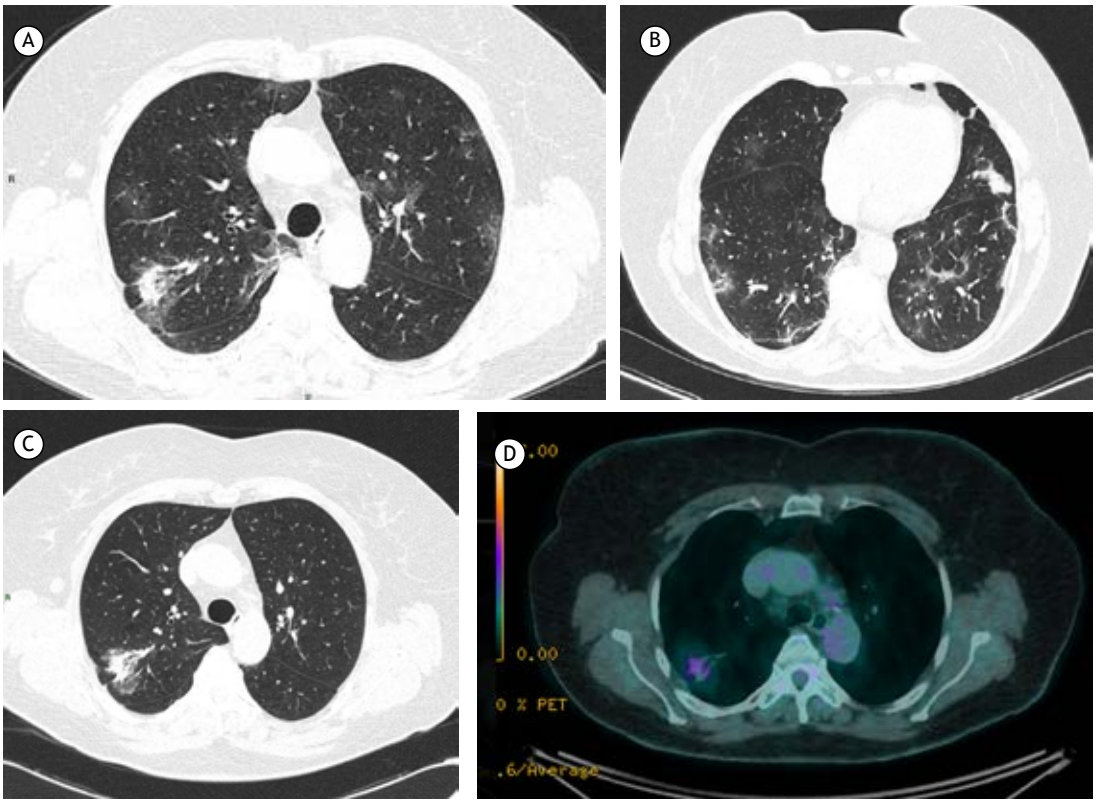


Figure 2. Chest CT scans. In A and B, part-solid nodule in the right upper lobe, as seen on the initial CT scan of a COVID-19 patient with pneumonia and other ground-glass and consolidative opacities. In C and D, part-solid nodule in the right upper lobe, as seen on the follow-up CT scan after regression of viral inflammatory lesions (in C), as well as FDG uptake on PET-CT scans (resected adenocarcinoma; in D).

Table 2. Detection of subsolid nodules before and during the COVID-19 pandemic.

Detection of SSNs	September of 2019	September of 2020	p	COVID-19
SSN, % (n/N)	10.6% (69/650)	7.9% (60/760)	0.10	6.7% (12/175)
Age, years (mean ± SD)	69 ± 13.3*	61.8 ± 13.7**	-	-
Female sex, %	73.9%	71.7%		58%
Symptoms[†]	36.2%	35%	0.9	
Solitary SSN	67%	72%	-	(11/12)
Multiple SSNs	33%	18%	-	(1/12)
Size < 20 mm[a]	95%	92%		
Upper lobes[b]	63.7%	60%	-	-

SSN: subsolid nodule; and COVID-19: patients referred for CT examination as COVID-19 patients (i.e., not necessarily presenting with a positive RT-PCR result). *p = 0.015. **p = 0.186. [†]Fever, dyspnea, cough, or any combination of the three. [a]Longest diameter of the nodule. [b]The most suspicious lesion was located in the upper lobes, in accordance with imaging criteria.

clinical significance, because it is known that SSNs tend to grow slowly or even remain stable for years. It is also of note that solitary and multiple SSNs are known to be potential (pre) malignant lesions, and previous studies have shown that up to 18% of resected adenocarcinomas are multiple.[12]

Women constituted the majority in our study and predominated in the SSN-positive subgroups. The detection of SSNs in women is a cause for concern, given that lung cancer screening studies have found that women are at a higher risk of cancer in a nonsolid nodule.[13] In addition, there has been an increasing frequency of lung cancer in nonsmokers.[14]

In our study, patients in the SSN-positive subgroups were older than the others in the 2019 and 2020 samples. The association between increasing age and persistent SSNs has been reported elsewhere.[13,15]

Of the 12 patients who were positive for SSNs in the COVID-19 subgroup, 1 had a PSN that turned out to be a lung adenocarcinoma. The nodule raised

suspicion at follow-up imaging only, having raised no suspicion during acute viral pneumonia. There are similar reports in the literature on lung cancer and concurrent pneumonia,[16,17] and one study conducted in China showed that lung cancer was the most common type of cancer in hospitalized COVID-19 patients.[18]

Although it is known that the growth rate of SSNs is slow,[19] a study by Kakinuma et al.[20] showed a mean period of 3.6 years for the appearance of a solid component in ground-glass lesions in lung cancer screening patients. Thus, it is essential to differentiate inflammatory from noninflammatory lesions accurately. A consensus statement on the management of lung nodules and lung cancer screening during the COVID-19 pandemic was released in 2020,[21] addressing various clinical situations; however, difficulties in correctly differentiating lesions on imaging were not addressed.

Our study has several limitations, including its single-center retrospective design. In addition, the findings on the reviewed images were not compared with those in the initial report, which was written as a nonstructured report. Our convenience sampling from the private health care system is another bias. However, in a recently published lung cancer screening trial conducted in Brazil,[22] no significant differences were found in the incidence of lung cancer, granulomatous disease, and Lung CT Screening Reporting and Data System category 4 nodules between patients in the public and private health care systems.

In conclusion, detection and characterization of pulmonary SSNs on CT scans were hindered during the COVID-19 pandemic, with fewer SSNs being diagnosed in COVID-19 patients than in pre-COVID-19 pandemic patients. However, the differences between the two samples of patients were not significant. Although follow-up CT is not recommended and is not cost-effective for all patients diagnosed with COVID-19, we must consider the possibility of missed proliferative lesions, especially in patients with demographic characteristics that increase the chance of persistent SSNs, such as being over 50 years of age and being female.

ACKNOWLEDGMENTS

We would like to thank the consultants and statisticians who participated in the study.

AUTHOR CONTRIBUTIONS

APZ, VBB, RDG, RRR, FTH, LCAJ, JFPS, GSG, and CFA: conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; validation; visualization; and writing, reviewing, and editing of the manuscript. APZ and CFA: supervision. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

DATA AVAILABILITY STATEMENT

The datasets generated or analyzed during the study are available from the corresponding author upon reasonable request.

REFERENCES

1. Hansell DM, Bankier AA, MacMahon H, McLoud TC, Müller NL, Remy J. Fleischner Society: glossary of terms for thoracic imaging. Radiology. 2008;246(3):697-722. https://doi.org/10.1148/radiol.2462070712
2. Kakinuma R, Noguchi M, Ashizawa K, Kuriyama K, Maeshima AM, Koizumi N, et al. Natural History of Pulmonary Subsolid Nodules: A Prospective Multicenter Study. J Thorac Oncol. 2016;11(7):1012-1028. https://doi.org/10.1016/j.jtho.2016.04.006
3. Henschke CI, Yankelevitz DF, Mirtcheva R, McGuinness G, McCauley D, Miettinen OS, et al. CT screening for lung cancer: frequency and significance of part-solid and nonsolid nodules. AJR Am J Roentgenol. 2002;178(5):1053-1057. https://doi.org/10.2214/ajr.178.5.1781053
4. National Lung Screening Trial Research Team; Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med. 2011;365(5):395-409. https://doi.org/10.1056/NEJMoa1102873
5. Koning HJ, van der Aalst CM, Jong PA, Scholten ET, Nackaerts K, et al. Reduced Lung-Cancer Mortality with Volume CT Screening in a Randomized Trial. N Engl J Med 2020; 382:503-513 DOI: 10.1056/NEJMoa1911793 https://doi.org/10.1056/NEJMoa1911793
6. Loftus TM, Wessling EG, Cruz DS, Schmidt MJ, Kim HS, McCarthy DM, et al. Impact of the COVID pandemic on emergency department CT utilization: where do we go from here?. Emerg Radiol. 2022;29(5):879-885. https://doi.org/10.1007/s10140-022-02071-z
7. Salehi S, Abedi A, Balakrishnan S, Gholamrezanezhad A. Coronavirus Disease 2019 (COVID-19): A Systematic Review of Imaging Findings in 919 Patients. AJR Am J Roentgenol. 2020;215(1):87-93. https://doi.org/10.2214/AJR.20.23034
8. Simpson S, Kay FU, Abbara S, Bhalla S, Chung JH, Chung M, et al. Radiological Society of North America Expert Consensus Document on Reporting Chest CT Findings Related to COVID-19: Endorsed by the Society of Thoracic Radiology, the American College of Radiology, and RSNA. Radiol Cardiothorac Imaging. 2020;2(2):e200152. https://doi.org/10.1148/ryct.2020200152
9. Duzgun SA, Durhan G, Demirkazik FB, Akpinar MG, Ariyurek OM. COVID-19 pneumonia: the great radiological mimicker. Insights Imaging. 2020;11(1):118. https://doi.org/10.1186/s13244-020-00933-z
10. Lynch DA, Austin JH, Hogg JC, Grenier PA, Kauczor HU, Bankier AA, et al. CT-Definable Subtypes of Chronic Obstructive Pulmonary Disease: A Statement of the Fleischner Society. Radiology. 2015;277(1):192-205. https://doi.org/10.1148/radiol.2015141579
11. Fleckenstein FN, Maleitzke T, Böning G, Kahl V, Petukhova-Greenstein A, Kucukkaya AS, et al. Changes of radiological examination volumes over the course of the COVID-19 pandemic: a comprehensive analysis of the different waves of infection. Insights Imaging. 2022;13(1):41. https://doi.org/10.1186/s13244-022-01181-z
12. Vazquez M, Carter D, Brambilla E, Gazdar A, Noguchi M, Travis WD,et al. Solitary and multiple resected adenocarcinomas after CT screening for lung cancer: histopathologic features and their prognostic implications. Lung Cancer. 2009;64(2):148-154. https://doi.org/10.1016/j.lungcan.2008.08.009
13. McWilliams A, Tammemagi MC, Mayo JR, Roberts H, Liu G, Soghrati K, et al. Probability of cancer in pulmonary nodules detected on first screening CT. N Engl J Med. 2013;369(10):910-919. https://doi.org/10.1056/NEJMoa1214726

14. Cufari ME, Proli C, De Sousa P, Raubenheimer H, Al Sahaf M, Chavan H, et al. Increasing frequency of non-smoking lung cancer: Presentation of patients with early disease to a tertiary institution in the UK. Eur J Cancer. 2017;84:55-59. https://doi.org/10.1016/j.ejca.2017.06.031
15. Guo X, Jia X, Zhang D, Feng H, Dou Y, Shi G. Indeterminate pulmonary subsolid nodules in patients with no history of cancer: growing prediction, CT pattern, and pathological diagnosis. Diagn Interv Radiol. 2022;28(3):230-238. https://doi.org/10.5152/dir.2022.211100
16. Guarnera A, Santini E, Podda P. COVID-19 Pneumonia and Lung Cancer: A Challenge for the RadiologistReview of the Main Radiological Features, Differential Diagnosis and Overlapping Pathologies. Tomography. 2022;8(1):513-528. https://doi.org/10.3390/tomography8010041
17. Yamanaka S, Ota S, Yoshida Y, Shinkai M. COVID-19 pneumonia and an indelible ground-glass nodule. Respirol Case Rep. 2021;9(5):e00751. https://doi.org/10.1002/rcr2.751
18. Dai M, Liu D, Liu M, Zhou F, Li G, Chen Z, et al. Patients with Cancer Appear More Vulnerable to SARS-CoV-2: A Multicenter Study during the COVID-19 Outbreak. Cancer Discov. 2020;10(6):783-791. https://doi.org/10.1158/2159-8290.CD-20-0422
19. Bueno J, Landeras L, Chung JH. Updated Fleischner Society Guidelines for Managing Incidental Pulmonary Nodules: Common Questions and Challenging Scenarios. Radiographics. 2018;38(5):1337-1350. https://doi.org/10.1148/rg.2018180017
20. Kakinuma R, Muramatsu Y, Kusumoto M, Tsuchida T, Tsuta K, Maeshima AM, et al. Solitary Pure Ground-Glass Nodules 5 mm or Smaller: Frequency of Growth. Radiology. 2015;276(3):873-882. https://doi.org/10.1148/radiol.2015141071
21. Mazzone PJ, Gould MK, Arenberg DA, Chen AC, Choi HK, Detterbeck FC, et al. Management of Lung Nodules and Lung Cancer Screening During the COVID-19 Pandemic: CHEST Expert Panel Report. Chest. 2020;158(1):406-415. https://doi.org/10.1016/j.chest.2020.04.020
22. Hochhegger B, Camargo S, da Silva Teles GB, Chate RC, Szarf G, Guimarães MD, et al. Challenges of Implementing Lung Cancer Screening in a Developing Country: Results of the Second Brazilian Early Lung Cancer Screening Trial (BRELT2). JCO Glob Oncol. 2022;8:e2100257. https://doi.org/10.1200/GO.21.00257

J Bras Pneumol. 2023;49(6):e20220438
https://dx.doi.org/10.36416/1806-3756/e20220438

Predictors of reduced incremental shuttle walk test performance in patients with long post-COVID-19

Mustafa Engin Sahin[1], Seher Satar[1], Pınar Ergün[1]

1. University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey.

Submitted: 16 November 2022.
Accepted: 12 September 2023.

Study carried out at the University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey.

ABSTRACT

Objective: One of the common limitations after COVID-19 pneumonia is the decrease in exercise capacity. The identification of the factors affecting exercise capacity and the assessment of patients at risk are important for determining treatment strategy. This study was conducted to determine the predictors of decreased exercise capacity in long post-COVID-19 patients. **Methods:** We investigated the association of exercise capacity as measured by the incremental shuttle walk test (ISWT) with age, sex, spirometric variables, respiratory and peripheral muscle strength, quality of life, fatigue, hospital anxiety depression scale, chest X-ray involvement, and hospitalization. The patients were divided into three groups: outpatients, inpatients, and ICU patients. Regression analysis was used to determine which parameters were significant predictors of exercise capacity. **Results:** Of the 181 patients included in the study, 56 (31%) were female. The mean ISWT in percentage of predicted values (ISWT%pred) was 43.20% in the whole sample, whereas that was 52.89%, 43.71%, and 32.21% in the outpatient, inpatient, and ICU patient groups, respectively. Linear regression analysis showed that predictors of decreased ISWT%pred were sex (β = 8.089; p = 0.002), mMRC scale score (β = –7.004; p ≤ 0.001), FVC%pred (β = 0.151; p = 0.003), and handgrip strength (β = 0.261; p = 0.030). **Conclusions:** In long post-COVID-19 patients, sex, perception of dyspnea, restrictive pattern in respiratory function, and decrease in peripheral muscle strength are predictors of reduced exercise capacity that persists three months after COVID-19. In this context, we suggest that pulmonary rehabilitation might be an important therapy for patients after COVID-19.

Keywords: COVID-19; Exercise; Muscle strength; Rehabilitation; Walk test.

INTRODUCTION

Post-acute illness symptoms in patients with COVID-19 can persist for months. The term long post-COVID-19 syndrome has been proposed to describe clinical symptoms lasting more than 12 weeks after the onset of acute symptoms.[1] The underlying causes of this situation are not fully understood. The most common symptoms are fatigue and dyspnea.[2,3] Severe limitations occur in some of these patients. One of them is the decrease in exercise capacity. Although studies are still ongoing, it has been suggested that various factors such as cardiac sequelae, decrease in diffusion capacity, limited lung function, and muscle weakness may be factors that might limit exercise capacity.[4,5] In another study, decreased exercise capacity three months after severe COVID-19 infection has been associated with respiratory limitation and decreased skeletal muscle mass and function rather than cardiac causes.[6,7] Moreover, studies in non-COVID-19 patients have demonstrated that decreased exercise capacity is an independent predictor of mortality.[8,9] In patients with chronic respiratory disease, normal exercise capacity improves quality of life and participation in daily activities while decreasing respiratory symptoms, anxiety, frequency of hospital visits and of hospitalizations, and social isolation. So, the determination of the factors affecting the limitation of exercise capacity and the prediction of which patients are at risk are important for managing treatment strategy. The application of an incremental shuttle walk test (ISWT) does not require the use of any specialized equipment. However, the estimated peak oxygen consumption ($V_{O_{2peak}}$) obtained by the ISWT revealed a moderate to strong correlation with maximal exercise performance as evaluated by the cardiopulmonary exercise test (CPET). The ISWT has been found to be a reliable test of cardiopulmonary exercise capacity, especially in COPD, and to produce a physiological response similar to the CPET.[10]

The aim of our study was to examine the relationship between the decrease in exercise capacity determined by ISWT and clinical, functional, or emotional factors in a patient cohort who recovered after COVID-19. A secondary aim was to discover predictors of decreased exercise capacity in long post-COVID-19 patients. Our hypothesis was that decreased exercise capacity in long post-COVID-19 patients would be predominantly related to muscle strength loss.

METHODS

This was a cross-sectional, prospective, single-center study. Between April 15, 2022, and June 14, 2022, a

Correspondence to:
Mustafa Engin Sahin. University of Health Sciences, Ankara Atatürk Sanatoryum Training and Research Hospital, Ankara, Turkey.
Tel. 905064074328. E-mail: drenginsahin@protonmail.com
Financial support: None

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

total of 217 patients who were seen at our pulmonary rehabilitation center with complaints of dyspnea and had COVID-19 at least three months but no more than six months prior to their visit were evaluated. The patients were referred to our center by the outpatient clinics which they had visited for COVID-19 control. Of the total sample, 186 patients met the inclusion criteria and agreed to participate in the study (Supplementary Material). All patients consulted with a cardiologist and underwent echocardiograms before evaluation, and myocardial dysfunction was ruled out. Three patients refused to participate in the study, and 2 patients were not approved for pulmonary rehabilitation (PR) by the cardiologist. Therefore, the final sample comprised 181 patients.

Inclusion criteria were as follows: having a confirmed diagnosis of COVID-19 by RT-PCR between three and six months before visiting our center, being diagnosed with long post-COVID by a pulmonologist, being ≥ 18 years of age, giving written consent to participate in the study, and having dyspnea at the time of admission, determined by the modified Medical Research Council (mMRC) dyspnea scale score ≥ 1. Exclusion criteria were being younger than 18 years of age; having uncontrolled psychiatric disease, orthopedic disability, movement-limiting neurological disease, active malignancy, uncontrolled hypertension, or a disease that was thought to reduce exercise capacity other than COVID-19; being a professional athlete; being pregnant; and participating in a rehabilitation or an intensive exercise program before ISWT.

In addition to demographic data, we collected information about comorbidities, length of hospital/ICU stay in days, chest X-rays, need for long-term oxygen therapy (LTOT), perception of dyspnea, body composition measurements, amount of weight loss, Borg scale score, spirometry, and peripheral and respiratory muscle strength in order to determine the factors affecting the decrease in exercise capacity of the participants. Hospital anxiety and depression scale (HADS), fatigue severity scale (FSS) and Nottingham Extended Activities of Daily Living Scale (NEADLS) were administered. Chest X-rays were evaluated visually. The use of LTOT (patients in need were started in the center to which they were referred) was recorded. The patients were divided into three groups according to the severity of the disease (outpatient, inpatient, and ICU follow-up), and their data were analyzed. Parameters that might be associated with the decrease in the percent of predicted ISWT (ISWT%pred) were investigated in all patients. Written informed consent form was obtained from all patients. The study protocol conformed to the Declaration of Helsinki and was approved by the Research Ethics Committee of the Ankara Atatürk Sanatoryum Training and Research Hospital (Protocol KAEK-15/2492).

The chest X-rays obtained during the admission process to our center were divided into six zones and their involvement was determined (bilateral, especially in the middle and lower regions, peripherally distributed, irregularly limited density increase and consolidation). The X-rays were evaluated by two different pulmonologists, and results were decided by consensus. Dyspnea was assessed using the mMRC scale.[11] BMI was calculated using the formula body mass (in kg) divided by the square of height (in m).

Exercise capacity was evaluated using the ISWT. The test was performed according to field walking test guidelines.[12] The predicted ISWT value was calculated by a reference equation,[13] which includes age, gender, and BMI. ISWT values were obtained as a percentage of the predicted value (ISWT%pred). Also, Vo_{2peak} value and in percentage of the predicted value were calculated using ISWT.[14]

Dyspnea intensity was measured throughout exercise using the modified 0-10 Borg scale. Spirometry was performed to determine FVC, FEV_1, and FEV_1/FVC ratio using a spirometer (AS-507, Minato Medical Science, Tokyo, Japan) in accordance with the American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines.[15] Respiratory muscle strength was evaluated by measuring MIP and MEP using a Micro-RPM respiratory pressure meter (Care Fusion, Hoechberg, Germany). MIP and MEP were measured in accordance with the recommendations of the ATS/ERS.[16] The test was repeated at least three times, and the best value was recorded. To assess peripheral muscle strength of the patients, a handgrip test was performed using a hand dynamometer (Jamar Hydraulic Hand Dynamometer, Mississauga, Canada).[17] Psychological status was assessed using the HADS,[18] whereas fatigue was assessed using the FSS, and activities of daily living were assessed using the validated Turkish version of NEADLS.[19]

Statistical analyses were performed with the IBM SPSS Statistics software package, version 26.0 (IBM Corporation, Armonk, NY, USA). Normally-distributed numeric variables were expressed as means and standard variations, while non-normally distributed variables were expressed as medians. Categorical variables were expressed as absolute and relative frequencies. To determine if the variables were normally distributed, visual (histograms and probability plots) and analytical methods (Shapiro-Wilk test, skewness coefficient, and kurtosis coefficient) were used. The statistical differences of normal and non-normal quantitative variables of demographic and baseline values across groups established according to hospitalization status were assessed using ANOVA and the Kruskal-Wallis test, respectively. Tukey's honestly significant difference test and the Games-Howell test were used for post hoc analyses. The correlation between two numeric variables with normal distribution and a linear correlation was analyzed using Pearson's correlation coefficient. The correlation between variables that did not show normal distribution was evaluated with Spearman's correlation coefficient. The predictors of ISWT%pred were analyzed by using linear regression analysis. A p-value < 0.05 was used to determine statistical significance.

RESULTS

Of the 181 patients studied, 125 (69%) and 56 (31%) were male and female, respectively. During the ISWT, 141 patients were unable to complete the test, 94 of whom developed leg fatigue, 19 of whom developed dyspnea, 17 of whom developed desaturation, and 3 of whom developed tachycardia exceeding submaximal heart rate. The $V_{O_{2peak}}$ calculated from the ISWT was above 80% of the predicted value in only 5 patients. The mean ISWT%pred was 43.20% ± 16.19% in the sample as a whole, whereas that in males and females, respectively, was 41.39% ± 15.57% and 47.23% ± 16.96%, and this difference was statistically significant ($p = 0.024$). The groups formed by disease severity were evaluated with one-way ANOVA. Age, comorbidities, BMI, Borg scale, HADS, and FSS results were similar among the groups. Regarding comorbidities, hypertension (in 22 patients), diabetes mellitus (in 15), coronary artery disease (in 2), and sleep apnea (in 1) were identified in the outpatient group; whereas hypertension (in 35), diabetes mellitus (in 24), coronary disease (in 2), sleep apnea (in 2), renal failure (in 1), and familial Mediterranean fever (in 1) were present in the inpatient group; and hypertension (in 15), diabetes mellitus (in 14), sleep apnea (in 2), coronary artery disease (in 1), and renal failure (in 1) were present and in the ICU group. Tables 1 and 2 provide detailed information on demographic data and other parameters evaluated, as well as p-values calculated by ANOVA for the sample as a whole and the groups by hospitalization status. ANOVA and post hoc analyses (Games-Howell) revealed statistically significant differences in ISWT%pred among the three groups ($p < 0.001$).

In the correlation analysis, ISWT%pred correlated with hospitalization status, length of hospital/ICU stay, extent of chest X-ray involvement, LTOT use, mMRC scale, amount of weight loss, Borg scale score, spirometry, handgrip strength, and NEADLS score. No relationship was found with emotional factors. Table 3 shows the parameters that correlated with ISWT%pred values in the correlation analysis performed using the whole sample. In the correlation analysis, a multivariable linear regression model was created with the parameters that correlated with the ISWT%pred. In the multiple linear regression analysis, sex, mMRC scale, FVC%pred, and handgrip strength were found to be the predictors of ISWT%pred. In the regression analysis model of ISWT%pred, the variables gender, hospitalization status, X-ray, mMRC scale, Borg scale, FVC%pred, handgrip strength, and NEADLS explained 60% of the reduced ISWT%pred (Table 4). The relationship of ISWT%pred with hospitalization status, mMRC scale, FVC%pred, and handgrip strength is seen in Figures 1 and 2.

DISCUSSION

In our study, we aimed to identify which patients with long post-COVID were at risk of having lower exercise capacity. We discovered that male gender, dyspnea perception, impaired lung function, and impaired peripheral muscle strength were the main predictors of decreased exercise capacity. Being male decreased the ISWT%pred by about 8 units. A 1-unit increase in the mMRC scale score was correlated with a 7-unit decrease in ISWT. Also, 1-unit increases in FVC%pred and in handgrip strength improved ISWT by 0.151 and 0.261 units, respectively. Because low exercise capacity negatively impacts the quality of life of patients by preventing them from regaining their pre-COVID-19 functional status, our results are crucial for identifying patients in the risk group and enabling early preventative therapy and measures to be applied.

Exercise capacity measured with field tests is also used to assess the success of pulmonary rehabilitation in addition to various indicators such as dyspnea and quality of life. Also, ISWT and endurance shuttle walk tests are used to prescribe exercise. When the reasons for test termination are considered, they might provide information about the cardiac or pulmonary causes of exercise limitation.

Previous studies have shown that ISWT performance is associated with age, FEV_1%pred, and peripheral

Table 1. Demographic characteristics and hospitalization data.[a]

Variable	Overall sample (N = 181)	Group			p	Comparison*		
		Outpatient (n = 45; 24.9%)	Inpatient (n = 92; 50.8%)	ICU (n = 44; 24.3%)		p^{1-2}	p^{2-3}	p^{1-3}
Male sex	125 (69.1)	21 (46.7)	74 (80.4)	30 (68.2)	< 0.001	< 0.001***	0.302***	0.100***
Age, years	55.7 ± 10.5	54.7 ± 10.9	55.5 ± 10.9	57.3 ± 9.2	0.502	0.897**	0.651**	0.487**
Smoking history, pack-years	27.9 ± 21.4	32.1 ± 18.2	31.4 ± 16.2	20.0 ± 12.1	0.030	0.341**	0.029**	0.487**
Comorbidities, yes	121(66.9)	34 (75.6)	58 (64.1)	29 (65.9)	0.381	0.355**	0.966**	0.599**
Length of hospital stay, days	-	-	12.6 ± 8.4	35.1 ± 16.2	-	-	-	-
Length of ICU stay, days	-	-	-	18.4 ± 13.7	-	-	-	-
X-ray, zone involvement	2.4 ± 1.9	1.6 ± 1.9	2.4 ± 1.8	3.1 ± 1.9	0.002	0.064**	0.128**	0.001**
LTOT, yes	69 (38.12)	3 (6.7)	36 (39.1)	30 (68.2)	< 0.001	< 0.001***	0.005***	< 0.001***

LTOT: long-term oxygen therapy. [a]Values expressed as n (%) or mean ± SD. *Games-Howell test: (1 = outpatient; 2 = inpatient; and 3 = ICU). **ANOVA or Kruskal-Wallis test. ***Tukey's honestly significant difference test.

Table 2. Exercise tests and other measurements/questionnaires.[a]

Variable	Overall sample (N = 181)	Group			p	Comparison*		
		Outpatient (n = 45; 24.9%)	Inpatient (n = 92; 50.8%)	ICU (n = 44; 24.3%)		p^{1-2}	p^{2-3}	p^{1-3}
mMRC (1/2/3/4)	23/44/21/12	38/58/4/0	24/44/22/10	7/30/36/27	< 0.001	< 0.001***	0.001***	< 0.001***
BMI, kg/m^2	28.9 ± 5.1	28.9 ± 4.3	28.6 ± 5.0	29.6 ± 5.9	0.531	0.939**	0.499**	0.767**
Weight loss, kg	9.3 ± 5.4	6.6 ± 2.2	8.2 ± 4.4	13.7 ± 6.8	0.003	0.379***	0.051***	0.013***
ISWT, m	345 ± 141	370 ± 91	365 ± 146	249 ± 131	< 0.001	0.282***	< 0.001***	< 0.001***
ISWT, % predicted	43.2 ± 16.2	52.9 ± 10.0	43.7 ± 15.6	32.2 ± 16.1	< 0.001	< 0.001***	< 0.001***	< 0.001***
SpO_2 before ISWT	97.2 ± 1.4	97.5 ± 0.9	97.2 ± 1.4	96.7 ± 1.8	0.140	0.657**	0.397**	0.117**
SpO_2 after ISWT	92.4 ± 4.4	94.4 ± 4.1	91.7 ± 4.3	90.9 ± 4.5	0.008	0.026**	0.753**	0.013**
HR before ISWT	88.6 ± 14.2	86.4 ± 11.2	89.7 ± 15.0	89.2 ± 16.3	0.607	0.592**	0.988**	0.771**
HR after ISWT	121 ± 14	121 ± 14	122 ± 16	119 ± 15	0.326	0.385**	0.979**	0.402**
Borg at rest	0 [0.0-0.5]	0 [0.0-0.5]	0 [0.0-0.5]	0 [0-1]	0.484	1.000***	0.529***	0.631***
Borg after ISWT	4 [3-4]	4 [2-4]	4 [3-4]	4 [3-5]	0.333	0.892***	0.223***	0.620***
Vo_{2peak}, % predicted	45.1 ± 12.5	51.6 ± 8.4	45.8 ± 12.7	36.6 ± 11.1	< 0.001	0.006***	< 0.001***	< 0.00*1**
FVC, % predicted	85.5 ± 22.4	94.4 ± 18.8	86.4 ± 22.5	72.1 ± 20.3	< 0.001	0.123*	0.004**	< 0.001**
FEV_1, % predicted	83.6 ± 21.3	88.9 ± 19.6	84.4 ± 21.2	74.9 ± 21.6	0.015	0.503*	0.073**	0.012**
FEV_1/FVC	79.8 ± 11.2	77.5 ± 9.1	79.2 ± 11.4	84.4 ± 12.2	0.022	0.725*	0.057**	0.022**
MIP, cmH_2O	95.5 ± 29.4	84.2 ± 26.5	99.1 ± 25.1	99.5 ± 36.6	0.046	0.056*	0.998**	0.089**
MEP, cmH_2O	122.5 ± 34.8	108.8 ± 29.7	129.5 ± 31.1	122.7 ± 41.8	0.026	0.019*	0.626**	0.230**
Handgrip test, kg	31.5 ± 10.2	29.7 ± 10.8	33.7 ± 9.3	28.7 ± 10.4	0.016	0.101*	0.026**	0.895**
HADS-Anxiety	7.1 ± 3.7	7.9 ± 3.9	6.6 ± 3.7	7.3 ± 3.6	0.148	0.138*	0.557**	0.739**
HADS-Depression	6.9 ± 3.4	7.0 ± 3.4	6.7 ± 3.6	7.1 ± 3.3	0.854	0.918*	0.870**	0.995**
FSS	4.5 ± 1.7	4.5 ± 1.8	4.3 ± 1.7	4.6 ± 1.7	0.590	0.797*	0.595**	0.959**
NEADLS	56.8 ± 11.5	61.3 ± 5.8	56.9 ± 10.3	52.3 ± 15.8	0.002	0.010**	0.214***	0.004***

mMRC: modified Medical Research Council scale; ISWT: incremental shuttle walk test; Vo_{2peak}: peak oxygen consumption; ,HADS: Hospital Anxiety and Depression Scale; FSS: Fatigue severity score; and NEADLS: Nottingham Extended Activities of Daily Living Scale. [a]Values expressed as %, mean ± SD, or median [IQR]. *Games-Howell test: (1 = outpatient; 2 = inpatient; and 3 = ICU). **ANOVA or Kruskal-Wallis test. ***Tukey's honestly significant difference test.

muscle strength in patients with COPD. ISWT was also associated with sniff nasal inspiratory pressure and peripheral muscle strength in lung cancer.[10,20] Age, body composition, dyspnea, respiratory function, and physical activity in daily life were found to be predictors of ISWT in bronchiectasis.[21] In our study, age and BMI were not correlated with ISWT%pred. This might be because COVID-19 patients are exposed to the disease for a shorter period of time than are those with chronic diseases. Although respiratory muscles do not correlate with ISWT, the correlation of peripheral muscle strength may be associated with disease-related immobility. Finally, the correlation of other parameters with ISWT and predictors of ISWT were similar to those in non-COVID-19 diseases. In a multicenter prospective cohort study including 1,226 hospitalized patients, post-COVID-19 dyspnea was associated with lower performance on the shuttle walk test and FVC, but not with obstructive airflow limitation.[22]

Our study showed that being male with persistent symptoms is a predictor for reduced exercise capacity. Previous studies have revealed that males are likely to have more severe disease.[23,24] In our study, the rates of hospitalization and ICU stay were higher in males. Lower ISWT%pred in men may be due to more severe disease and more hospitalizations.

According to an earlier study, patients with COVID-19 had higher MRC scale scores, and those scores rise in line with the severity of the disease.[25] However, in another study, it was found that the MRC scale score did not differ between hospitalized and non-hospitalized patients.[24] In our study, the mMRC scale score was statistically significantly different among the three severity groups. In addition, the mMRC scale score was found to be a predictor for ISWT%pred.

In our study, it was found that one of the causes contributing to the reduction in exercise capacity was the decrease in FVC%pred. Restriction on spirometry has been linked to decreased exercise capacity and increased desaturation in patients with post-COVID-19 persistent dyspnea.[26] Due to their exercise-induced desaturation, post-COVID-19 patients with normoxemia at rest also resemble those having interstitial lung disease.[27] The strength of respiratory muscles may be the cause of the FVC%pred decline. ISWT%pred and respiratory muscle strength, however, did not correlate in our study. The correlation between ISWT%pred and radiological results ($p = 0.001$; $r = -0.276$) led us to believe that parenchymal injury was the cause of the decline in FVC%pred. This restrictive pattern increases with the severity of the disease.

Investigations are currently ongoing to determine the causes of decreased exercise capacity in post-COVID-19

Table 3. Correlations of the incremental shuttle walk test in % of predicted values with selected variables.

Variable	Correlation coefficient	p
Sex	0.167*	0.025
Age, years	−0.103	0.167
Smoking history, pack-years	−0.035	0.728
Comorbidities, no/yes	−0.107	0.154
Hospitalization status	−0.449**	< 0.001
Length of hospital stay, days	−0.554**	< 0.001
Length of ICU stay, days	−0.464**	0.001
X-ray, zone involvement, n	−0.330**	< 0.001
LTOT use	−0.459**	< 0.001
mMRC scale score	−0.680**	< 0.001
BMI, kg/m^2	0.104	0.171
Weight loss, kg	−0.542**	< 0.001
Borg scale score at rest	−0.208**	0.005
Borg scale score after exercise	−0.163*	0.031
FVC, % pred	0.590**	< 0.001
FEV_1, % pred	0.554**	< 0.001
FEV_1/FVC	−0.134	0.096
MIP, cmH_2O	0.030	0.744
MEP, cmH_2O	0.118	0.190
Handgrip test	0.238**	0.002
HADS-Anxiety score	−0.017	0.823
HADS-Depression score	−0.081	0.287
FSS score	−0.029	0.719
NEADLS score	0.354**	< 0.001

LTOT: long-term oxygen therapy; % pred: % of the predicted value; mMRC: modified Medical Research Council; HADS: hospital anxiety and depression scale; FSS: fatigue severity score; and NEADLS: Nottingham Extended Activities of Daily Living Scale.

Table 4. Multivariate linear regression analyses of the incremental shuttle walk test in % of predicted values.

Variable	Unstandardized coefficient (β)	Standardized coefficient	t	p	95% CI for β	
					Lower bound	Upper bound
Sex	8.089	0.246	3.133	0.002	2.978	13.201
Hospitalization status	−2.163	−0.099	−1.429	0.156	−5.159	0.834
X-ray, zone involvement, n	−0.156	−0.020	−0.304	0.761	−1.172	0.860
mMRC scale score	−7.004	−0.428	−5.525	< 0.001	−9.514	−4.495
FVC, % pred	0.151	0.220	2.991	0.003	0.051	0.251
Borg scale score at rest	0.152	0.080	0.080	0.936	−3.620	3.925
Borg scale score after exercise	−0.005	−0.001	−0.007	0.994	−1.470	1.459
Handgrip test	0.261	0.166	2.192	0.030	0.025	0.496
NEADLS score	0.153	0.107	1.644	0.103	−0.031	0.337

mMRC: modified Medical Research Council; % pred: % of the predicted value; and NEADLS: Nottingham Extended Activities of Daily Living Scale.

patients. Existing studies indicate that sarcopenia and decreased skeletal muscle strength are important reasons for limiting exercise.[6,28,29] There may be a number of causes for the decline in muscle strength. Atrophy as a result of insufficient physical activity, critical illness polyneuropathy, and muscle or central nervous system damage caused by SARS-CoV-2 are possible causes.[30] Increased length of hospital stay, probable corticosteroid use, and weight loss as the disease progresses pose a risk for sarcopenia and muscle weakness. In our study, mean handgrip strength was found to be high in hospitalized patients, but it should be noted that the majority of these patients were male. According to our results, a decrease in peripheral muscle strength is an important predictor of prolonged reduced exercise capacity after the third month in long post-COVID-19 patients. In our study, the rate of patients who terminated the exercise due to respiratory reasons was 18.8%, while the number of patients who developed leg fatigue was more than half (51.9%). This demonstrates the importance of reduction in muscle strength in limiting exercise capacity in patients with COVID-19.

Previous studies showed that decreased lung function and impaired exercise capacity were associated with

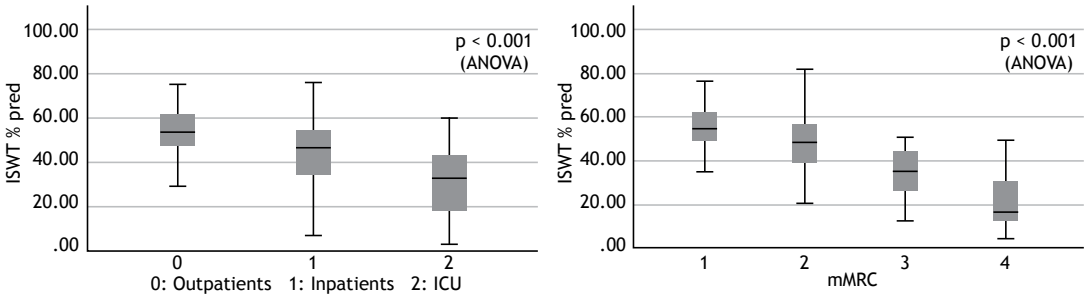


Figure 1. Incremental shuttle walk test in percentage of the predicted value (ISWT%pred) by hospitalization status and modified Medical Research Council (mMRC) scale score.

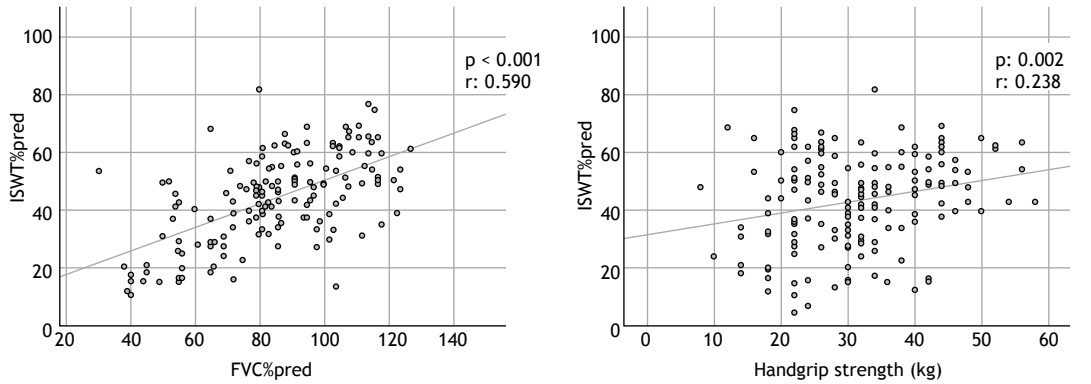


Figure 2. Incremental shuttle walk test in percentage of the predicted value (ISWT%pred) by FVC in percentage of predicted value (FVC%pred) and handgrip strength.

reduced skeletal muscle mass and function three months after COVID-19 infection. No significant deterioration in cardiac function was detected.[6] In our study, similarly to previous studies, the restrictive pattern in respiratory function and decreased skeletal muscle strength were important predictors of reduced exercise capacity. During the tests, only 3 patients developed tachycardia exceeding the submaximal heart rate.

In our study, although BMI was higher than normal in all groups, it did not differ among them. Even if the FSS score was above the normal limit in all groups, no differences were found and that was not associated with exercise capacity. According to several studies, fatigue develops at a higher rate in patients who had severe COVID-19.[31] However, there are also studies showing that persistent fatigue is independent of the severity of COVID-19 infection.[32] Previous studies presented a relationship between maximal exercise capacity and activities of daily living. Reduced exercise capacity has a negative effect on daily activities.[33] In our study, we found that exercise capacity in long post-COVID-19 patients was correlated with the NEADLS score. However, the NEADLS was not a predictor of exercise capacity.

We think that individualized pulmonary rehabilitation programs that include appropriate exercise training, as well as medical treatment, are important in the follow-up and treatment of these patients.

The most important limitation of this study is the single-center design. However, our center is a referral hospital, and patients come from all over the country. Another limitation was that our study had no control group. A cohort of non- COVID-19 patients might be beneficial for comparing baseline results. Due to the ongoing pandemic, DL_{CO} could not be performed in this study.

As a conclusion, in long post-COVID patients, male gender, perception of dyspnea, restrictive pattern in respiratory function, and decrease in peripheral muscle strength were predictors of reduced exercise capacity that persisted after three months. In addition, hospitalization was a risk factor for exercise limitation.

AUTHOR CONTRIBUTIONS

MES: literature search, data collection, study design, data analysis, manuscript preparation, and manuscript review. SS: literature search, data collection, study design, data analysis, manuscript preparation, and manuscript review. PE: literature search, study design, data analysis, manuscript preparation, and manuscript review. All authors have read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Fernández-de-Las-Peñas C. Long COVID: current definition. Infection. 2022;50(1):285-286. https://doi.org/10.1007/s15010-021-01696-5
2. Cabrera Martimbianco AL, Pacheco RL, Bagattini ÂM, Riera R. Frequency, signs and symptoms, and criteria adopted for long COVID-19: A systematic review. Int J Clin Pract. 2021;75(10):e14357. https://doi.org/10.1111/ijcp.14357
3. Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-615. https://doi.org/10.1038/s41591-021-01283-z
4. Magdy DM, Metwally A, Tawab DA, Hassan SA, Makboul M, Farghaly S. Long-term COVID-19 effects on pulmonary function, exercise capacity, and health status. Ann Thorac Med. 2022;17(1):28-36. https://doi.org/10.4103/atm.atm_82_21
5. Clavario P, Marzo VD, Lotti R, Barbara C, Porcile A, Russo C, et al. Assessment of functional capacity with cardiopulmonary exercise testing in non-severe COVID-19 patients at three months follow-up. medRxiv; 2020. https://doi.org/10.1101/2020.11.15.20231985
6. Ribeiro Baptista B, d'Humières T, Schlemmer F, Bendib I, Justeau G, Al-Assaad L, et al. Identification of factors impairing exercise capacity after severe COVID-19 pulmonary infection: a 3-month follow-up of prospective COVulnerability cohort. Respir Res. 2022;23(1):68. https://doi.org/10.1186/s12931-022-01977-z
7. Mohr A, Dannerbeck L, Lange TJ, Pfeifer M, Blaas S, Salzberger B, et al. Cardiopulmonary exercise pattern in patients with persistent dyspnoea after recovery from COVID-19. Multidiscip Respir Med. 2021;16(1):732. https://doi.org/10.4081/mrm.2021.732
8. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med. 2002;346(11):793-801. https://doi.org/10.1056/NEJMoa011858
9. Gulati M, Black HR, Shaw LJ, Arnsdorf MF, Merz CNB, Lauer MS, et al. The prognostic value of a nomogram for exercise capacity in women. N Engl J Med. 2005;353(5):468-475. https://doi.org/10.1056/NEJMoa044154
10. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446. https://doi.org/10.1183/09031936.00150314
11. Standardised questionnaire on respiratory symptoms : a statement prepared and approved by the MRC Committee on the Aetiology of Chronic Bronchitis (MRC breathlessness score). BMJ. 1960;2:1665.
12. Singh SJ, Jones PW, Evans R, Morgan MD. Minimum clinically important improvement for the incremental shuttle walking test. Thorax. 2008;63(9):775-777. https://doi.org/10.1136/thx.2007.081208
13. Probst VS, Hernandes NA, Teixeira DC, Felcar JM, Mesquita RB, Gonçalves CG, et al. Reference values for the incremental shuttle walking test. Respir Med. 2012;106(2):243-248. https://doi.org/10.1016/j.rmed.2011.07.023
14. Singh SJ, Morgan MD, Hardman AE, Rowe C, Bardsley PA. Comparison of oxygen uptake during a conventional treadmill test and the shuttle walking test in chronic airflow limitation. Eur Respir J. 1994;7(11):2016-2020. https://doi.org/10.1183/09031936.94.07112016
15. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. Eur Respir J. 2005;26(2):319-338. https://doi.org/10.1183/09031936.05.00034805
16. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624. https://doi.org/10.1164/rccm.166.4.518
17. Fess EE, Moran CA. Clinical Assessment Recommendations. Mount Laurel (NJ): American Society of Hand Therapists; 1981.
18. Zigmond AS, Snaith RP. The hospital anxiety and depression scale. Acta Psychiatr Scand. 1983;67(6):361-370. https://doi.org/10.1111/j.1600-0447.1983.tb09716.x
19. Sahin F, Yilmaz F, Ozmaden A, Kotevoglu N, Sahin T, Kuran B. Reliability and validity of the Turkish version of the Nottingham Extended Activities of Daily Living Scale. Aging Clin Exp Res. 2008;20(5):400-405. https://doi.org/10.1007/BF03325144
20. Steiner MC, Singh SJ, Morgan MD. The contribution of peripheral muscle function to shuttle walking performance in patients with chronic obstructive pulmonary disease. J Cardiopulm Rehabil. 2005;25(1):43-49. https://doi.org/10.1097/00008483-200501000-00010
21. de Camargo AA, Amaral TS, Rached SZ, Athanazio RA, Lanza FC, Sampaio LM, et al. Incremental shuttle walking test: a reproducible and valid test to evaluate exercise tolerance in adults with noncystic fibrosis bronchiectasis. Arch Phys Med Rehabil. 2014;95(5):892-899. https://doi.org/10.1016/j.apmr.2013.11.019
22. Daines L, Zheng B, Elneima O, Harrison E, Lone NI, Hurst JR, et al. Characteristics and risk factors for post-COVID-19 breathlessness after hospitalisation for COVID-19. ERJ Open Res. 2023;9(1):00274-2022. https://doi.org/10.1183/23120541.00274-2022
23. Mughal MS, Kaur IP, Jaffery AR, Dalmacion DL, Wang C, Koyoda S, et al. COVID-19 patients in a tertiary US hospital: Assessment of clinical course and predictors of the disease severity. Respir Med. 2020;172:106130. https://doi.org/10.1016/j.rmed.2020.106130
24. Johnsen S, Sattler SM, Miskowiak KW, Kunalan K, Victor A, Pedersen L, et al. Descriptive analysis of long COVID sequelae identified in a multidisciplinary clinic serving hospitalised and non-hospitalised patients. ERJ Open Res. 2021;7(3):00205-2021. https://doi.org/10.1183/23120541.00205-2021
25. Wu X, Liu X, Zhou Y, Yu H, Li R, Zhan Q, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. Lancet Respir Med. 2021;9(7):747-754. https://doi.org/10.1016/S2213-2600(21)00174-0
26. Cortés-Telles A, López-Romero S, Figueroa-Hurtado E, Pou-Aguilar YN, Wong AW, Milne KM, et al. Pulmonary function and functional capacity in COVID-19 survivors with persistent dyspnoea. Respir Physiol Neurobiol. 2021;288:103644. https://doi.org/10.1016/j.resp.2021.103644
27. Vitacca M, Paneroni M, Brunetti G, Carlucci A, Balbi B, Spanevello A, et al. Characteristics of COVID-19 Pneumonia Survivors With Resting Normoxemia and Exercise-Induced Desaturation. Respir Care. 2021;66(11):1657-1664. https://doi.org/10.4187/respcare.09029
28. Vonbank K, Lehmann A, Bernitzky D, Gysan MR, Simon S, Schrott A, et al. Predictors of Prolonged Cardiopulmonary Exercise Impairment After COVID-19 Infection: A Prospective Observational Study. Front Med (Lausanne). 2021;8:773788. https://doi.org/10.3389/fmed.2021.773788
29. Clavario P, De Marzo V, Lotti R, Barbara C, Porcile A, Russo C, et al. Cardiopulmonary exercise testing in COVID-19 patients at 3 months follow-up. Int J Cardiol. 2021;340:113-118. https://doi.org/10.1016/j.ijcard.2021.07.033
30. Orsucci D, Ienco EC, Nocita G, Napolitano A, Vista M. Neurological features of COVID-19 and their treatment: a review. Drugs Context. 2020;9:2020-5-1. https://doi.org/10.7573/dic.2020-5-1
31. Verveen A, Wynberg E, van Willigen HDG, Boyd A, de Jong MD, de Bree G, et al. Severe Fatigue in the First Year Following SARS-CoV-2 Infection: A Prospective Cohort Study. Open Forum Infect Dis. 2022;9(5):ofac127. https://doi.org/10.1093/ofid/ofac127
32. Townsend L, Dyer AH, Jones K, Dunne J, Mooney A, Gaffney F, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. PLoS One. 2020;15(11):e0240784. https://doi.org/10.1371/journal.pone.0240784
33. Tekerlek H, Cakmak A, Calik-Kutukcu E, Arikan H, Inal-Ince D, Saglam M, et al. Exercise Capacity and Activities of Daily Living are Related in Patients With Chronic Obstructive Pulmonary Disease. Arch Bronconeumol (Engl Ed). 2020;56(4):208-213. https://doi.org/10.1016/j.arbr.2019.06.018

J Bras Pneumol. 2023;49(6):e20230227
https://dx.doi.org/10.36416/1806-3756/e20230227

ORIGINAL ARTICLE

ELMO CPAP: an innovative type of ventilatory support for COVID-19-related acute respiratory distress syndrome

Andréa Mazza Beliero[1,2], Ana Paula Pires Lázaro[3,4], Marza de Sousa Zaranza[1,5], Giovanna Mazza Cruz Lima[4], Álvaro Rolim Guimarães[5], Nilcyeli Linhares Aragão[5], Gdayllon Cavalcante Meneses[5], Marcelo Alcantara Holanda[5,6], Polianna Lemos Moura Moreira Albuquerque[4,7], Geraldo Bezerra da Silva Júnior[3,4], Paula Frassinetti Castelo Branco Camurça Fernandes[2]

1. Instituto Dr. José Frota, Prefeitura Municipal de Fortaleza, Fortaleza (CE) Brasil.
2. Programa de Pós-Graduação em Saúde Coletiva, Centro de Ciências da Saúde, Universidade Estadual do Ceará, Fortaleza (CE) Brasil.
3. Programa de Pós-Graduação em Saúde Coletiva, Centro de Ciências da Saúde, Universidade de Fortaleza, Fortaleza (CE) Brasil.
4. Curso de Medicina, Centro de Ciências da Saúde, Universidade de Fortaleza, Fortaleza (CE) Brasil.
5. Programa de Pós-Graduação em Ciências Médicas, Departamento de Medicina Interna, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza (CE) Brasil.
6. Departamento de Medicina Clínica, Faculdade de Medicina, Universidade Federal do Ceará, Fortaleza (CE) Brasil.
7. Departamento de Análises Clínicas e Toxicológicas, Faculdade de Farmácia, Universidade Federal do Ceará, Fortaleza (CE) Brasil.

Submitted: 24 July 2023.
Accepted: 27 October 2023.

Study carried out at the Instituto Dr. José Frota, Prefeitura Municipal de Fortaleza, Fortaleza (CE) Brasil and under the auspices of the Programa de Pós-Graduação em Saúde Coletiva, Universidade Estadual do Ceará, Fortaleza (CE) Brasil.

ABSTRACT

Objective: To assess whether the use of ELMO, a helmet for noninvasive ventilation created in Brazil, had a positive impact on the prognosis of patients with hypoxemic respiratory failure caused by severe COVID-19. **Methods:** This is a retrospective study of 50 critically ill COVID-19 patients. Epidemiological, clinical, and laboratory data were collected on ICU admission, as well as before, during, and after ELMO use. Patients were divided into two groups (success and failure) according to the outcome. **Results:** ELMO use improved oxygenation parameters such as Pao_2, FIO_2, and the Pao_2/FIO_2 ratio, and this contributed to a gradual reduction in FIO_2, without an increase in CO_2, as determined by arterial blood gas analysis. Patients in the success group had significantly longer survival ($p < 0.001$), as determined by the Kaplan-Meier analysis, less need for intubation ($p < 0.001$), fewer days of hospitalization, and a lower incidence of acute kidney injury in comparison with those in the failure group. **Conclusions:** The significant improvement in oxygenation parameters, the longer survival, as reflected by the reduced need for intubation and by the mortality rate, and the absence of acute kidney injury suggest that the ELMO CPAP system is a promising tool for treating ARDS and similar clinical conditions.

Keywords: Respiratory distress syndrome; COVID-19; Noninvasive ventilation; Intensive care units.

INTRODUCTION

COVID-19 emerged as a pandemic in March of 2020. The shortage of mechanical ventilators and specialized health workforce in ICUs were the crucial points in resource allocation and planning.[1] The use of invasive mechanical ventilation (IMV) was often associated with an extremely high mortality rate during the first and second waves in Brazil, reaching up to 80% and 89.5% in two observational studies.[2,3] Therefore, noninvasive respiratory support strategies to prevent orotracheal intubation (OTI) were very much needed during the pandemic and were unfortunately not sufficiently available to the large number of severely ill patients, making the situation even more challenging to the Brazilian public health system.

Infection by COVID-19 leads to systemic inflammation and hypercytokinemia, causing endothelial dysfunction and a hypercoagulable state.[4,5] The clinical spectrum ranges from mild symptoms to more severe complications with multisystemic involvement, such as vascular disorders, acute kidney injury (AKI), heart failure, and circulatory shock, as well as long-term neurological, motor, and cardiopulmonary sequelae.[6,7] The main cause of ICU admissions is acute respiratory distress syndrome (ARDS), which often requires respiratory support.[8]

The need for alternative respiratory support strategies led to the development of innovative technologies to address these problems. ELMO is a new helmet interface that offers high-flow CPAP and up to 100% FIO_2 to treat COVID-19-related acute hypoxemic respiratory failure. It was originally designed to be used without ventilators and outside the ICU.[9,10] It provides complete neck sealing and respiratory

Correspondence to:
Andréa Mazza Beliero. Rua Cícero Alves de Souza, 126, CEP 60822-810, Fortaleza, CE, Brasil.
Tel.: 55 85 99949-1004. E-mail: andreamazza2009@hotmail.com
Financial support: This study received financial support from the Brazilian *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior* (CAPES, Office for the Advancement of Higher Education; Grants no. 88881.505364/2020-01 and no. 88881.507066/2020-01).

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

isolation of the patient's head, resulting in significant improvement of oxygenation parameters, no carbon dioxide rebreathing, and good patient comfort as shown in a pilot feasibility study.[11] This innovative, noninvasive equipment was designed in the state of Ceará, Brazil, in July of 2020 by a multidisciplinary taskforce from six different institutions involving the government, the industry, a public health school, and universities (Patent no. BR 20 2020 014212 2; ANVISA 82072609001).

The present investigation was designed to assess the impact of the use of the ELMO CPAP system on the prognosis of patients with hypoxemic respiratory failure caused by severe COVID-19 and to compare the major clinical and laboratory variables associated with its successful use, defined as improvement in respiratory failure without the need for IMV.

METHODS

Study design and selected COVID-19 patients

This was an observational, retrospective, single-center cohort study of critically ill COVID-19 patients admitted to the ICU of the *Instituto Dr José Frota*, a tertiary hospital located in the city of Fortaleza, Brazil, from March to May of 2021.

Data on clinical characteristics, treatment, and prognosis of these individuals were collected and correlated with mortality, survival, temporary and permanent sequelae in various organs, as well as the use of renal replacement therapy.

The sample comprised 50 adult patients (≥ 18 years of age) with a diagnosis of COVID-19 confirmed by RT-PCR who presented with hypoxemic respiratory failure secondary to COVID-19, were unresponsive to conventional oxygen therapy (non-response was defined as inability to achieve an Spo_2 ≥ 92% or with no clinical relief of tachypnea or dyspnea when using a nasal catheter with a flow ≤ 5 L/min or a reservoir mask with a flow ≤ 10 L/min), were admitted to the ICU and had an indication for ELMO use according to a pre-defined protocol. Patients admitted to the ICU were eligible for ELMO use if they were alert and cooperative.

Patients with exacerbations of lung diseases, such as asthma, COPD, and pulmonary fibrosis, were excluded. Patients with hemodynamic instability, heart disease, and/or chronic kidney disease, as well as those in use of vasoactive drugs, were excluded; these factors alone increase COVID-19 severity and the chance of needing IMV. Patients with clinically evident signs of respiratory muscle fatigue (paradoxical breathing or vigorous use of respiratory accessory muscles), nausea, vomiting, and/or ear canal disorders and those using a nasogastric or nasoenteric tube were also excluded because they had no indication for ELMO helmet use.

Data collection was performed using a cloud-based database program (Epimed Monitor ICU System; Epimed Solutions, Rio de Janeiro, Brazil). Demographic and epidemiological data, such as comorbidities (systemic arterial hypertension, diabetes mellitus, alcoholism, and lung disease), time from symptom onset to ICU admission, length of ICU stay, and outcome (discharge or death) were collected. Clinical and laboratory data were collected at ICU admission, as well as before, during, and after ELMO use.

Disease severity of patients admitted to the ICU was estimated using the Simplified Acute Physiology Score 3 (SAPS 3) collected at admission. For the diagnosis of AKI, the Kidney Disease: Improving Global Outcomes[12] criteria were used, and serum creatinine levels were measured three times within the first seven days of ICU stay.

Patients in whom ELMO use was considered successful were those who accepted and adapted well to wearing the helmet for at least eight continuous hours for at least three days, as well as showing improvement in vital signs, such as reduced respiratory effort, lower respiratory rate, and lower heart rate, resulting in an increase in Spo_2, in addition to improvement in arterial blood gases.

Clinical results were described: first, ELMO use failure and final outcome (discharge or death) were considered and, second, the time from hospital admission to discharge or death and reasons for ELMO use failure.

To verify the effects of ELMO use on pulmonary gas exchange, two arterial blood gas samples were collected: one at 30 min before ELMO use and one after 1 h of ELMO use. During the use of ELMO, the Pao_2/Fio_2 ratio (in mmHg/%) was measured, and improvement in this ratio was considered indicative of a good response to therapy. Vital signs were continuously monitored and recorded before and during ELMO use, as well as 1 h after ELMO removal. PEEP levels varied between 5 and 12 cmH_2O, and Fio_2 resulting from the gas mixture reached a flow of 60 L/min, being progressively reduced according to the patient's needs.

More details on the protocol for ELMO use are shown in the supplementary file.

Statistical analysis

Categorical data were evaluated as absolute and relative frequencies. For comparison of relative frequencies between groups, the chi-square test or the Fisher's exact test was used according to expected frequencies in 2 × 2 tables. Variables with continuous data were first explored for normality using the Shapiro-Wilk test, and, for the analysis of data asymmetry, histograms and Q-Q plots were used. Normal data were expressed as means ± standard deviations, whereas non-normal data were expressed as medians and interquartile ranges. For comparisons of continuous data between independent groups, the Student's t-test or the Mann-Whitney test was used according to normality. For dependent groups, paired t-test or Wilcoxon test (in non-normal data) was used.

Moreover, the prognostic value of ELMO use from ICU admission for chance of two-month survival was evaluated using Kaplan-Meier analysis treating intubation and death as dependent events. To test the differences between the groups regarding ELMO use, the log-rank Mantel-Cox test was applied. Data were analyzed using the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA). Values of $p < 0.05$ were considered statistically significant.

Ethical aspects

This study was approved by the institutional Research Ethics Committee (CAAE Protocol no. 67933523.1.0000.5047) and registered on the Brazilian National Research Ethics Committee platform (Protocol no. 4.026.888). All procedures are in accordance with Resolution no. 466/2012, which regulates research involving human participants in Brazil. The patients were informed about the study purpose, and upon acceptance to participate, they signed the free and informed consent form before the beginning of the evaluation. As some admitted patients required immediate ICU care and were unable to sign the term, a family member signed it.

RESULTS

During the study period, of the 296 patients admitted to the ICU, 53 (17.9%) met the criteria for ELMO use; however, 1 patient was excluded from the study due to incomplete data, and 2 were excluded because they died within the first 48 h of the study. Of the 50 patients who were included in the study, the majority were male (n = 31; 62%), and the mean age was 53.2 ± 13.6 years. A success rate of 56% (28/50 patients) was observed (Figure 1). Demographic characteristics, ventilatory parameters, and acid-base parameters on patient admission are described in Table 1.

All patients in the study had at least one comorbidity, often systemic arterial hypertension (in 44%) and diabetes mellitus (in 20%); however, there were no statistically significant differences between the failure and success groups regarding comorbidities (Table 1). Patients in the failure group had a higher mean SAPS 3 when compared with those in the success group (Table 1). All patients reported dyspnea at admission despite being on oxygen therapy. More than half of the patients (56%) had hypoxemia despite oxygen therapy use. No hypercapnia was observed in either group upon admission.

Improvement in oxygenation parameters was observed in both groups during ELMO use, but it was higher in the success group, mainly in Pao_2 and the Pao_2/Fio_2 ratio. $Paco_2$ did not significantly change in either group (Figure 2 and Table 2).

The average number of days from symptom onset to ICU admission was similar between the groups (Table 3). Regarding the causes of ELMO therapy failure, it was observed that 10 individuals (45.4%) showed signs of delirium, characterized by agitation, and altered level of consciousness, and therefore were unable to use ELMO. In addition. 11 patients (50%) developed worsening of symptoms, requiring subsequent intubation. Of the 22 patients in the failure group, only 1 rejected

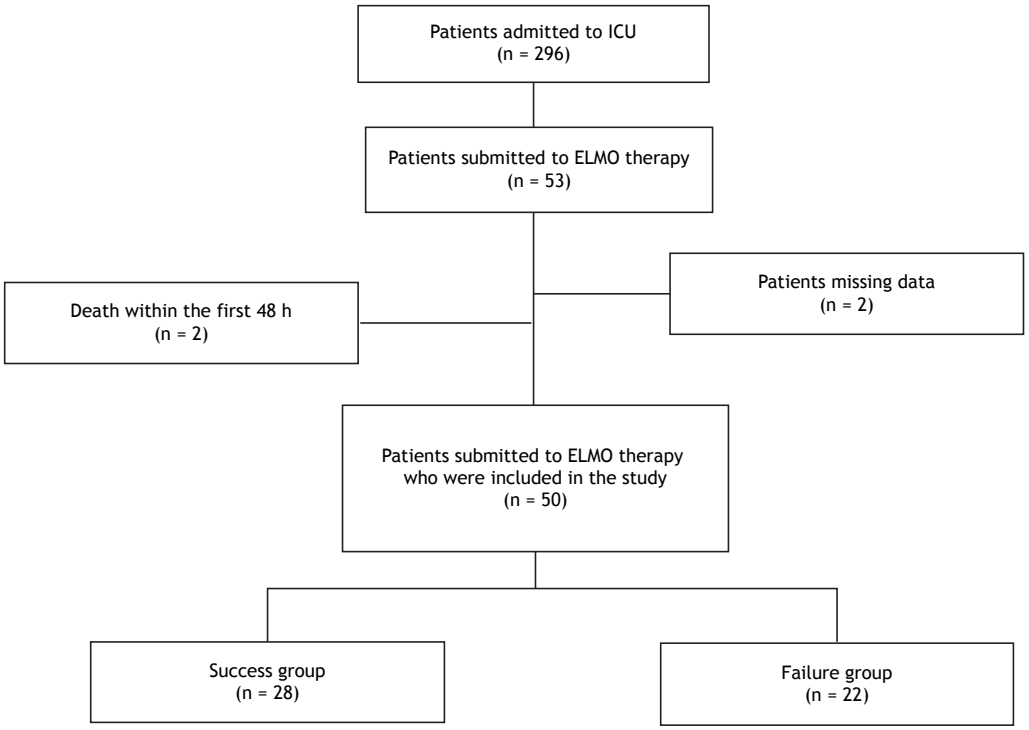


Figure 1. Flow chart of the patient selection process.

Table 1. Clinical and epidemiological characteristics, and ventilatory and biochemical parameters at ICU admission of patients with severe COVID-19 who used the ELMO system, by treatment outcome.[a]

Characteristic	Total	Group		p
		Failure	Success	
	(n = 50)	(n = 22)	(n = 28)	
Sex, male	31 (62.0)	11 (50.0)	20 (71.4)	0.121
Age, years	53.2 ± 13.6	53.8 ± 12.9	52.7 ± 14.3	0.940
SAPS 3	57.21 ± 9.67	60.45 ± 9.44	53.80 ± 8.90	0.030
Previous lung disease	7 (14.0)	4 (18.2)	3 (10.7)	0.684
Diabetes mellitus	10 (20.0)	5 (22.7)	5 (17.9)	0.732
Alcoholism	3 (6.0)	1 (4.5)	2 (7.1)	1.000
Systemic arterial hypertension	22 (44.0)	11 (50.0)	11 (39.3)	0.449
Hypoxemia (Spo_2 < 92%)	28 (56.0)	15 (68.2)	13 (46.4)	0.124
Dyspnea	50 (100)	22 (100)	28 (100)	-
Ventilatory and biochemical parameters				
Spo_2, mmHg	89.47 ± 14.59	84.86 ± 21.21	92.93 ± 4.05	0.147
pH	7.44 ± 0.06	7.45 ± 0.04	7.43 ± 0.07	0.102
Pao_2, mmHg	83.8 ± 30.8	81.6 ± 31.4	85.5 ± 30.8	0.538
$Paco_2$, mmHg	37.1 ± 9.6	35.8 ± 7.2	38.2 ± 11.2	0.443
HCO_3, mmol/L	24.7 ± 2.2	24.3 ± 2.2	25.0 ± 2.1	0.339
BE, mmol/L	1.2 [−0.2 to 2.3]	0.2 [−1.1 to 2.5]	1.25 [0.05-2.13]	0.292
Lactate, mmol/L	1.73 [1.13-2.17]	1.85 [1.13-2.52]	1.48 [1.09-2.13]	0.97
Sao_2, %	93.2 ± 4.3	92.5 ± 4.9	93.7 ± 3.8	0.049
Pao_2/Fio_2	126.3 ± 42.5	126.7 ± 49.1	125.9 ± 37.4	0.435

[a]Values expressed as n (%), mean ± SD, or median [IQR]. SAPS 3: Simplified Acute Physiology Score 3; HCO_3: bicarbonate; and BE: base excess.

ELMO use due to claustrophobia, anxiety symptoms, and increased respiratory rate (> 40 breaths/min).

The median length of ICU stay for patients in the failure and success groups was 19 and 15 days, respectively ($p < 0.05$). Overall, only 40.9% of the patients in the failure group were discharged from the ICU, while all the patients in the success group were discharged. The average daily duration of ELMO use was approximately 8 h.

It was observed that all patients who were successfully treated with ELMO CPAP therapy survived over the days until discharge without the need for OTI. However, 59.1% of the patients in the failure group died during the hospitalization period (Table 3 and Figure 3). The level of CPAP used ranged from 5 to 12 cmH_2O in both groups.

DISCUSSION

Many patients with COVID-19 experience mild to moderate symptoms (81%); however, if ARDS is present, oxygen therapy and some type of ventilatory support are essential.[10] This study showed satisfactory results with the use of the ELMO CPAP system in patients with mild to moderate hypoxemic respiratory failure due to complications from COVID-19.

Analysis of the acute effects on gas exchange before and during ELMO use disclosed a significant improvement in Sao_2, Pao_2 and the Pao_2/Fio_2 ratio. Its use is based on the rationale that PEEP and Fio_2 are the mainstays of respiratory support when the use of a nasal catheter and/or a reservoir mask fails. The improvement in oxygen levels related to the use of the ELMO helmet may have contributed to the survival of more than half of the patients who used it in this study. Patients with COVID-19 have diffuse alveolar damage, reduced respiratory system compliance, and impaired gas exchange.[13] Thus, adequate management of the pressures offered during assisted ventilation and of oxygenation parameters is essential for survival of these patients.

In the present study, we found that the use of the ELMO system was able to offer CPAP through a continuous oxygen flow and compressed air to patients who needed oxygen therapy for severe hypoxemia, resulting in improved oxygenation and gas exchange, allowing the gradual reduction of Fio_2, and avoiding the deleterious effects of oxygen without causing carbon dioxide rebreathing or hypercapnia. The device was used successfully in 28 patients. Moreover, our study showed a significant increase in the median Pao_2/Fio_2 ratio within the first hour of ELMO use.

One study demonstrated that when the Pao_2/Fio_2 ratio doubled from a median of 100 mmHg to 200 mmHg and remained above 150 mmHg during the first week, there was an association with a 91% probability of patient recovery without the need for OTI. This effect can be explained by the effect of CPAP on the recruitment of edematous and/or collapsed alveoli, with immediate improvement in the ventilation/perfusion ratio.[14]

Some studies support the hypothesis that positive pressure may favor a more uniform distribution of

perfusion, diverting blood flow from pulmonary areas with shunt and edema to those with a high ventilation/perfusion ratio.[15]

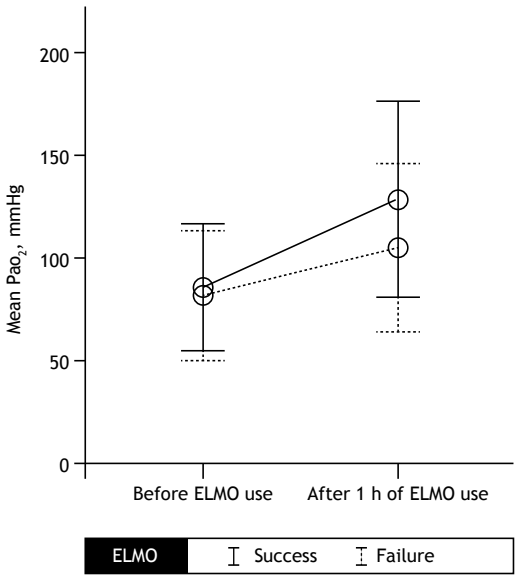


Figure 2. Box plot of Pao_2 before and after 1 h of ELMO use by outcome group (failure and success).

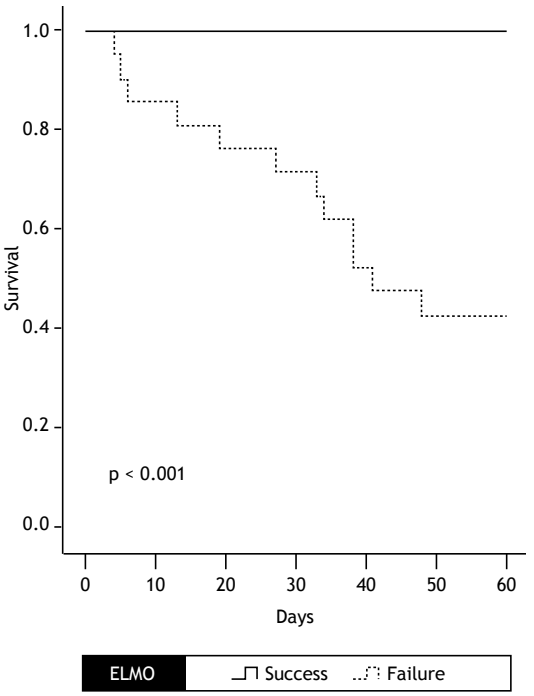


Figure 3. Chance of two-month survival—dependent events: death and intubation—by outcome group (failure and success). *Log-rank Mantel-Cox test.

Table 2. Ventilatory and biochemical parameters of patients with COVID-19 before and during ELMO use, by treatment outcome.[a]

Parameter	Failure group (n = 22)		p	Success group (n = 28)		p
	Before ELMO use	During ELMO use		Before ELMO use	During ELMO use	
Sao_2, %	92.5 ± 4.9	95.9 ± 2.5	0.001	93.7 ± 3.8	96.2 ± 2.4	0.010
pH	7.45 ± 0.04	7.44 ± 0.04	0.567	7.43 ± 0.07	7.43 ± 0.04	0.908
Pao_2,mmHg	81.6 ± 31.4	104.8 ± 41.1	0.067	85.5 ± 30.8	128.1 ± 47.8	< 0.001
$Paco_2$, mmHg	35.8 ± 7.2	35.5 ± 3.1	0.694	38.2 ± 11.2	37.6 ± 5.6	0.797
HCO_3, mmol/L	24.3 ± 2.2	24.3 ± 2.5	0.651	25.2 ± 2.1	25.2 ± 2.2	0.48
BE, mmol/L	0.2 [−1.1 to 2.5]	0.6 [−0.5 to 3.6]	0.173	1.25 [0.05-2.13]	0.9 [0.0-2.7]	0.948
Lactate, mmol/L	1.85 [1.13-2.52]	1.6 [1.0-2.12]	0.511	1.48 [1.09-2.13]	1.66 [1.23-2.00]	0.518
Pao_2/Fio_2	126.7 ± 49.1	177.08 ± 83.27	0.024	125.9 ± 37.4	217.56 ± 113.13	< 0.001

[a]Values expressed as mean ± SD or median [IQR]. HCO_3: bicarbonate; and BE: base excess.

Table 3. Clinical complications and outcomes of patients with severe COVID-19 who used the ELMO system in the ICU at a tertiary care hospital in the city of Fortaleza, Brazil.[a]

Variable	Group		p
	Failure (n = 22)	Success (n = 28)	
From symptom onset to ICU admission, days	10.5 [8-13]	10 [8.5-12.0]	0.655
Final outcome			
Hospital discharge	9 (40.9)	28 (100)	< 0.001
Death	13 (59.1)	0 (0.0)	
Time from admission to death, days	30 [9.5-38.0]	0	< 0.001
Time from admission to discharge, days	19 [15-30]	15 [11-16]	< 0.001
Acute renal injury			
Yes	12 (54.5)	0 (0.0)	< 0.001
No	10 (45.5)	28 (100)	

[a]Values expressed as n (%) or median [IQR].

In our study, patients in the failure group were more severely ill according to the SAPS 3 already on admission. Although SAPS 3 is not part of the ELMO protocol, there are similar parameters among the forms of assessment, such as vital signs and use of IVM. In a study of 1.464 patients, SAPS 3 was found to perform satisfactorily in the prognosis of in-hospital mortality in patients with COVID-19 admitted to the ICU.[16]

The patients in our study wore the ELMO helmet for at least eight continuous hours a day, with an initial PEEP of 5 cmH_2O, increased according to Spo_2 levels. After ELMO helmet removal, the patients were placed on oxygen therapy using a nasal catheter with a flow at 3-5 L/min, according to Spo_2 levels. A study carried out with the same helmet showed no adverse effects in such patients.[11]

During the period when the intervention took place, there was a reduction in the number of patients who required IMV. Of the 50 patients that comprised the study sample, 28 (56%) did not require IMV and were discharged from the hospital, corroborating the recommendations of previous studies, which hypothesized a reduction of approximately 60% of cases that later required IMV.

In the present study, it was possible to observe that none of the patients in whom ELMO was used successfully developed AKI. However, half of the patients in the failure group developed AKI, and some died, in line with studies that correlated the occurrence of AKI, COVID-19, and increased mortality.[17] Although IMV is sometimes necessary as a lifesaving intervention in critically ill patients, its implementation affects the renal system, reaching a three-fold increased risk of AKI,[18,19] especially when associated with IMV and elevated PEEP.[20,21]

The main findings of the present study, such as improvement in oxygenation parameters and possibly better prognosis of patients with COVID-19-related ARDS, suggest that the new ELMO helmet is a promising technological innovation with a positive impact on these individuals.

The limitations of this study are primarily related to the lack of a control group, making it impossible to compare the intervention with other types of non-invasive ventilatory support. Second, this study was carried out in a single center and had a retrospective design. Third, insufficient recording of data in some medical records limited the access to information for a more in-depth evaluation. On the other hand, the study adds some little explored information related to the use of NIV, the use of a new type of helmet, and its direct and indirect effects on renal function in severely hypoxemic patients, stimulating the construction of alternative strategies that can minimize the undesirable effects of IMV with positive pressure. Another advantage is that ELMO can be used outside the ICU.

Future research will be necessary to evaluate different groups, with similar clinical pictures prospectively and over a longer period of time, comparing the use of the ELMO CPAP with other types of respiratory support in order to verify their clinical effects in critically ill patients with hypoxemic respiratory failure of other etiologies.

ACKNOWLEDGEMENTS

We are incredibly grateful to the entire team of professionals at the *Instituto Dr. José Frota* who joined forces to care for the critically ill patients with COVID-19 and contributed to the collection of the data used in this study.

AUTHOR CONTRIBUTIONS

AMB: study conception and planning, data selection and interpretation, and project administration. APPL, MSZ, ARG, ARG MMPD, GMCL, NLA, and LCBCF: study design, and literature research and selection. GBSJ, MAH, and PFCBCF: critical revision of the manuscript. GCM: study design, data interpretation, and formal analysis. PLMMA: funding acquisitions. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

MAH participated as the final reviewer of this manuscript. However, this author was one of the technical developers of the ELMO helmet and holds the patent registration. The other authors have no conflict of interest to disclose.

REFERENCES

1. Chang R, Elhusseiny KM, Yeh YC, Sun WZ. COVID-19 ICU and mechanical ventilation patient characteristics and outcomes-A systematic review and meta-analysis. PLoS One. 2021;16(2):e0246318. https://doi.org/10.1371/journal.pone.0246318
2. Ranzani OT, Bastos LSL, Gelli JGM, Marchesi JF, Baião F, Hamacher S, et al. Characterisation of the first 250,000 hospital admissions for COVID-19 in Brazil: a retrospective analysis of nationwide data. Lancet Respir Med. 2021;9(4):407-418. https://doi.org/10.1016/s2213-2600(20)30560-9
3. Porto APM, Neto JX, Moreira FJF, Júnior ABV, das Dores CCC, Júnior ARC, et al. Mortality in a swiftly repurposed hospital in northeast Brazil during the first and second COVID-19 waves: A retrospective cohort study. IJID Reg. 2023;7:182-190. https://doi.org/10.1016/j.ijregi.2023.03.009
4. Jose RJ, Manuel A. COVID-19 cytokine storm: the interplay between inflammation and coagulation. Lancet Respir Med. 2020 Jun;8(6):e46-e47. https://doi.org/10.1016/S2213-2600(20)30216-2
5. Ye Q, Wang B, Mao J. The pathogenesis and treatment of the `Cytokine Storm' in COVID-19. J Infect. 2020 Jun;80(6):607-613. https://doi.org/10.1016/j.jinf.2020.03.037
6. Lázaro APP, Albuquerque PLMM, Meneses GC, Zaranza MS, Batista AB, Aragão NLP, et al. Critically ill COVID-19 patients in northeast Brazil: mortality predictors during the first and second waves including SAPS 3. Trans R Soc Trop Med Hyg. 2022;116(11):1054-1062. https://doi.org/10.1093/trstmh/trac046
7. Pecly IMD, Azevedo RB, Muxfeldt ES, Botelho BG, Albuquerque GG, Diniz PHP, et al. A review of Covid-19 and acute kidney injury: from pathophysiology to clinical results. J Bras Nefrol. 2021;43(4):551-571. https://doi.org/10.1590/2175-8239-jbn-2020-0204

8. da Silva SJR, do Nascimento JCF, Germano Mendes RP, Guarines KM, Targino Alves da Silva C, da Silva PG, et al. Two Years into the COVID-19 Pandemic: Lessons Learned. ACS Infect Dis. 2022;8(9):1758-1814. https://doi.org/10.1021/acsinfecdis.2c00204
9. Holanda MA, Tomaz BS, Menezes DGA, Lino JA, Gomes GC. ELMO 1.0: a helmet interface for CPAP and high-flow oxygen delivery. J Bras Pneumol. 2021;47(3):e20200590. https://doi.org/10.36416/1806-3756/e20200590
10. Mazza M, Fiorentino G, Esquinas AM. ELMO helmet for CPAP to treat COVID-19-related acute hypoxemic respiratory failure outside the ICU: aspects of/comments on its assembly and methodologyAuthors' replyPatient self-inflicted lung injury and positive end-expiratory pressure for safe spontaneous breathingELMO 1 0: a helmet interface for CPAP and high-flow oxygen deliveryProtecting healthcare workers from SARS-CoV-2 infection practical indications. J Bras Pneumol. 2022;48(2):e20220072. https://doi.org/10.36416/1806-3756/e20220072
11. Tomaz BS, Gomes GC, Lino JA, Menezes DGA, Soares JB, Furtado V, et al. ELMO, a new helmet interface for CPAP to treat COVID-19-related acute hypoxemic respiratory failure outside the ICU: a feasibility study. J Bras Pneumol. 2022;48(1):e20210349. https://doi.org/10.36416/1806-3756/e20210349
12. Kellum JA, Lameire N; KDIGO AKI Guideline Work Group. Diagnosis, evaluation, and management of acute kidney injury: a KDIGO summary (Part 1). Crit Care. 2013;17(1):204. https://doi.org/10.1186/cc11454
13. Arabi YM, Aldekhyl S, Al Qahtani S, Al-Dorzi HM, Abdukahil SA, Al Harbi MK, et al. Effect of Helmet Noninvasive Ventilation vs Usual Respiratory Support on Mortality Among Patients With Acute Hypoxemic Respiratory Failure Due to COVID-19: The HELMET-COVID Randomized Clinical Trial. JAMA. 2022;328(11):1063-1072. https://doi.org/10.1001/jama.2022.15599
14. Penkins GD, Ji C, Connolly BA, Couper K, Lall R, Baillie JK, et al. Effect of Noninvasive Respiratory Strategies on Intubation or Mortality Among Patients With Acute Hypoxemic Respiratory Failure and COVID-19: The RECOVERY-RS Randomized Clinical Trial. JAMA. 2022;327(6):546-558. https://doi.org/10.1001/jama.2022.0028
15. Coppadoro A, Benini A, Fruscio R, Verga L, Mazzola P, Bellelli G, et al. Helmet CPAP to treat hypoxic pneumonia outside the ICU: an observational study during the COVID-19 outbreak. Crit Care. 2021;25(1):80. https://doi.org/10.1186/s13054-021-03502-y
16. Metnitz PGH, Moreno RP, Fellinger T, Posch M, Zajic P. Evaluation and calibration of SAPS 3 in patients with COVID-19 admitted to intensive care units. Intensive Care Med. 2021;47(8):910-912. https://doi.org/10.1007/s00134-021-06436-9
17. Moitinho MS, Belasco AGDS, Barbosa DA, Fonseca CDD. Acute Kidney Injury by SARS-CoV-2 virus in patients with COVID-19: an integrative review. Rev Bras Enferm. 2020;73 Suppl 2:e20200354. https://doi.org/10.1590/0034-7167-2020-0354
18. Camporota L, Vasques F, Sanderson B, Barrett NA, Gattinoni L. Identification of pathophysiological patterns for triage and respiratory support in COVID-19. Lancet Respir Med. 2020;8(8):752-754. https://doi.org/10.1016/S2213-2600(20)30279-4
19. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area [published correction appears in JAMA. 2020 May 26;323(20):2098]. JAMA. 2020;323(20):2052-2059. https://doi.org/10.1001/jama.2020.6775
20. Cosentini R, Brambilla AM, Aliberti S, Bignamini A, Nava S, Maffei A, et al. Helmet continuous positive airway pressure vs oxygen therapy to improve oxygenation in community-acquired pneumonia: a randomized, controlled trial. Chest. 2010;138(1):114-120. https://doi.org/10.1378/chest.09-2290
21. Cunha NVA, Magro MCS. Acute kidney injury in critically ill patients on positive pressure mechanical ventilation. Acta Paul Enferm. 2022;35:eAPE0326345. https://doi.org/10.37689/acta-ape/2022AO0326345

J Bras Pneumol. 2023;49(6):e20230269
https://dx.doi.org/10.36416/1806-3756/e20230269

SPECIAL ARTICLE

Brazilian Thoracic Association recommendations for the management of post-tuberculosis lung disease

Denise Rossato Silva[1], Ana Paula Santos[2,3], Dina Visca[4,5], Sidney Bombarda[6], Margareth Maria Pretti Dalcolmo[7], Tatiana Galvão[8], Silvana Spíndola de Miranda[9], Ana Alice Amaral Ibiapina Parente[10], Marcelo Fouad Rabahi[11], Roberta Karla Barbosa de Sales[12], Giovanni Battista Migliori[13], Fernanda Carvalho de Queiroz Mello[2]

1. Faculdade de Medicina, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.
2. Instituto de Doenças do Tórax, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
3. Hospital Universitário Pedro Ernesto, Universidade do Estado do Rio de Janeiro – UERJ – Rio de Janeiro (RJ) Brasil.
4. Dipartimento di Pneumologia Riabilitativa, Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.
5. Dipartimento di Medicina e Chirurgia, Malattie Respiratorie, Università Degli Studi Dell'Insubria, Varese-Como, Italia.
6. Secretaria de Estado da Saúde de São Paulo, Centro de Vigilância Epidemiológica Professor Alexandre Vranjac – CVE-SSP-SP – São Paulo (SP) Brasil
7. Centro de Referência Hélio Fraga, Fundação Oswaldo Cruz – Fiocruz – Rio de Janeiro (RJ) Brasil.
8. Hospital Universitário Professor Edgar Santos. Universidade Federal da Bahia – UFBA – Salvador (BA) Brasil.
9. Faculdade de Medicina, Universidade Federal de Minas Gerais – UFMG – Belo Horizonte (MG) Brasil.
10. Departamento de Pediatria, Universidade Federal do Rio de Janeiro – UFRJ – Rio de Janeiro (RJ) Brasil.
11. Faculdade de Medicina, Universidade Federal de Goiás, Goiânia (GO) Brasil.
12. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
13. Servizio di Epidemiologia Clinica delle Malattie Respiratorie, Istituti Clinici Scientifici Maugeri – IRCCS – Tradate, Italia.

Submitted: 14 August 2023.
Accepted: 29 September 2023.

ABSTRACT

Historically, all efforts against tuberculosis were focused on rapid diagnosis and effective treatment to break the chain of transmission of *Mycobacterium tuberculosis*. However, in the last few years, more and more evidence has been found on the dramatic consequences of the condition defined as post-tuberculosis lung disease (PTLD). Approximately one third of patients surviving pulmonary tuberculosis face considerable ongoing morbidities, including respiratory impairment, psychosocial challenges, and reduced health-related quality of life after treatment completion. Given the important global and local burden of tuberculosis, as well as the estimated burden of PTLD, the development of a consensus document by a Brazilian scientific society—*Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT)—was considered urgent for the prevention and management of this condition in order to allocate resources to and within tuberculosis services appropriately and serve as a guide for health care professionals. A team of eleven pulmonologists and one methodologist was created by the SBPT to review the current evidence on PTLD and develop recommendations adapted to the Brazilian context. The expert panel selected the topics on the basis of current evidence and international guidelines. During the first phase, three panel members drafted the recommendations, which were divided into three sections: definition and prevalence of PTLD, assessment of PTLD, and management of PTLD. In the second phase, all panel members reviewed, discussed, and revised the recommendations until a consensus was reached. The document was formally approved by the SBPT in a special session organized during the 2023 SBPT Annual Conference.

Keywords: Tuberculosis; Post-infectious disorders; Disease management.

INTRODUCTION

Tuberculosis, in addition to the physical and psychological problems that are associated with the disease, the disease-related stigma, and considerable financial costs, also entails a condition defined as post-tuberculosis lung disease (PTLD), which has so far been little studied, but which has recently received the spotlight.[1]

Historically, all efforts against tuberculosis were focused on rapid diagnosis and effective treatment, trying to break the chain of transmission of *Mycobacterium tuberculosis*. However, in the last few years, the impact of damaging long-term sequelae due to pulmonary tuberculosis has duly been valued for individual patients, their households, their communities, and health systems.[2]

Approximately one third of patients who survive pulmonary tuberculosis face, after treatment completion, a considerable and often underrecognized burden of ongoing morbidity, including respiratory impairment, psychosocial challenges, and reduced health-related quality of life.[3,4] Even mortality is higher in PTLD patients, with a risk of death up to six times higher than in the general population.[5,6]

Despite the recent increase in PTLD-related publications, epidemiological data of the global burden and morbidity associated with PTLD are still limited because of lack of priority by national tuberculosis programs and the relative complexity of the

Correspondence to:
Denise Rossato Silva. Rua Ramiro Barcelos, 2350, sala 2050, Santa Cecília, CEP 90035-903, Porto Alegre, RS, Brasil.
Tel.: 55 55 3359-8241. E-mail: denise.rossato@terra.com.br
Financial support: The present document received financial support from the GSK by means of an educational grant to the Brazilian Thoracic Association.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

diagnostic approach, which includes, among others, clinical, radiological, and lung function assessment.[7,8]

It is evident that PTLD sequelae contribute to excess mortality and morbidity,[9] causing radiological and functional disabilities, favoring other complications (e.g., other infections, hemoptysis, etc.), impairing quality of life, and, therefore, boosting hospitalization and costs to health care systems. Early assessment and management of PTLD-related morbidity guided by solid recommendations by a scientific society are of paramount importance to ensure appropriate allocation of resources to and within tuberculosis services in order to provide quality-assured PTLD prevention, diagnosis, and treatment.[3]

The present *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) recommendations apply to patients with PTLD in the Brazilian context. A panel of 11 pulmonologists and one methodologist, including two international experts, were invited by the SBPT to review the current knowledge on the topic and develop Brazilian-specific recommendations. An expert panel selected the topics based on current evidence and international guidelines available as of July of 2023. During the first phase, three panel members drafted the recommendations, which were divided into three sections: PTLD description and prevalence; PTLD assessment; and PTLD management. In the second phase, all panel members reviewed, discussed, and revised the recommendations until a consensus was reached. The document was formally approved by the SBPT in a special session organized during the 2023 SBPT Annual Conference, held in the city of Curitiba, Brazil.

DEFINITION

PTLD was defined during the First International Symposium on Post-Tuberculosis disease, held in Stellenbosch, South Africa, as the "evidence of chronic respiratory abnormality, with or without symptoms, attributable at least in part to previous (pulmonary) tuberculosis."[1] PTLD includes a wide variety of functional and structural lung sequelae, ranging from mild to severe disorders. Cavitation, bronchiectasis, pleural thickening, fibrosis, and pulmonary hypertension are some examples of tuberculosis sequelae. In addition, patients may suffer colonization and infection with *Aspergillus fumigatus*, nontuberculous mycobacteria, and other bacteria.[1,10-16] Lung function deficits described in patients with PTLD include obstruction, restriction, or a mixed pattern, and approximately 10% of those lose more than half of their lung function.[17] In fact, as compared to the general population, patients with PTLD are twice more likely to have spirometric abnormalities.[18] As a consequence of lung sequelae, persistent respiratory symptoms are frequent, such as dyspnea, cough, wheezing, and reduced exercise capacity.[19]

EPIDEMIOLOGY

Despite the recent increase in the number of PTLD-related publications, the real epidemiological burden of PTLD is not well known.[12] It is estimated that up to 50% of tuberculosis survivors live with some kind of sequelae.[20] Also, the mortality rate in this group of patients can be up to 3-to 6-fold higher when compared with that in the general population.[5,6,21]

According to previous studies, the prevalence of PTLD can vary from 18% to 87%.[22] This wide range can be attributed to the different scenarios analyzed and to the diverse parameters used to diagnose PTLD. In a recent comparison of three different cohort studies involving PTLD patients in Brazil, Italy, and Mexico, pulmonary function tests showed different results, the majority of which showed obstructive, mixed, and normal patterns, respectively.[23]

Another study used radiological patterns to evaluate the prevalence of PTLD, and the results varied according to the type of examination (chest CT or X-ray) and the residual abnormality found (cavitation, bronchiectasis, fibrosis, nodules, emphysema, or consolidation).[24]

The possible different ways to characterize and define PTLD hinder the generalization of several studies, and few data can correlate structural damage identified in chest radiological imaging, functional impairment, respiratory symptoms, and quality of life. In 2022, a meta-analysis conducted by Maleche-Obimbo et al.[25] identified pooled prevalence of abnormal lung function, persistent respiratory symptoms, and radiological abnormalities of 46.7%, 41.0%, and 64.6%, respectively. The magnitude of any type of PTLD varied according to HIV status, geographic settings, smoking habits, and urban/rural settings.

ASSESSMENT OF PTLD

Ideally, every patient completing tuberculosis treatment should be clinically evaluated to identify post-tuberculosis sequelae as soon as possible.[26] Essential examinations/investigations recommended to identify PTLD are described in Chart 1. It is likely that not all of those examinations/investigations can be performed in many settings. In that case, some examinations/investigations should be prioritized, especially in those patients with persistent symptoms.[1,4,10,12,22,26-32]

Clinical history and examination

The clinical patterns of PTLD include a wide spectrum of signs and symptoms, varying from asymptomatic to severe disability. Tuberculosis survivors usually present with a high prevalence of respiratory manifestations such as chronic cough and dyspnea.[33] The clinical examination must focus on respiratory rate, heart rate, and BMI on a routine basis.[1]

Patients with residual structural abnormalities can have infectious exacerbations and are even at a higher risk of having active tuberculosis again.[34] Bacterial,

Chart 1. Recommended examinations to be conducted at the end of tuberculosis treatment.

Parameter	Measurement tool
Clinical history and examination	Symptoms: cough, dyspnea, wheezing[a] Environmental exposures[a] Comorbidities[a] Physical examination: respiratory rate, heart rate, and BMI[a]
Chest imaging	Chest X-ray[a] Chest CT scanning
Pulmonary function testing	Spirometry, including pre- and post-bronchodilator test[a] Plethysmography DL_{CO} Six-minute walk test[a]
Blood gas analysis	Arterial blood gas analysis Pulse oximetry[a]
Cardiopulmonary evaluation	Cardiopulmonary exercise testing
Subjective evaluation	Symptom score and quality-of-life instrument[a]

[a]Examinations/investigations that should be prioritized when all cannot be carried out.

viral, fungal, and nontuberculous mycobacterial diseases, which might complicate due to subsequent hemoptysis, can be severe and potentially life-threatening.[7] Patients also experience high rates of hospitalization and respiratory-related mortality.[33]

It is noteworthy that factors other than tuberculosis sequelae can influence PTLD and its outcomes, such as environmental exposure to smoking, substance abuse, biomass smoke and occupational exposures. In addition, cardiopulmonary comorbidities and those caused by other diseases can also worsen PTLD outcomes.[1,7,22]

Chest imaging

Although chest imaging is an important tool for evaluating PTLD patients, it should not be used alone to define post-tuberculosis lung damage, as patients can be asymptomatic or have no functional impairment, and have abnormal imaging indicating post-tuberculosis cure.[35]

Both chest X-rays and chest CTs are useful in the evaluation of lung structural damage of tuberculosis survivors.[24] Although CT imaging showed to be more sensitive in the identification of a diverse range of residual pathologies,[24] CT availability, costs, and radiation impact must be taken into consideration to decide which option best fits each specific case and scenario.

The most common radiological patterns of PTLD reported in a systematic review were cavitation, bronchiectasis, and fibrosis. In addition, nodules, consolidation, emphysema, pleural thickening, and mosaic patterns can also be noticed.[35] Figure 1 shows some radiological patterns of PTLD.

Pulmonary function testing

In 2015, a study designated Burden of Obstructive Lung Disease[11] assessed the association of pulmonary function impairment with a history of tuberculosis in a large, international, population-based sample and found that previous tuberculosis was associated with both airflow obstruction and spirometric restriction, and it should be considered as a potentially important cause of obstructive disease and reduced lung function.

Until now, there has been no consensus on which disorder is the most prevalent in individuals with tuberculosis sequelae. A recent prospective cohort study conducted in Malawi showed that 34.4% of participants had abnormal spirometry by the end of antituberculosis treatment.[33] After 3 years, 27.9% still presented abnormal pulmonary function test results, mostly of obstructive nature (15.8%).[33]

The healing process that the lungs undergo during and after antituberculosis treatment is likely to cause structural damage, leading to loss of parenchymal tissue and restrictive pattern on spirometry. It is less clear what mechanisms cause airflow obstruction associated with tuberculosis. The two most widely accepted hypotheses are (i) the development of airway disease (bronchiectasis and bronchial stenosis), and (ii) immunological factors that can induce bronchial hyperresponsiveness.[11]

Therefore, whenever plethysmography or lung volume measurements are feasible, they should complement spirometry to confirm obstructive, restrictive, or even mixed patterns of pulmonary disease since the type of ventilatory defect can be heterogeneous and vary in different populations.[23]

Decreases in DLCO can occur even in patients with normal spirometry and could be a better tool for lung function evaluation in PTLD patients.[36] Furthermore, they can also correlate with cardiopulmonary exercise testing and predict oxygen consumption when that test is unavailable.[37]

As well as for the evaluation of other pulmonary and cardiac diseases, the six-minute walk test (6MWT) helps evaluate PTLD patients. This test is cheap, simple, and very useful for studying functional limitations in tuberculosis survivors and for designing appropriate rehabilitation programs for PTLD patients.[38]

Blood gas analysis

In patients with severe clinical, radiological, and/or functional disabilities, arterial blood gas analysis

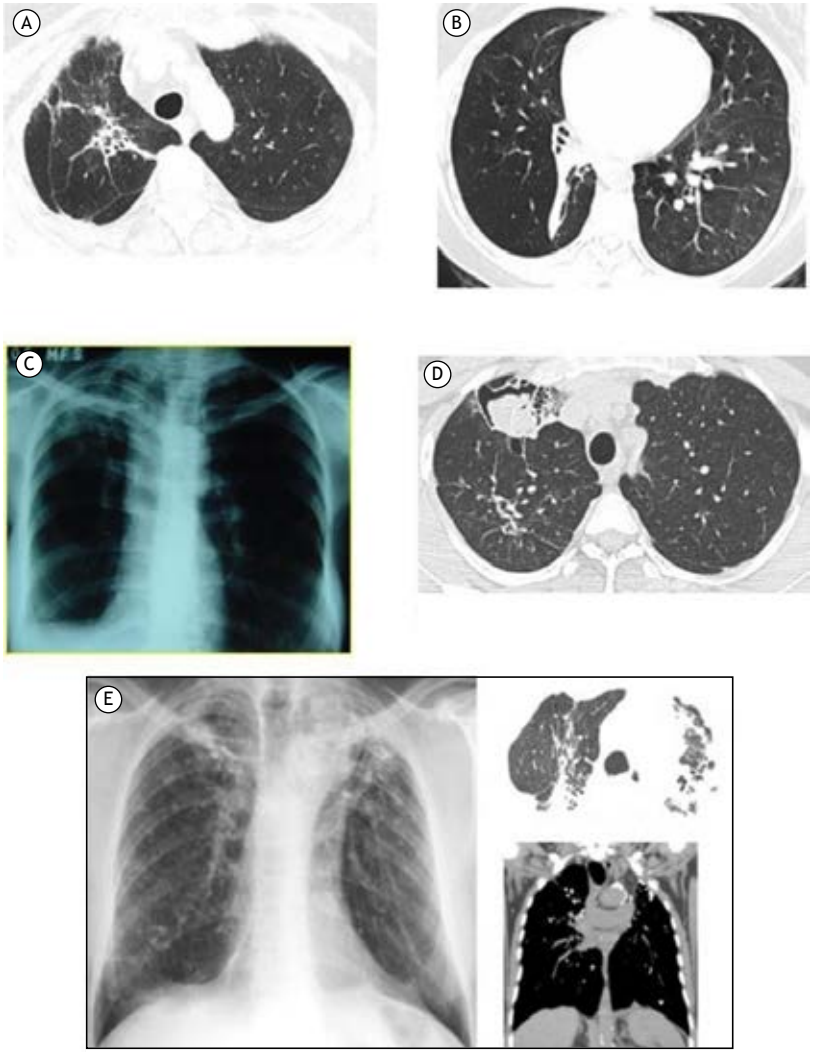


Figure 1. Radiological patterns of post-tuberculosis lung disease. In A, a chest CT scan showing irregular dense opacity with bronchiectasis from the hilum to the right lung apex associated with apical pleural thickening, elevation of the hilum, and volumetric reduction on this side. In B, a chest CT scan showing consolidative opacity with a fibroatelectatic appearance in the right lower lobe, predominantly affecting the anterior, lateral, and posterior basal segments, determining its volumetric reduction and highlighting the associated bronchiectasis in the anterior basal segment. Cylindrical bronchiolectasis in the upper segment of the right lower lobe. In C, a chest X-ray showing fibrotic opacity in the right upper lobe with pleural thickening and volumetric reduction of the right lung, leading to elevation of the right phrenic dome. In D, a chest CT scan showing a residual excavated lesion in the anterior segment of the right upper lobe filled with mobile contents upon change of decubitus, corroborating repercussions of superimposed saprophytic fungal infectious involvement. In E, imaging scans showing confluent laminar atelectasis, volumetric loss, and architectural distortion in the upper lobes, with intervening calcifications, favoring chronic/residual changes.

(whenever possible) or even oxygen saturation measurement using pulse oximetry can identify hypoxemic patients.

The indications for home oxygen therapy should be the same as those for patients with chronic airway diseases, that is, Pa_{O_2} < 55 mmHg, Sp_{O_2} < 88% on room air, Pa_{O_2} between 56 and 59 mmHg associated with *cor pulmonale*, and/or hematocrit > 55%.[39]

Cardiopulmonary exercise testing

Cardiopulmonary exercise testing provides a global assessment of integrative exercise responses involving cardiovascular, respiratory, muscular, and metabolic systems during exertion, being considered the gold standard for cardiorespiratory functional assessment.[40]

In 2022, Curry et al.[37] found that, although statistically significant, the correlations of any lung function patterns, if measured using spirometry, DL_{CO}, or even plethysmography, with oxygen consumption measured on cardiopulmonary exercise testing, which is considered to be the gold standard for lung capacity measurement, were weak.[1] Despite its importance, cardiopulmonary exercise testing is not always available.

Symptom and quality of life scores

Specific severity scores are still unavailable for PTLD patients, but there is consensus on the urgency of a scoring system evaluating mortality, health-related quality of life, rate of lung function decline, exacerbations/hospitalizations, and tuberculosis recurrence.[1]

Different questionnaires of health-related quality of life are available and should be used in the follow-up of PTLD patients, such as the St George's Respiratory Questionnaire and the Short-Form Health Survey (with 12 or 36 questions).[1,26]

Specific considerations for children

Evaluation at the end of treatment should follow the same recommendations proposed for adults, although there is a lack of data regarding children. Chest CT is not usually indicated due to radiation exposure, but it may be considered in cases with chronic symptoms and abnormal radiological findings in order to assess the extent of disease and/or exclude other diagnoses. Pulmonary function tests should be considered in all 4-to 6-year-old children with severe lung impairment. In children ≥ 4 years of age, exercise capacity can be assessed using the 6MWT. Quality of life questionnaires such as the EQ-5D-Y and the Toddler and Infant (TANDI) instrument can be used with local adaptations for younger children.[26]

MANAGEMENT OF PTLD

Currently, there are no evidence-based guidelines for PTLD management, but the increasing scientific literature on the topic has raised several issues that could help the follow-up of these patients.[2,26]

Inhaled and oral treatment

For those whose functional obstructive disease has been established, inhaled bronchodilators may be useful to reduce symptoms of dyspnea and prevent a decline in lung function.[7] Despite the absence of evidence to recommending routine bronchodilator use in PTLD, small studies have suggested that long-acting β_2 agonists and long-acting muscarinic antagonists could improve lung function and dyspnea.[7,24]

Inhaled corticosteroids must be avoided since they can increase the frequency of exacerbations and the risk of mycobacterial diseases.[41,42] However, following the recommendations applied to noncystic bronchiectasis, in cases of PTLD associated with asthma, inhaled corticosteroid therapy may be justified.[24] Similarly, for chronic inflammation in patients with noncystic fibrosis bronchiectasis, the use of macrolides is recommended for a minimum period of 6-12 months in patients with bronchiectasis and at least two exacerbations per year.[39]

Infectious complications

Clinical approach to exacerbations of infectious and noninfectious etiology must be the same as those applied for noncystic fibrosis bronchiectasis.[39]

In addition to respiratory infections of bacterial and viral etiology, fungal complications are frequent in post-tuberculosis lung sequelae. *Aspergillus* sp. can present in different ways and severity levels—from only colonization in a fungus ball shaping (aspergilloma) to infiltration in the lung parenchyma and/or pleural tissue with destruction and new cavities (chronic pulmonary aspergillosis).[7,32] Diagnostic criteria for this last presentation include the presence of respiratory or constitutional symptoms for at least 3 months, suggestive radiological findings, and serological or microbiological evidence of *Aspergillus* sp. Treatment for aspergillomas in asymptomatic patients could be only "follow-up"; however, surgical management is necessary in cases with multiple episodes of hemoptysis. On the other hand, invasion and destruction of lung parenchyma will require antifungal management.[32] Prescription of long-term oral antifungal drugs, such as itraconazole at a dose of 400 mg/day or voriconazole at a dose of 400 mg/day, administered for at least 6 months is the recommended first-line therapy for chronic pulmonary aspergillosis and has been associated with improvement in quality of life, relief of symptoms, and delay in disease progression.[43]

Pulmonary rehabilitation

Former tuberculosis patients with clinical, functional, or radiological findings consistent with PTLD should be evaluated for pulmonary rehabilitation (PR).[26] Chart 2 shows the indications for PR in detail, including impaired pulmonary function and/or impaired DLco[44]; abnormal blood gas analysis results and/or nocturnal

Chart 2. Indications for pulmonary rehabilitation.

- Impaired pulmonary function showing airflow obstruction or restriction (or mixed abnormalities) and bronchodilator response and/or impaired DL_{co}
- Abnormal blood gas: Pao_2 < 80 mmHg and/or $Paco_2$ > 45 mmHg and/or nocturnal and exercise-induced desaturation
- Impaired exercise capacity
- Persistent respiratory symptoms (dyspnea, cough, sputum, wheezing, chest pain, and fatigue)
- Ineffective cough and/or difficulty to clear bronchial secretions
- At least one hospitalization or two exacerbations within the last 12 months
- Presence of comorbid conditions, including COPD, asthma, bronchiectasis, pulmonary fibrosis, pulmonary hypertension, and/or need for surgery
- Impaired quality of life

Chart 3. Core components of a rehabilitation program.

Component	Indication	Methods	
		Intervention	Adaptation to special settings and situations
Aerobic exercise: endurance training	Impaired exercise capacity, limited by dyspnea and/or other respiratory symptoms Restriction in activities of daily living[11,32]	• Treadmill and/or cycle ergometer • 30 min. 2-5 times/week for 4-8 weeks • Intensity set according to maximal oxygen consumption, Luxton equation, or 80% of maximum heart rate adjusted for dyspnea • Inpatients, outpatients, or telemonitoring • Suggest maintenance program	• Free walking • 30 min. 2-5 times/week for 4-8 weeks • Intensity set according to perceived dyspnea • Outpatients or home setting • Suggest maintenance program
Strength training: upper and lower extremities (limited evidence for tuberculosis)	Reduced muscle mass and strength of peripheral muscles; lower muscle weakness with risk for falls Impaired activities of daily living involving the upper extremities (including dressing, bathing, and household tasks)[11]	• Free weights (dumbbells and ankle-braces) • 20-30 min. 2-5 times/ week for 4-8 weeks • 2-3 sets of 6-12 repetitions • Intensity set to 80% of maximal voluntary contraction and/or adjusted for muscle fatigue • Inpatients, outpatients, or telemonitoring • Suggest maintenance program	• Free weights (dumbbells and ankle-braces) • 20-30 min. 2-5 times/ week for 4-8 weeks • 2-3 sets of 6-12 repetitions • Intensity set according to perceived muscle fatigue • Outpatients or home setting • Suggest maintenance program
Inspiratory muscle training (limited evidence for tuberculosis)	Impaired respiratory muscle function, altered respiratory mechanics, decreased chest wall compliance, or pulmonary hyperinflation	• Load threshold devices, seated and using a nose clip • Interval training: sets of 10 exercise repetitions interspersed with 10-second breaks • 15-20 min. 2-5 times/ week for 4-8 weeks • Loads from 30% to 80% of maximal inspiratory pressure	• Not applicable
Airway clearance techniques	Difficult-to-remove secretions or mucous plugs; frequent bronchial exacerbations (≥ 2/ year) Concomitant diagnosis of bronchiectasis	• Choose the suitable technique for the subject among those available, based on respiratory capacity, mucus rheology, patient collaboration, and patient preferences • 15-30 min. one or more times/day • Choose the duration of treatment based on chronic (long-term) or acute (short-term) problem • Suggest maintenance program when needed	• Choose the suitable technique for the subject among those available, based on respiratory capacity, mucus rheology, patient collaboration, and patient preferences • 15-30 min. one or more times/day • Choose the duration of treatment based on chronic (long-term) or acute (short-term) problem • Suggest maintenance program when needed

Continue...▶

Chart 3. Core components of a rehabilitation program. (Continued...)

Component	Indication	Methods	
		Intervention	Adaptation to special settings and situations
Long-term oxygen therapy (limited evidence for tuberculosis)	Resting hypoxemia despite stable condition and optimal medical therapy (partial pressure of oxygen < 55 mmHg or ≤ 60 mmHg with evidence of peripheral edema, polycythemia [haematocrit ≥ 55%], or pulmonary hypertension)	• Titrate oxygen flow to maintain oxygen saturation > 92-93%. • Long-term oxygen therapy should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until oxygen saturation > 90% at rest has been achieved • An arterial blood gas analysis should then be performed to confirm that the target partial pressure of oxygen ≥ 60 mmHg at rest has been achieved • Ambulatory and nocturnal oximetry may be performed to allow more accurate flow rates to be prescribed for exercise and sleep, respectively • Provide formal education to patients referred home • Schedule periodic reassessment at 3 months	• Titrate oxygen flow to maintain oxygen saturation > 92-93%. • Long-term oxygen therapy should be initiated on a flow rate of 1 L/min and titrated up in 1 L/min increments until oxygen saturation > 90% at rest has been achieved. • Non-hypercapnic patients initiated on long-term oxygen therapy should have their flow rate increased by 1 L/min during sleep in the absence of any contraindications • Ambulatory oximetry may be performed to allow more accurate flow rates to be prescribed for exercise • Provide formal education to patients referred home • Schedule periodic reassessment every 3 months
Long-term nocturnal noninvasive mechanical ventilation (limited evidence for tuberculosis)	Chronic stable hypercapnia (partial pressure of carbon dioxide > 45-60 mmHg) despite optimal medical therapy Noninvasive ventilation could be applied during aerobic training in case of severe breathlessness or reduced exercise resistance	• Not initiating long-term noninvasive ventilation during admission for acute or chronic hypercapnic respiratory failure, favoring reassessment at 2-4 weeks after resolution • Titrate noninvasive ventilation settings • Titrate mask • Plan education • Consider noninvasive ventilation during exercise • Schedule an educational meeting and verify the ability of the subject and/or a caregiver to manage noninvasive ventilation at home	• Probably not applicable
Nutritional support	Malnutrition (BMI < 16 kg/m^2 or < 17 kg/m^2 in patients with tuberculosis-HIV coinfection, patients with MDR tuberculosis, or in those who are pregnant or are lactating mothers)	• Nutritional assessment • Tailored treatment: foods and medical supplements • Need for financial incentive and transportation access should be evaluated	• Nutritional assessment • Tailored treatment: foods and medical supplements • Need for financial incentive and transportation access should be evaluated
Psychological support	Social isolation, depression, and/or anxiety Impaired health status and/or quality of life despite optimal pharmacological treatment Low adherence to medical treatment	• Psychological assessment • Psychological support • Consider self-help group	• Psychological assessment • Psychological support • Consider self-help group

min.: minutes; and MDR: multidrug resistant.

Chart 4. Evaluation of pulmonary rehabilitation effectiveness.

Essential and conditional examinations/investigations	Adaptation to special settings and situations
Lung function	
• Spirometry (FEV_1, FVC, FEV_1/FVC) • Plethysmography	• Spirometry (FEV_1, FVC, FEV_1/FVC)
Gas transfer	
• Pao_2 • $Paco_2$ • Pulse oximetry (SpO_2, % desaturation) • DLco, Kco	• Pulse oximetry (SpO_2, % desaturation)
Exercise capacity	
• 6MWT • Vo_2max • ISWT • 5STS	• 6MWT • 5STS
Health-related quality of life	
• EUROHIS-QoL 8 • SGRQ • WHOQOL-BREF • Pediatric: EQ-5D-Y and TANDI	• EUROHIS-QoL 8 • SGRQ • WHOQOL-BREF • Pediatric: EQ-5D-Y and TANDI
Self-reported symptoms	
• mMRC • VAS • modified Borg scale	• mMRC • VAS • modified Borg scale
Acute infectious exacerbations (e.g., in bronchiectasis) requiring antibiotic and/or steroid treatment	
Number of episodes	Number of episodes
Hospitalization	
Number of episodes/hospital days	Number of episodes/hospital days
Mortality	
Number of deaths	Number of deaths

Kco: carbon monoxide transfer coefficient; 6MWT: six-minute walk test; ISWT: incremental shuttle walk test; 5STS: 5 repetitions sit-to-stand test; EUROHIS-QoL: European Health Interview Survey-Quality of Life; SGRQ: St. George's Respiratory Questionnaire; WHOQOL-BREF: World Health Organization Quality of Life Instrument, brief version; TANDI: Toddler and Infant (instrument); mMRC: modified Medical Research Council; and VAS: visual analogue scale.

and exercise-induced desaturation[45]; impaired exercise capacity[1,38,46,47]; persistent respiratory symptoms[48-51]; ineffective cough and/or difficulty to clear bronchial secretions[52,53]; at least one hospitalization or two exacerbations in the last 12 months[1,28,54,55]; presence of comorbid conditions, including COPD, asthma, bronchiectasis, pulmonary fibrosis, pulmonary hypertension, and/or need for surgery[11,18,56]; and impaired quality of life.[57-59]

The PR program should be coordinated according to the local organization of health services, taking into consideration feasibility, effectiveness, and cost-effectiveness criteria.[26] The core components of a PR program are summarized in Chart 3.

Evaluation of effectiveness of PR should be carried out by comparing the core variables before and after PR,[26] as shown in Chart 4.

Vaccination

Similarly to other chronic respiratory disorders, PTLD may cause infectious complications, and some of these can be prevented with vaccinations. Influenza, pneumococcal, and COVID-19 vaccines should be recommended for PTLD patients.

Influenza vaccination must be repeated annually following local vaccination campaigns. For pneumococcal prevention, the Brazilian Immunization Association recommends either the 13-valent pneumococcal conjugate vaccine or the 15-valent pneumococcal conjugate vaccine, which has stronger immunogenic—use depends on availability—and, 6 months to 1 year later, the 23-valent pneumococcal polysaccharide vaccine, which can be boosted by a second dose administered 5 years later.[24]

There are some vaccines recommended for the general population (or specific age groups) of which PTLD patients are likely to benefit from, such as those against tetanus, diphtheria, pertussis, measles, and shingles. Measles vaccination is recommended if there is no evidence of immunity (e.g., being born before 1957, lack of documented proof of having received the measles-mumps-rubella vaccine, or laboratory evidence of immunity or disease) is lacking. Patients with PTLD > 50 years of age can also benefit from vaccination against shingles. The tetanus-diphtheria-pertussis vaccine is recommended for the general population and should be considered for not previously vaccinated PTLD patients; also, booster doses should be repeated every 10 years in adults.[60]

Education and counseling for PTLD patients

Every patient who participates in a PR program should undergo counseling and health education. Patients should be educated on the basic principles of the disease (epidemiology, clinical aspects, transmission, diagnosis, and treatment); common symptoms that they might experience after acute disease; how to monitor and manage their symptoms at home, and when they should visit a health care facility/call a doctor; and risks of reinfection and how they can manage this risk. In addition, patients should be counseled about the benefits of a healthy lifestyle (such as physical activity, adequate nutrition, and smoking cessation). Telehealth, videos, and booklets can be used for patient education. Family member of patients should also be encouraged to participate. Counseling/health education should include maintenance of the results obtained with PR through a follow-up plan.[26,61]

FINAL CONSIDERATIONS

As more and more evidence is available on the deleterious consequences of PTLD, the development of a consensus statement directed toward this condition has become a priority for the SBPT. Approximately one third of patients who survive pulmonary tuberculosis can face a considerable ongoing morbidity, and the present recommendations apply to them. In the present manuscript, prepared by 11 pulmonologists and one methodologist with extensive experience in this area, recommendations for prevention, diagnosis, and management have been made, and the latest international guidelines have been adapted to the Brazilian context.

ACKNOWLEDGMENTS

We would like to acknowledge the support from Lia D'Ambrosio (Public Health Consulting Group, Lugano, Switzerland) and Rosella Centis (Istituti Clinici Scientifici Maugeri, IRCCS, Tradate, Italy) for their useful comments on the manuscript.

AUTHOR CONTRIBUTIONS

DRS, APS, GBM, and FCQM: drafting of the manuscript. All authors reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Allwood BW, van der Zalm MM, Amaral AFS, Byrne A, Datta S, Egere U, et al. Post-tuberculosis lung health: perspectives from the First International Symposium. Int J Tuberc Lung Dis. 2020;24(8):820-828. https://doi.org/10.5588/ijtld.20.0067
2. van Kampen SC, Wanner A, Edwards M, Harries AD, Kirenga BJ, Chakaya J, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. BMJ Glob Health. 2018;3(4):e000745. https://doi.org/10.1136/bmjgh-2018-000745
3. van Kampen SC, Wanner A, Edwards M, Harries AD, Kirenga BJ, Chakaya J, et al. International research and guidelines on post-tuberculosis chronic lung disorders: a systematic scoping review. BMJ Glob Health. 2018;3(4):e000745. https://doi.org/10.1136/bmjgh-2018-000745
4. Nightingale R, Carlin F, Meghji J, McMullen K, Evans D, van der Zalm MM, et al. Post-TB health and wellbeing. Int J Tuberc Lung Dis. 2023;27(4):248-283. https://doi.org/10.5588/ijtld.22.0514
5. Romanowski K, Baumann B, Basham CA, Ahmad Khan F, Fox GJ, Johnston JC. Long-term all-cause mortality in people treated for tuberculosis: a systematic review and meta-analysis. Lancet Infect Dis. 2019;19(10):1129-1137. https://doi.org/10.1016/S1473-3099(19)30309-3
6. Ranzani OT, Rodrigues LC, Bombarda S, Minto CM, Waldman EA, Carvalho CRR. Long-term survival and cause-specific mortality of patients newly diagnosed with tuberculosis in São Paulo state, Brazil, 2010-15: a population-based, longitudinal study. Lancet Infect Dis. 2020;20(1):123-132. https://doi.org/10.1016/S1473-3099(19)30518-3
7. Allwood BW, Byrne A, Meghji J, Rachow A, van der Zalm MM, Schoch OD. Post-Tuberculosis Lung Disease: Clinical Review of an Under-Recognised Global Challenge. Respiration. 2021;100(8):751-763. https://doi.org/10.1159/000512531
8. Visca D, D Ambrosio L, Centis R, Pontali E, Tiberi S, Migliori GB. Post-TB disease: a new topic for investigation-and why it matters. Int J Tuberc Lung Dis. 2021;25(4):258-261. https://doi.org/10.5588/ijtld.21.0040
9. Dodd PJ, Yuen CM, Jayasooriya SM, van der Zalm MM, Seddon JA. Quantifying the global number of tuberculosis survivors: a modelling study. Lancet Infect Dis. 2021;21(7):984-992. https://doi.org/10.1016/S1473-3099(20)30919-1
10. Pasipanodya JG, McNabb SJ, Hilsenrath P, Bae S, Lykens K, Vecino E, et al. Pulmonary impairment after tuberculosis and its contribution to TB burden. BMC Public Health. 2010;10:259. https://doi.org/10.1186/1471-2458-10-259
11. Amaral AF, Coton S, Kato B, Tan WC, Studnicka M, Janson C, et al. Tuberculosis associates with both airflow obstruction and low lung function: BOLD results. Eur Respir J. 2015;46(4):1104-1112. https://doi.org/10.1183/13993003.02325-2014
12. Allwood BW, Stolbrink M, Baines N, Louw E, Wademan DT, Lupton-Smith A, et al. Persistent chronic respiratory symptoms despite TB cure is poorly correlated with lung function. Int J Tuberc Lung Dis. 2021;25(4):262-270. https://doi.org/10.5588/ijtld.20.0906
13. Menzies NA, Quaife M, Allwood BW, Byrne AL, Coussens AK, Harries AD, et al. Lifetime burden of disease due to incident tuberculosis: a global reappraisal including post-tuberculosis sequelae [published correction appears in Lancet Glob Health. 2022 Mar;10(3):e336]. Lancet Glob Health. 2021;9(12):e1679-e1687. https://doi.org/10.1016/S2214-109X(21)00367-3
14. Pontali E, Silva DR, Marx FM, Caminero JA, Centis R, D'Ambrosio L, et al. Breathing Back Better! A State of the Art on the Benefits of Functional Evaluation and Rehabilitation of Post-Tuberculosis and Post-COVID Lungs. Arch Bronconeumol. 2022;58(11):754-763. https://doi.org/10.1016/j.arbres.2022.05.010
15. Martinez-Garcia MA, Guan WJ, de-la-Rosa D, Athanazio R, Oscullo G, Shi MX, et al. Post-TB bronchiectasis: from pathogenesis to rehabilitation. Int J Tuberc Lung Dis. 2023;27(3):175-181. https://doi.org/10.5588/ijtld.22.0566
16. Hsu D, Irfan M, Jabeen K, Iqbal N, Hasan R, Migliori GB, et al Post tuberculosis treatment infectious complications. Int J Infect Dis. 2020;92S:S41-S45. https://doi.org/10.1016/j.ijid.2020.02.032
17. Pasipanodya JG, Miller TL, Vecino M, Munguia G, Garmon R, Bae S, et al Pulmonary impairment after tuberculosis. Chest. 2007;131(6):1817-1824. https://doi.org/10.1378/chest.06-2949
18. Tiberi S, Torrico MM, Rahman A, Krutikov M, Visca D, Silva DR, et al. Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation. J Bras Pneumol. 2019;45(2):e20180324. https://doi.org/10.1590/1806-3713/e20180324
19. Migliori GB, Caminero Luna J, Kurhasani X, van den Boom M, Visca D, D'Ambrosio L, et al. History of prevention, diagnosis, treatment

and rehabilitation of pulmonary sequelae of tuberculosis. Presse Med. 2022;51(3):104112. https://doi.org/10.1016/j.lpm.2022.104112

20. Mpagama SG, Msaji KS, Kaswaga O, Zurba LJ, Mbelele PM, Allwood BW, et al. The burden and determinants of post-TB lung disease. Int J Tuberc Lung Dis. 2021;25(10):846-853. https://doi.org/10.5588/ijtld.21.0278
21. Miller TL, Wilson FA, Pang JW, Beavers S, Hoger S, Sharnprapai S, et al. Mortality hazard and survival after tuberculosis treatment. Am J Public Health. 2015;105(5):930-937. https://doi.org/10.2105/AJPH.2014.302431
22. Ravimohan S, Kornfeld H, Weissman D, Bisson GP. Tuberculosis and lung damage: from epidemiology to pathophysiology. Eur Respir Rev. 2018;27(147):170077. https://doi.org/10.1183/16000617.0077-2017
23. Silva DR, Freitas AA, Guimarães AR, D'Ambrosio L, Centis R, Muñoz-Torrico M, et al. Post-tuberculosis lung disease: a comparison of Brazilian, Italian, and Mexican cohorts. J Bras Pneumol. 2022;48(2):e20210515.
24. Meghji J, Simpson H, Squire SB, Mortimer K. A Systematic Review of the Prevalence and Pattern of Imaging Defined Post-TB Lung Disease. PLoS One. 2016;11(8):e0161176. https://doi.org/10.1371/journal.pone.0161176
25. Maleche-Obimbo E, Odhiambo MA, Njeri L, Mburu M, Jaoko W, Were F, et al. Magnitude and factors associated with post-tuberculosis lung disease in low- and middle-income countries: A systematic review and meta-analysis. PLOS Glob Public Health. 2022;2(12):e0000805. https://doi.org/10.1371/journal.pgph.0000805
26. Migliori GB, Marx FM, Ambrosino N, Zampogna E, Schaaf HS, van der Zalm MM, et al. Clinical standards for the assessment, management and rehabilitation of post-TB lung disease. Int J Tuberc Lung Dis. 2021;25(10):797-813. https://doi.org/10.5588/ijtld.21.0425
27. Chesov D, Butov D, Reimann M, Heyckendorf J, Myasoedov V, Butov T, et al. Impact of lung function on treatment outcome in patients with TB. Int J Tuberc Lung Dis. 2021;25(4):277-284. https://doi.org/10.5588/ijtld.20.0949
28. Muñoz-Torrico M, Rendon A, Centis R, D'Ambrosio L, Fuentes Z, Torres-Duque C, et al. Is there a rationale for pulmonary rehabilitation following successful chemotherapy for tuberculosis?. J Bras Pneumol. 2016;42(5):374-385. https://doi.org/10.1590/S1806-37562016000000226
29. Tiberi S, Torrico MM, Rahman A, Krutikov M, Visca D, Silva DR, et al. Managing severe tuberculosis and its sequelae: from intensive care to surgery and rehabilitation. J Bras Pneumol. 2019;45(2):e20180324. https://doi.org/10.1590/1806-3713/e20180324
30. Muñoz-Torrico M, Cid-Juárez S, Gochicoa-Rangel L, Torre-Bouscolet L, Salazar-Lezama MA, Villarreal-Velarde H, et al. Functional impact of sequelae in drug-susceptible and multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2020;24(7):700-705. https://doi.org/10.5588/ijtld.19.0809
31. Ross J, Ehrlich RI, Hnizdo E, White N, Churchyard GJ. Excess lung function decline in gold miners following pulmonary tuberculosis. Thorax. 2010;65(11):1010-1015. https://doi.org/10.1136/thx.2009.129999
32. Bongomin F. Post-tuberculosis chronic pulmonary aspergillosis: An emerging public health concern. PLoS Pathog. 2020;16(8):e1008742. https://doi.org/10.1371/journal.ppat.1008742
33. Nightingale R, Chinoko B, Lesosky M, Rylance SJ, Mnesa B, Banda NPK, et al. Respiratory symptoms and lung function in patients treated for pulmonary tuberculosis in Malawi: a prospective cohort study. Thorax. 2022;77(11):1131-1139. https://doi.org/10.1136/thoraxjnl-2021-217190
34. Marx FM, Floyd S, Ayles H, Godfrey-Faussett P, Beyers N, Cohen T. High burden of prevalent tuberculosis among previously treated people in Southern Africa suggests potential for targeted control interventions. Eur Respir J. 2016;48(4):1227-1230. https://doi.org/10.1183/13993003.00716-2016
35. Singh S, Allwood BW, Chiyaka TL, Kleyhans L, Naidoo CC, Moodley S, et al. Immunologic and imaging signatures in post tuberculosis lung disease. Tuberculosis (Edinb). 2022;136:102244. https://doi.org/10.1016/j.tube.2022.102244
36. Gupta MB, Bagri S, Garg A, Singh DK, Choudhary P, Sahni S. Pulmonary function in cured pulmonary tuberculosis cases. Indian J Tuberc. 2022;69(4):535-538. https://doi.org/10.1016/j.ijtb.2021.08.024
37. Curry BD, van T Wout E, Maasdorp E, Nortje A, Irusen EM, Maree D, et al. Correlation between lung function tests and peak oxygen consumption in post-TB lung disease. Int J Tuberc Lung Dis. 2022;26(3):259-267. https://doi.org/10.5588/ijtld.21.0504
38. Sivaranjini S, Vanamail P, Eason J. Six minute walk test in people with tuberculosis sequelae. Cardiopulm Phys Ther J. 2010;21(3):5-10. https://doi.org/10.1097/01823246-201021030-00002
39. Pereira MC, Athanazio RA, Dalcin PTR, Figueiredo MRF, Gomes M, Freitas CG, et al. Brazilian consensus on non-cystic fibrosis bronchiectasis. J Bras Pneumol. 2019;45(4):e20190122. https://doi.org/10.1590/1806-3713/e20190122
40. American Thoracic Society; American College of Chest Physicians. ATS/ACCP Statement on cardiopulmonary exercise testing [published correction appears in Am J Respir Crit Care Med. 2003 May 15;1451-2]. Am J Respir Crit Care Med. 2003;167(2):211-277. https://doi.org/10.1164/rccm.167.2.211
41. Venkitakrishnan R, Ramachandran D, Augustine J, Cleetus M. Inhaled corticosteroids and risk of tuberculosis-How bad is the risk?. Indian J Tuberc. 2022;69(2):128-130. https://doi.org/10.1016/j.ijtb.2021.06.010
42. Martínez-García MÁ, Oscullo G, García-Ortega A, Matera MG, Rogliani P, Cazzola M. Inhaled Corticosteroids in Adults with Non-cystic Fibrosis Bronchiectasis: From Bench to Bedside. A Narrative Review. Drugs. 2022;82(14):1453-1468. https://doi.org/10.1007/s40265-022-01785-1
43. Bongomin F, Harris C, Hayes G, Kosmidis C, Denning DW. Twelve-month clinical outcomes of 206 patients with chronic pulmonary aspergillosis. PLoS One. 2018;13(4):e0193732. https://doi.org/10.1371/journal.pone.0193732
44. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. Eur Respir J. 2005;26(5):948-968. https://doi.org/10.1183/09031936.05.00035205
45. Crapo RO, Jensen RL, Hegewald M, Tashkin DP. Arterial blood gas reference values for sea level and an altitude of 1,400 meters. Am J Respir Crit Care Med. 1999;160(5 Pt 1):1525-1531. https://doi.org/10.1164/ajrccm.160.5.9806006
46. Holland AE, Spruit MA, Troosters T, Puhan MA, Pepin V, Saey D, et al. An official European Respiratory Society/American Thoracic Society technical standard: field walking tests in chronic respiratory disease. Eur Respir J. 2014;44(6):1428-1446. https://doi.org/10.1183/09031936.00150314
47. Jones SE, Kon SS, Canavan JL, Patel MS, Clark AL, Nolan CM, et al. The five-repetition sit-to-stand test as a functional outcome measure in COPD. Thorax. 2013;68(11):1015-1020. https://doi.org/10.1136/thoraxjnl-2013-203576
48. Grønseth R, Vollmer WM, Hardie JA, Ólafsdóttir IS, Lamprecht B, Buist AS, et al. Predictors of dyspnoea prevalence: results from the BOLD study. Eur Respir J. 2014;43(6):1610-1620. https://doi.org/10.1183/09031936.00036813
49. Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax. 1999;54(7):581-586. https://doi.org/10.1136/thx.54.7.581
50. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc. 1982;14(5):377-381. https://doi.org/10.1249/00005768-198205000-00012
51. Gift AG. Validation of a vertical visual analogue scale as a measure of clinical dyspnea. Rehabil Nurs. 1989;14(6):323-325. https://doi.org/10.1002/j.2048-7940.1989.tb01129.x
52. Sancho J, Servera E, Díaz J, Marín J. Comparison of peak cough flows measured by pneumotachograph and a portable peak flow meter. Am J Phys Med Rehabil. 2004;83(8):608-612. https://doi.org/10.1097/01.PHM.0000133431.70907.A2
53. American Thoracic Society/European Respiratory Society. ATS/ERS Statement on respiratory muscle testing. Am J Respir Crit Care Med. 2002;166(4):518-624. https://doi.org/10.1164/rccm.166.4.518
54. Kim SJ, Lee J, Park YS, Lee CH, Lee SM, Yim JJ, et al. Effect of airflow limitation on acute exacerbations in patients with destroyed lungs by tuberculosis. J Korean Med Sci. 2015;30(6):737-742. https://doi.org/10.3346/jkms.2015.30.6.737
55. Global Initiative for Chronic Obstructive Lung Disease (GOLD) [homepage on the Internet]. Bethesda: GOLD [cited 2023 May 29]. 2020 Global Strategy for Prevention, Diagnosis and Management of COPD: 2023 Report. Available from: https://goldcopd.org/2023-gold-report-2/
56. Linn BS, Linn MW, Gurel L. Cumulative illness rating scale. J Am Geriatr Soc. 1968;16(5):622-626. https://doi.org/10.1111/j.1532-5415.1968.tb02103.x

57. Datta S, Gilman RH, Montoya R, Quevedo Cruz L, Valencia T, Huff D, et al. Quality of life, tuberculosis and treatment outcome; a case-control and nested cohort study. Eur Respir J. 2020;56(2):1900495. https://doi.org/10.1183/13993003.00495-2019
58. Silva PA, Soares SM, Santos JF, Silva LB. Cut-off point for WHOQOL-bref as a measure of quality of life of older adults. Rev Saude Publica. 2014;48(3):390-397. https://doi.org/10.1590/S0034-8910.2014048004912
59. Jo YS, Park S, Kim DK, Yoo CG, Lee CH. The cutoff point of clinical chronic obstructive pulmonary disease questionnaire for more symptomatic patients. BMC Pulm Med. 2018;18(1):38. https://doi.org/10.1186/s12890-018-0601-0
60. Nasiri MJ, Silva DR, Rommasi F, Zahmatkesh MM, Tajabadi Z, Khelghati F, et al. Vaccination in post-tuberculosis lung disease management: A review of the evidence [published online ahead of print, 2023 Sep 5]. Pulmonology. 2023;S2531-0437(23)00129-0. https://doi.org/10.1016/j.pulmoe.2023.07.002
61. Siddiq MAB, Rathore FA, Clegg D, Rasker JJ. Pulmonary Rehabilitation in COVID-19 patients: A scoping review of current practice and its application during the pandemic. Turk J Phys Med Rehabil. 2020;66(4):480-494. https://doi.org/10.5606/tftrd.2020.6889

Use of elexacaftor+tezacaftor+ivacaftor in individuals with cystic fibrosis and at least one *F508del* allele: a systematic review and meta-analysis

Luiz Vicente Ribeiro Ferreira da Silva Filho[1], Rodrigo Abensur Athanazio[2], Carolina Rodrigues Tonon[3], Juliana Carvalho Ferreira[2], Suzana Erico Tanni[3]

1. Unidade de Pneumologia Pediátrica, Instituto da Criança e do Adolescente, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Botucatu, (SP) Brasil.

Submitted: 27 May 2023.
Accepted: 11 August 2023.

Study carried out in the Unidade de Pneumologia Pediátrica, Instituto da Criança e do Adolescente, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To evaluate the effect of treatment with the combination of three cystic fibrosis transmembrane conductance regulator (CFTR) modulators—elexacaftor+tezacaftor+ivacaftor (ETI)—on important clinical endpoints in individuals with cystic fibrosis. **Methods:** This was a systematic review and meta-analysis of randomized clinical trials that compared the use of ETI in individuals with CF and at least one *F508del* allele with that of placebo or with an active comparator such as other combinations of CFTR modulators, following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations and the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. We searched the following databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and ClinicalTrials.gov from their inception to December 26th, 2022. The risk of bias was assessed using the Cochrane risk-of-bias tool, and the quality of evidence was based on the Grading of Recommendations Assessment, Development and Evaluation (GRADE). **Results:** We retrieved 54 studies in the primary search. Of these, 6 met the inclusion criteria and were analyzed (1,127 patients; 577 and 550 in the intervention and control groups, respectively). The meta-analysis revealed that the use of ETI increased FEV_1% [risk difference (RD), +10.47%; 95% CI, 6.88-14.06], reduced the number of acute pulmonary exacerbations (RD, −0.16; 95% CI, −0.28 to −0.04), and improved quality of life (RD, +14.93; 95% CI, 9.98-19.89) and BMI (RD, +1.07 kg/m^2; 95% CI, 0.90-1.25). Adverse events did not differ between groups (RD, −0.03; 95% CI, −0.08 to 0.01), and none of the studies reported deaths. **Conclusions:** Our findings demonstrate that ETI treatment substantially improves clinically significant, patient-centered outcomes.

Keywords: Cystic fibrosis/therapy; Cystic fibrosis transmembrane conductance regulator; Membrane transport modulators.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disease that results in dysfunction of the cystic fibrosis transmembrane conductance regulator (CFTR) protein, a chloride and bicarbonate channel expressed in the apical portion of epithelial cells of several organs of the human body.[1] CFTR protein dysfunction results in diverse and potentially severe clinical manifestations, primarily involving the respiratory, gastrointestinal, and reproductive systems, reducing quality of life and life expectancy.[2] More than 2,000 variants have been described as related to CF or CF-like manifestations, and the most common variant worldwide has at least one *F508del* allele,[3] reported in approximately 60% of CF individuals in Brazil.[4]

Described more than 70 years ago, CF is yet a condition with no definitive cure, although it has now a totally different and much more favorable therapeutic and prognostic horizon for affected individuals than in the past.[5] This new scenario of hope was created mainly by the discovery of CFTR protein modulators, small molecules that have been shown to be able to rescue protein function or expression.[6] The first CFTR modulator described, ivacaftor, interacts with mutant CFTR proteins expressed at the cell surface and increase channel activity; therefore, it has been labeled as a 'potentiator'.[7] Because F508del mutant proteins have defective processing and trafficking at the endoplasmic reticulum, the use of molecules able to increase protein expression is critical to rescue CFTR function[8]; some of these compounds, named "correctors," have also been identified (lumacaftor, tezacaftor, and elexacaftor).[9] However, F508del mutant proteins rescued by these correctors do not exhibit sufficient channel activity when expressed at the cell surface, and, therefore, there is a need to combine at least one corrector with a potentiator to promote significant CFTR function.[8]

Correspondence to:
Luiz Vicente Ribeiro Ferreira da Silva Filho. Unidade de Pneumologia Pediátrica, ICr-HCFMUSP, Avenida Dr. Enéas Carvalho de Aguiar, 647, Cerqueira Cesar, CEP 05409-011, São Paulo, SP, Brasil.
Tel.: 55 11 2661-8500. E-mail: luizvic@me.com
Financial support: None.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

Initial results of combination therapies in *F508del* homozygous CF patients showed less expressive improvements in lung function compared to the effects of ivacaftor for individuals with gating variants.[6] A step forward was the recognition that F508del CFTR mutants have more than one critical defect that needs to be tackled to overcome the endoplasmic reticulum checkpoints of protein quality and to result in CFTR expression at the cell membrane.[10,11] These findings led to clinical trials testing the combination of two correctors and a potentiator (ivacaftor) to rescue F508del CFTR mutants, the combination of elexacaftor+tezacaftor+ivacaftor (ETI).[12]

Initial results of the studies of ETI use for CF individuals with F508del CFTR variants were promising, and even patients with only one copy of the variant allele combined with another minimal function variant allele showed substantial improvements in key outcomes such as lung function, quality of life, nutrition, and frequency of exacerbations.[12-14] Subsequently, initial results of pivotal studies, extension studies, and interventions in different age groups were also published.[15,16]

In Brazil, recently published clinical practice guidelines[17] focusing on the treatment of CF did not include a question regarding the use of ETI in CF patients because their clinical questions had been developed before this drug combination was available in the country. However, this reality is rapidly changing, and given that F508del CFTR mutations are the most prevalent type of mutations causing CF worldwide, it is important to estimate the cumulative effect of ETI on important clinical outcomes in patients with CF. Therefore, we conducted a systematic review and meta-analysis on the effects of ETI in patients with CF and at least one *F508del* allele.

METHODS

This systematic review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[18]

The study protocol followed the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, and the question of interest followed the Patients of interest, Intervention to be studied, Comparison of interventions, and Outcome of interest (PICO) methodology. With the use of highly effective CFTR modulators as the intervention of interest, the PICO framework was as follows: Patients, patients with CF; Intervention, use of elexacaftor+tezacaftor+ivacaftor; Comparison, other modulators or placebo; and Outcome, mortality rate due to any cause, acute pulmonary exacerbations, adverse events, lung function (measured by FEV_1), quality of life (measured by the respiratory domain score of the Cystic Fibrosis Questionnaire), and BMI.

We aimed to include all randomized controlled trials (RCTs) on the topic. No restrictions were imposed with regard to the date of publication, language, age group, or availability of full texts of papers. The protocol was registered on the International Prospective Register of Systematic Reviews (PROSPERO) platform (Protocol no. 2023 CRD42023386782).

Two authors developed search strategies that were 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. A specific search strategy was used for the databases: (Fibrosis Cystic OR Mucoviscidosis OR Pulmonary Cystic Fibrosis OR Pancreatic Cystic Fibrosis OR Fibrocystic Disease of Pancreas OR Pancreas Fibrocystic Disease OR Pancreas Fibrocystic Diseases OR Cystic Fibrosis of Pancreas) AND (elexacaftor ivacaftor tezacaftor OR elexacaftor ivacaftor tezacaftor drug combination OR Trikafta OR VX445); For the Cochrane Central Register of Controlled Trials, the following strategy was used: fibrosis cystic AND elexacaftor ivacaftor tezacaftor.

Two researchers independently selected and extracted data from the studies included. First, studies were selected based on their titles and abstracts. Then, the full texts were evaluated for inclusion or exclusion, and disagreements were resolved by consensus or following a discussion with a third researcher. Data regarding authorship, year of publication, patient description, interventions (ETI and control), absolute numbers of each outcome, and follow-up duration were extracted from the studies by two researchers independently, and the extracted values were compared.

The risk of bias for RCTs was assessed using the modified Cochrane risk-of-bias tool (RoB 2),[19,20] as were other fundamental elements, and were expressed as very serious, serious, or non-serious. The risk of bias assessment was conducted by two reviewers independently, and, in case of disagreement, a third reviewer deliberated the assessment. The quality of the evidence was extrapolated from the risk of bias based on the GRADE terminology as very low, low, or high, using the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada).[21]

Categorical outcomes were expressed by group (ETI and control), as was the calculated risk in percentage (by dividing the number of events by the total number of patients in each group). If the risk difference (RD) between the groups was significant, a 95% CI was expressed, and the number needed to treat or the number needed to harm was calculated. Continuous outcomes were expressed by groups (ETI and control) as means and standard deviations, as well as the risk difference between the groups.

We used a fixed-effect or a random-effect model for the meta-analysis to evaluate the effect of ETI vs. control on the outcomes of interest when these data were available in at least two RCTs. The effects were reported as RDs and corresponding 95% CIs; a 95% CI which encompassed the value 0 in its range indicated that there was no difference in the effect between the ETI and control arms. RD expresses the absolute effect size when compared with the

relative risk or odds ratio, and this technique can be used when the binary outcome is zero in both study arms. Heterogeneity of the 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 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).[22]

RESULTS

A total of 54 studies were retrieved from the selected databases. After eliminating duplicates and including studies that met the eligibility criteria, 12 studies were selected for assessment of full texts. Of these, 6 were excluded (Figure 1). Therefore, 6 RCTs involving 1,127 individuals, 577 and 550 of whom were in the intervention and control groups, respectively, were included in the meta-analysis,[12-16,23] as detailed in Table 1.

One study[12] included only adults (≥ 18 years of age; N = 123), and one[16] included 6-12 year-old children (N = 121). Four other studies included CF individuals ≥ 12 years of age. Duration of follow-up was 24 weeks in 4 studies, and 4-8 weeks in 2 others. Two studies reported a 96-week follow-up extension.[13,14] Most of the studies used an active comparator group (tezacafor/ivacaftor), and only 2[13,16] compared ETI to placebo (N = 526). The characteristics of each study, risk of bias, and quality of evidence are presented in Tables 1, 2, and 3, respectively. We considered that the risk of bias in the included studies to support the conclusions about treatment as serious. The quality of the evidence in the ETI group varied according to the outcome analyzed: exacerbations (low), FEV_1 (very low), BMI (very low), quality of life (very low), adverse events (moderate), and number of deaths (moderate).

The studies reported no deaths during the follow-up period. Therefore, it was impossible to estimate the

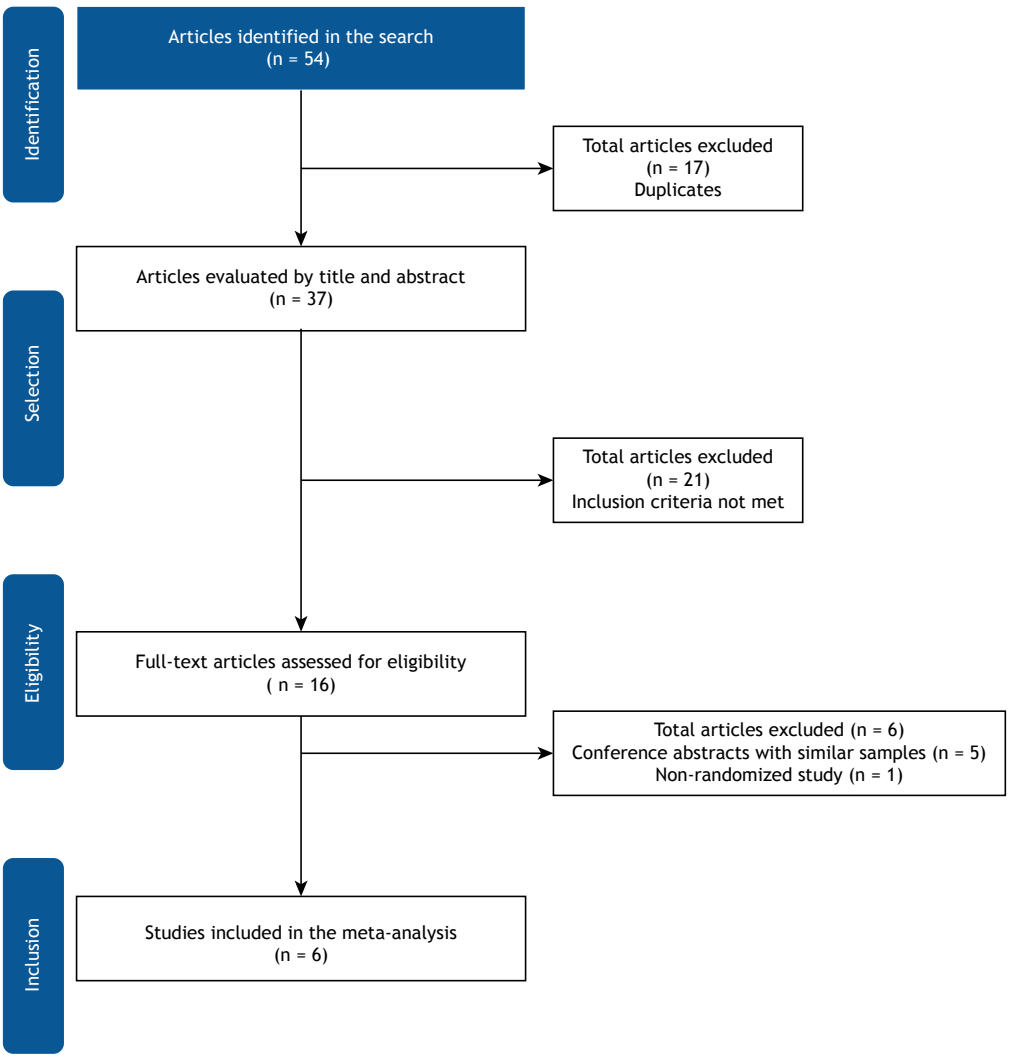


Figure 1. Flow diagram of study selection in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations.[18]

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

Study	Design	Population	Intervention (N)	Comparator (N)	Outcome	Duration
Barry et al.[23] (NCT04058353) North America, Europe, and Australia	Phase 3 double-blind RCT with active control arm	≥ 12-year-olds with CF and *F508del*-gating or *F508del*-residual function genotypes	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 132)	TI or I I: 150 mg every 12 h; T: 100 mg once daily (N = 126)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	8 weeks
Heijerman et al.[14] (NCT03525548) Belgium, Netherlands, UK, and USA (NCT03525574-extension)	Phase 3 double-blind RCT with active control arm Open label extension	≥ 12-year-olds with CF and homozygous for *F508del* mutation, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 55)	TI T: 100 mg once daily; I: 150 mg, every 12 h (N = 52)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	4 weeks 96-week extension
Keating et al.[12] (NCT03227471) USA, Netherlands, Belgium, and Australia	Phase 2 double-blind RCT with active control arm or placebo	≥ 18-year-olds with CF *F508del*-MF genotype patients were randomized to receive triple therapy or a triple placebo control Patients homozygous for the *F508del* mutation genotype were randomized to receive triple therapy or active control arm	*F508del*-MF genotype: ETI E: 50,100, or 200 mg once daily); I: 150 mg every 12 h; T: 100 mg once daily (n = 53) or VX-445 in triple combination with T and VX-561 (n = 22) Homozygous for *F508del*: ETI E: 200 mg/day p.o.; T: 100 mg/day; I: 150 mg every 12 h (n = 21) [64 patients received E 200 mg per day p.o.] (N = 96)	*F508del*-MF genotype: placebo (n = 12) or VX-445 in triple combination (n = 8) Homozygous for *F508del*: TI I: 150 mg every 12 h; T: 100 mg once daily (n = 7) (N = 27)	FEV_1%, score on CFQ respiratory domain, adverse events	4 weeks

Continue...▶

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

Study	Design	Population	Intervention (N)	Comparator (N)	Outcome	Duration
Mall et al.[16] (NCT04353817) Australia, Canada, Denmark, France, Germany, Israel, Netherlands, Spain, Switzerland, and UK	Phase 3 double-blind placebo-controlled RCT	6-12-year-olds with CF and *F508del*-MF genotypes, FEV_1 40-90%, stable CF	Children < 30 kg: E: 100 mg once daily; T: 50 mg once daily; I: 75 every 12 h Children ≥ 30 kg: E: 200 mg once daily; T: 100 mg once daily; I: 150 every 12 h (N = 60)	Placebo (N = 61)	FEV_1%, lung clearance index, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks
Middleton et al.[13] (NCT03525444) USA, Europe, and Australia Extension (NCT03525574)	Phase 3 double-blind placebo-controlled RCT Open label-extension	≥ 12-year-olds with CF and heterozygous for the *F508del*-MF genotype, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 201)	Placebo (N = 204)	FEV_1%, exacerbations, BMI, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks 96-week extension
Sutharsan et al.[15] (NCT04105972) Australia, Belgium, Germany, and UK	Phase 3 double-blind RCT with active control arm	≥ 12-year-olds with CF and homozygous for *F508del*, FEV_1 40-90%, stable CF	ETI E: 200 mg once daily; I: 150 mg every 12 h; T: 100 mg once daily (N = 87)	TI I: 150 mg every 12 h; T: 100 mg once daily (N = 88)	FEV_1%, sweat chloride concentration, score on CFQ respiratory domain, adverse events	24 weeks

RCT: randomized controlled trial; CF: cystic fibrosis; E: elexacaftor; T: tezacaftor; I: ivacaftor; CFQ: Cystic Fibrosis Questionnaire; and MF: minimal function.

impact on mortality with a moderate quality of evidence. Results of the meta-analysis revealed a statistically significant improvement in the respiratory domain of the quality of life questionnaire (RD, +14.93; 95% CI, 9.98-19.89), with very low quality of evidence (Figure 2A); a statistically significant effect on FEV_1 in the ETI group (RD; +10.47%; 95% CI, 6.88-14.06], with very low quality of evidence (Figure 2B); and also a statistically significant difference in BMI (RD, +1.07 kg/m^2; 95% CI, −0.90 to 1.25), with very low quality of evidence (Figure 2C). We also observed a statistically significant reduction in the number of acute pulmonary exacerbations (RD, −0.16, 95% CI, −0.28 to −0.04), with low quality of evidence (Figure 3A), but no significant impact on the occurrence of adverse effects (RD, −0.03; 95% CI, −0.08 to 0.01), with moderate quality of evidence (Figure 3B).

DISCUSSION

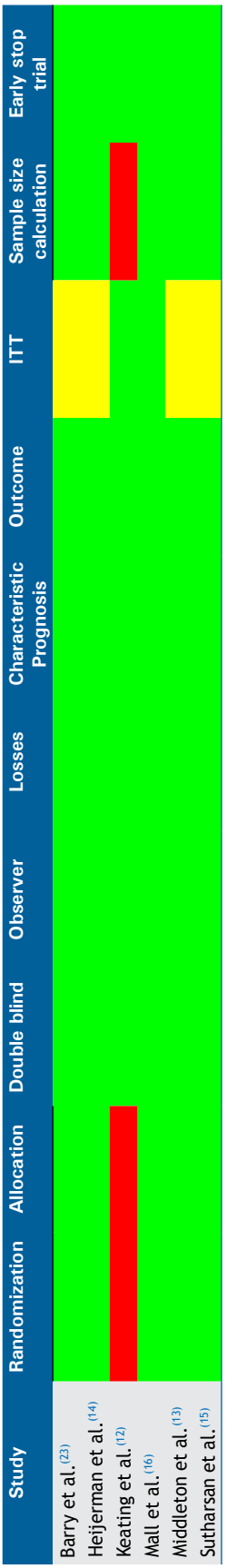
In this systematic review and meta-analysis regarding the efficacy and safety of the combination of three CFTR modulators (ETI) in patients with CF and at least one *F508del* allele, we found that treatment with ETI, compared with treatment with placebo or other CFTR modulators, reduced exacerbations and improved lung function, BMI, and quality of life. There were no significant differences in adverse events or mortality.

Our findings support the adoption of ETI combination therapy for patients with CF and at least one *F508del* allele, given that this combination led to substantial improvements in clinically significant, patient-centered outcomes, without a significant impact on adverse events. A previous systematic review, also including 6 studies, about the triple therapy for CF patients found similar results.[24] However, 1 of the studies included used a different combination of modulators (VX-659 instead of elexacaftor, combined with ivacaftor and tezacaftor),[25] and because the search was limited to December of 2021, it did not include the study by Mall et al.,[16] published in 2022 and included in our study. The similarity of the findings reinforces the robustness of data supporting the clinical effectiveness of ETI therapy.

Recent clinical practice guidelines by the Brazilian Thoracic Society addressing other common treatments for CF[17] did not include the ETI treatment, because the clinical questions were formulated before ETI therapy was available in Brazil. Therefore, this systematic review and meta-analysis complements the findings of the clinical practice guidelines[17] and offers robust information to the scientific literature that could support health care decisions in Brazil and in other countries. The magnitude of clinical impact observed with the ETI treatment in CF patients with at least one *F508del* allele was remarkable, and comparable to that observed with ivacaftor for patients with CFTR gating mutations.[26]

Our results are also in line with findings of recent observational studies on ETI in real life scenarios.[27,28]

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



ITT: intention to treat. [a]Red: risk of bias; yellow: unclear; and green: without risk of bias.

Table 3. Quality of evidence regarding the use of elexacaftor+tezacaftor+ivacaftor triple combination in cystic fibrosis patients.

Certainty assessment							No of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Elexacaftor + tezacaftor + ivacaftor	Placebo or active control	Relative (95% CI)	Absolute (95% CI)		
Mortality												
6	randomized trials	serious[a]	not serious	not serious	not serious	none	0/577 (0.0%)	0/550 (0.0%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O Moderate	CRÍTICAL
Adverse events												
6	randomized trials	serious[a]	not serious	not serious	not serious	none	470/577 (81.5%)	464/550 (84.4%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 more)	⊕⊕⊕O Moderate	CRÍTICAL
Quality of life												
6	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	577	550	-	mean 14.93 points higher (9.98 higher to 19.89 higher)	⊕OOO Very low	CRÍTICAL
Pulmonary exacerbations												
6	randomized trials	serious[a]	serious[b]	not serious	not serious	none	65/577 (11.3%)	165/550 (30.0%)	not estimable	0 fewer per 1000 (from 0 fewer to 0 fewer)	⊕⊕OO Low	IMPORTANT
FEV_1												
6	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	577	550	-	mean 10.47 pp higher (6.88 higher to 14.06 higher)	⊕OOO Very low	IMPORTANT
BMI												
3	randomized trials	serious[a]	serious[b]	not serious	serious[c]	none	343	344	-	mean 1.07 kg/m² higher (0.9 lower to 1.25 higher)	⊕OOO Very low	IMPORTANT

pp: percentage points.
Explanations
a. Randomization and no mentioning of intention to treat
b. High heterogeneity
c. Large confidence interval

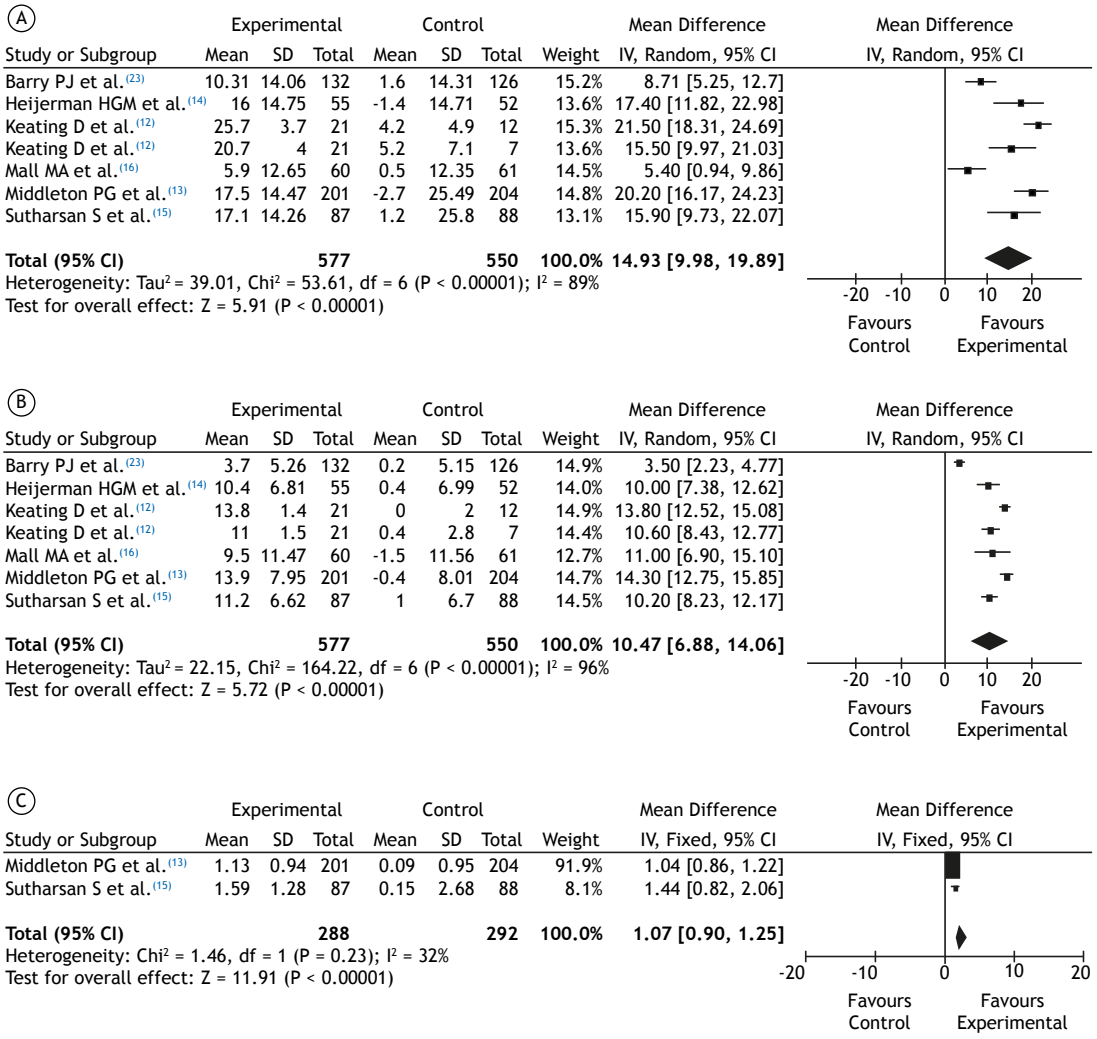


Figure 2. Forest plots of the included studies evaluating the efficacy of elexacaftor+tezacaftor+ivacaftor vs. placebo in individuals with cystic fibrosis and at least one *F508del* allele. In A, quality of life determined by the respiratory domain score of the Cystic Fibrosis Questionnaire respiratory domain; in B, FEV_1 in percentage of the predicted value; and, in C, BMI. IV: inverse of the variance; and df: degrees of freedom

A recently published interim analysis of a registry-based study reported the impact of ETI treatment for 2 years on more than 16,000 North American CF individuals.[27] Treatment with ETI was associated with significant and sustained improvements in lung function and reductions in acute pulmonary exacerbations and hospital admissions. Moreover, no new safety concerns were identified, and there was a 72% lower rate of mortality and 85% lower rate of lung transplantation in regard to the year before ETI availability.[27] Similar findings were described in a French cohort of 245 patients with CF and severely impaired lung function, who experienced decreases in long-term supplemental oxygen therapy, noninvasive ventilation, and enteral tube feeding requirements, in addition to a decrease in lung transplant listing.[28]

The combined data from the RCTs included in this meta-analysis indicate that the mean gain in lung function (FEV_1 in % of predicted value) with the ETI therapy was +10.4%. This result is clinically significant and superior to that of most of the therapies adopted to treat CF-related lung disease, such as dornase alpha (+5.8%)[29] and azithromycin (+6.2%),[30] and comparable to that of inhaled tobramycin for patients chronically infected with *Pseudomonas aeruginosa* (+10%).[31] This gain in lung function is even more impressive if we take into account that the average lung function of the current CF population included in the ETI studies has been much higher than it was in the past,[32] making those improvements of such magnitude even more remarkable. The efficacy results even in CF individuals with only one *F508del* allele combined with any minimal function mutation[13] are also remarkable and indicate that the minimum amount of functional CFTR needed to result in a significant clinical impact may be in fact around 10-30% of CFTR function, as previously estimated.[33]

The reduction of acute pulmonary exacerbations and improvements in the respiratory domain of quality of life questionnaires are very consistent across the studies;

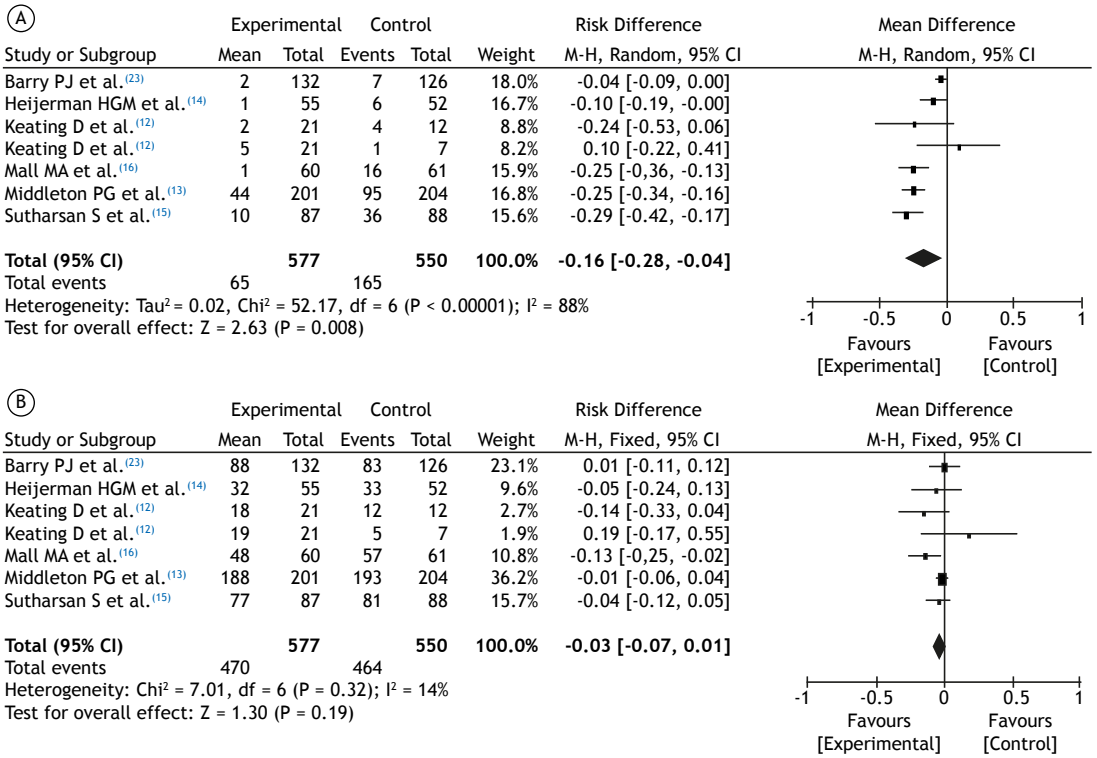


Figure 3. Forest plots of the included studies evaluating the efficacy of elexacaftor+tezacaftor+ivacaftor vs. placebo in individuals with cystic fibrosis and at least one *F508del* allele. In A, acute pulmonary exacerbations; and, in B, adverse events. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

all of the 6 studies showed improvements in quality of life, and 5 showed reductions in the number of exacerbations. Acute exacerbations in CF are associated with several negative outcomes, such as an increase in the number of work or school days missed, weight loss, worse quality of life, and increased health care costs,[34] and, therefore, are a very important patient-centered outcome in CF. Although none of the included studies was designed or powered to estimate the effect of ETI on mortality, the finding that ETI reduces exacerbations underscores the potential impact of this therapy on long-term survival. We found that ETI adverse events were similar to those of other treatment options or placebo. Most of the studies reported only mild and transient adverse effects, the most worrisome ones being rashes, liver function alterations, and psychiatric effects such as anxiety.[35] Such effects were described as reversible with temporary drug discontinuation, and, in most cases, they did not result in permanent discontinuation of treatment, allowing its continuation after some days or weeks.[35]

Our findings have important implications for patients with CF, given that other treatment options are scarce. Initial studies of combinations of two drugs for CF patients with *F508del* CFTR mutations showed a modest impact on lung function or sweat chloride measurements,[36] while the use of lumacaftor as the corrector resulted in safety concerns.[37] However, the combination of lumacaftor and ivacaftor was the only option for young (2-5 years of age) CF individuals homozygous for *F508del* until May of 2023, when ETI therapy was approved by the Food and Drug Administration to treat these patients after the publication of results of a phase-3 open-label study.[38] Since early lung disease do occur in some patients with a significant clinical impact,[39] more studies on CFTR modulators in younger CF children are imperative.

Our study has several limitations. First, only RCTs were included. New data stemming from real-life studies are significantly expanding the knowledge about the effectiveness of new treatments in the CF population,[27,40-42] and such studies should be considered in future analyses on health care benefits of these interventions. Second, only 6 studies were included. However, CF is a rare disease, and ETI is a new and expensive medication, which has been available only for a few years. Third, we were underpowered to detect the impact of ETI on mortality since all of the studies followed patients for just a few weeks/months and typically reported only few or no deaths. Additionally, data regarding benefits and risks of using ETI in CF individuals with preserved lung function and good quality of life were limited. Finally, our study does not include a cost-effectiveness analysis.

The current annual cost per patient of the ETI treatment paid by countries with negotiated agreements is more than US$250,000, which is very expensive for governments and private health care insurers in

low- and middle-income countries such as Brazil.[43] As negotiations between governments and the company are occurring, our findings highlight the effectiveness of ETI in improving patient-centered outcomes and may help inform future public health policies to provide evidence-based care for individuals with CF living in such countries, changing the landscape of long-term survival in CF.[44]

AUTHOR CONTRIBUTIONS

LVRFSF and RAA: study conception. CRT, JCF, and SET: data collection and analysis. All of the authors contributed to drafting and reviewing the manuscript and approved the final version.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Ratjen F, Bell SC, Rowe SM, Goss CH, Quittner AL, Bush A. Cystic fibrosis. Nat Rev Dis Primers. 2015;1:15010. https://doi.org/10.1038/nrdp.2015.10
2. O'Sullivan BP, Freedman SD. Cystic fibrosis. Lancet. 2009;373(9678):1891-1904. https://doi.org/10.1016/S0140-6736(09)60327-5
3. Bobadilla JL, Macek M Jr, Fine JP, Farrell PM. Cystic fibrosis: a worldwide analysis of CFTR mutations–correlation with incidence data and application to screening. Hum Mutat. 2002;19(6):575-606. https://doi.org/10.1002/humu.10041
4. da Silva Filho LVRF, Maróstica PJC, Athanazio RA, Reis FJC, Damaceno N, Paes AT, et al. Extensive CFTR sequencing through NGS in Brazilian individuals with cystic fibrosis: unravelling regional discrepancies in the country. J Cyst Fibros. 2021;20(3):473-484. https://doi.org/10.1016/j.jcf.2020.08.007
5. Bell SC, Mall MA, Gutierrez H, Macek M, Madge S, Davies JC, et al. The future of cystic fibrosis care: a global perspective [published correction appears in Lancet Respir Med. 2019 Dec;7(12):e40]. Lancet Respir Med. 2020;8(1):65-124. https://doi.org/10.1016/S2213-2600(19)30337-6
6. Habib AR, Kajbafzadeh M, Desai S, Yang CL, Skolnik K, Quon BS. A Systematic Review of the Clinical Efficacy and Safety of CFTR Modulators in Cystic Fibrosis. Sci Rep. 2019;9(1):7234. https://doi.org/10.1038/s41598-019-43652-2
7. Rowe SM, Heltshe SL, Gonska T, Donaldson SH, Borowitz D, Gelfond D, et al. Clinical mechanism of the cystic fibrosis transmembrane conductance regulator potentiator ivacaftor in G551D-mediated cystic fibrosis. Am J Respir Crit Care Med. 2014;190(2):175-184. https://doi.org/10.1164/rccm.201404-0703OC
8. Mall MA, Mayer-Hamblett N, Rowe SM. Cystic Fibrosis: Emergence of Highly Effective Targeted Therapeutics and Potential Clinical Implications. Am J Respir Crit Care Med. 2020;201(10):1193-1208. https://doi.org/10.1164/rccm.201910-1943SO
9. Capurro V, Tomati V, Sondo E, Renda M, Borrelli A, Pastorino C, et al. Partial Rescue of F508del-CFTR Stability and Trafficking Defects by Double Corrector Treatment. Int J Mol Sci. 2021;22(10):5262. https://doi.org/10.3390/ijms22105262
10. Mendoza JL, Schmidt A, Li Q, Nuvaga E, Barrett T, Bridges RJ, et al. Requirements for efficient correction of ΔF508 CFTR revealed by analyses of evolved sequences. Cell. 2012;148(1-2):164-174. https://doi.org/10.1016/j.cell.2011.11.023
11. Rabeh WM, Bossard F, Xu H, Okiyoneda T, Bagdany M, Mulvihill CM, et al. Correction of both NBD1 energetics and domain interface is required to restore ΔF508 CFTR folding and function. Cell. 2012;148(1-2):150-163. https://doi.org/10.1016/j.cell.2011.11.024
12. Keating D, Marigowda G, Burr L, Daines C, Mall MA, McKone EF, et al. VX-445-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med. 2018;379(17):1612-1620. https://doi.org/10.1056/NEJMoa1807120
13. Middleton PG, Mall MA, Dřevínek P, Lands LC, McKone EF, Polineni D, et al. Elexacaftor-Tezacaftor-Ivacaftor for Cystic Fibrosis with a Single Phe508del Allele. N Engl J Med. 2019;381(19):1809-1819. https://doi.org/10.1056/NEJMoa1908639
14. Heijerman HGM, McKone EF, Downey DG, Van Braeckel E, Rowe SM, Tullis E, et al. Efficacy and safety of the elexacaftor plus tezacaftor plus ivacaftor combination regimen in people with cystic fibrosis homozygous for the F508del mutation: a double-blind, randomised, phase 3 trial [published correction appears in Lancet. 2020 May 30;395(10238):1694]. Lancet. 2019;394(10212):1940-1948. https://doi.org/10.1016/S0140-6736(19)32597-8
15. Sutharsan S, McKone EF, Downey DG, Duckers J, MacGregor G, Tullis E, et al. Efficacy and safety of elexacaftor plus tezacaftor plus ivacaftor versus tezacaftor plus ivacaftor in people with cystic fibrosis homozygous for F508del-CFTR: a 24-week, multicentre, randomised, double-blind, active-controlled, phase 3b trial. Lancet Respir Med. 2022;10(3):267-277. https://doi.org/10.1016/S2213-2600(21)00454-9
16. Mall MA, Brugha R, Gartner S, Legg J, Moeller A, Mondejar-Lopez P, et al. Efficacy and Safety of Elexacaftor/Tezacaftor/Ivacaftor in Children 6 Through 11 Years of Age with Cystic Fibrosis Heterozygous for F508del and a Minimal Function Mutation: A Phase 3b, Randomized, Placebo-controlled Study. Am J Respir Crit Care Med. 2022;206(11):1361-1369. https://doi.org/10.1164/rccm.202202-0392OC
17. Athanazio RA, Tanni SE, Ferreira J, Dalcin PTR, Fuccio MB, Esposito C, et al. Brazilian guidelines for the pharmacological treatment of the pulmonary symptoms of cystic fibrosis. Official document of the Sociedade Brasileira de Pneumologia e Tisiologia (SBPT, Brazilian Thoracic Association). J Bras Pneumol. 2023;49(2):e20230040. https://doi.org/10.36416/1806-3756/e20230040
18. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
19. Sterne JAC, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:l4898. https://doi.org/10.1136/bmj.l4898
20. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Synth Methods. 2021;12(1):55-61. https://doi.org/10.1002/jrsm.1411
21. GRADEpro GDT [homepage on the Internet]. Hamilton, Canada: McMaster University and Evidence Prime; c2021. GRADEpro Guideline Development Tool [Software]. Available from: https://www.gradepro.org/
22. Review Manager (RevMan) [Computer Program]. version 5.4. The Cochrane Collaboration, 2020.
23. Barry PJ, Mall MA, Álvarez A, Colombo C, de Winter-de Groot KM, Fajac I, et al. Triple Therapy for Cystic Fibrosis Phe508del-Gating and -Residual Function Genotypes. N Engl J Med. 2021;385(9):815-825. https://doi.org/10.1056/NEJMoa2100665
24. Wang Y, Ma B, Li W, Li P. Efficacy and Safety of Triple Combination Cystic Fibrosis Transmembrane Conductance Regulator Modulators in Patients With Cystic Fibrosis: A Meta-Analysis of Randomized Controlled Trials. Front Pharmacol. 2022;13:863280. https://doi.org/10.3389/fphar.2022.863280
25. Davies JC, Moskowitz SM, Brown C, Horsley A, Mall MA, McKone EF, et al. VX-659-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and One or Two Phe508del Alleles. N Engl J Med. 2018;379(17):1599-1611. https://doi.org/10.1056/NEJMoa1807119
26. Ramsey BW, Davies J, McElvaney NG, Tullis E, Bell SC, Drevinek P, et al. A CFTR potentiator in patients with cystic fibrosis and the G551D mutation. N Engl J Med. 2011;365(18):1663-1672. https://doi.org/10.1056/NEJMoa1105185
27. Bower JK, Volkova N, Ahluwalia N, Sahota G, Xuan F, Chin A, et al. Real-world safety and effectiveness of elexacaftor/tezacaftor/ivacaftor in people with cystic fibrosis: Interim results of a long-term registry-based study [published online ahead of print, 2023 Mar 22]. J Cyst Fibros. 2023;S1569-1993(23)00066-8. https://doi.org/10.1016/j.jcf.2023.03.002
28. Burgel PR, Durieu I, Chiron R, Ramel S, Danner-Boucher I, Prevotat A, et al. Rapid Improvement after Starting Elexacaftor-Tezacaftor-Ivacaftor in Patients with Cystic Fibrosis and Advanced Pulmonary

Disease. Am J Respir Crit Care Med. 2021;204(1):64-73. https://doi.org/10.1164/rccm.202011-4153OC

29. Fuchs HJ, Borowitz DS, Christiansen DH, Morris EM, Nash ML, Ramsey BW, et al. Effect of aerosolized recombinant human DNase on exacerbations of respiratory symptoms and on pulmonary function in patients with cystic fibrosis. The Pulmozyme Study Group. N Engl J Med. 1994;331(10):637-642. https://doi.org/10.1056/NEJM199409083311003
30. Saiman L, Marshall BC, Mayer-Hamblett N, Burns JL, Quittner AL, Cibene DA, et al. Azithromycin in patients with cystic fibrosis chronically infected with Pseudomonas aeruginosa: a randomized controlled trial. JAMA. 2003;290(13):1749-1756. https://doi.org/10.1001/jama.290.13.1749
31. Ramsey BW, Pepe MS, Quan JM, Otto KL, Montgomery AB, Williams-Warren J, et al. Intermittent administration of inhaled tobramycin in patients with cystic fibrosis. Cystic Fibrosis Inhaled Tobramycin Study Group. N Engl J Med. 1999;340(1):23-30. https://doi.org/10.1056/NEJM199901073400104
32. Goss CH, Sykes J, Stanojevic S, Marshall B, Petren K, Ostrenga J, et al. Comparison of Nutrition and Lung Function Outcomes in Patients with Cystic Fibrosis Living in Canada and the United States. Am J Respir Crit Care Med. 2018;197(6):768-775. https://doi.org/10.1164/rccm.201707-1541OC
33. Goss CH. Acute pulmonary exacerbation in cystic fibrosis. Semin Respir Crit Care Med. 2019;40(6):792-803. https://doi.org/10.1055/s-0039-1697975
34. Amaral MD. Processing of CFTR: traversing the cellular maze--how much CFTR needs to go through to avoid cystic fibrosis?. Pediatr Pulmonol. 2005;39(6):479-491. https://doi.org/10.1002/ppul.20168
35. Bacalhau M, Camargo M, Magalhães-Ghiotto GAV, Drumond S, Castelletti CHM, Lopes-Pacheco M. Elexacaftor-Tezacaftor-Ivacaftor: A Life-Changing Triple Combination of CFTR Modulator Drugs for Cystic Fibrosis. Pharmaceuticals (Basel). 2023;16(3):410. https://doi.org/10.3390/ph16030410
36. Wainwright CE, Elborn JS, Ramsey BW, Marigowda G, Huang X, Cipolli M, et al. Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis Homozygous for Phe508del CFTR. N Engl J Med. 2015;373(3):220-231. https://doi.org/10.1056/NEJMoa1409547
37. McColley SA. A safety evaluation of ivacaftor for the treatment of cystic fibrosis. Expert Opin Drug Saf. 2016;15(5):709-715. https://doi.org/10.1517/14740338.2016.1165666
38. Goralski JL, Hoppe JE, Mall MA, McColley SA, McKone E, Ramsey B, et al. Phase 3 Open-Label Clinical Trial of Elexacaftor/Tezacaftor/Ivacaftor in Children Aged 2-5 Years with Cystic Fibrosis and at Least One F508del Allele. Am J Respir Crit Care Med. 2023;208(1):59-67. https://doi.org/10.1164/rccm.202301-0084OC
39. Grasemann H, Ratjen F. Early lung disease in cystic fibrosis. Lancet Respir Med. 2013;1(2):148-157. https://doi.org/10.1016/S2213-2600(13)70026-2
40. Greenawald L, Shenoy A, Elidemir O, Livingston F, Schaeffer D, Chidekel A. Real World Effectiveness of Ivacaftor in Pediatric Cystic Fibrosis Patients. Pediatric Pulmonology. 2018;53(S2):157. https://doi.org/10.1002/ppul.24152
41. Burgel PR, Munck A, Durieu I, Chiron R, Mely L, Prevotat A, et al. Real-Life Safety and Effectiveness of Lumacaftor-Ivacaftor in Patients with Cystic Fibrosis. Am J Respir Crit Care Med. 2020;201(2):188-197. https://doi.org/10.1164/rccm.201906-1227OC
42. Bell SC, Mainz JG, MacGregor G, Madge S, MacEy J, Fridman M, et al. Patient-reported outcomes in patients with cystic fibrosis with a G551D mutation on ivacaftor treatment: results from a cross-sectional study. BMC Pulm Med. 2019;19(1):146. https://doi.org/10.1186/s12890-019-0887-6
43. Zampoli M, Kashirskaya N, Karadag B, Filho LVRFDS, Paul GR, Noke C. Global access to affordable CFTR modulator drugs: Time for action!. J Cyst Fibros. 2022;21(3):e215-e216. https://doi.org/10.1016/j.jcf.2022.03.006
44. da Silva Filho LVRF, Zampoli M, Cohen-Cymberknoh M, Kabra SK. Cystic fibrosis in low and middle-income countries (LMIC): A view from four different regions of the world. Paediatr Respir Rev. 2021;38:37-44. https://doi.org/10.1016/j.prrv.2020.07.004

Effectiveness of wearing masks during the COVID-19 outbreak in cohort and case-control studies: a systematic review and meta-analysis

Idevaldo Floriano[1], Antônio Silvinato[1,2], Hélio Arthur Bacha[3], Alexandre Naime Barbosa[4], Suzana Tanni[5], Wanderley Marques Bernardo[2,6]

1. Cooperativa Baixa Mogiana, Medicina Baseada em Evidências, Mogi-Guaçu (SP) Brasil.
2. Associação Médica Brasileira, Medicina Baseada em Evidências, São Paulo (SP) Brasil.
3. Hospital Israelita Albert Einstein, São Paulo (SP) Brasil.
4. Disciplina de Moléstias Infecciosas e Parasitárias, Departamento de Infectologia, Dermatologia, Diagnóstico por Imagem e Radioterapia, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
5. Disciplina de Pneumologia, Departamento de Clínica Médica, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista – UNESP – Botucatu (SP) Brasil.
6. Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.

Submitted: 1 March 2023.
Accepted: 6 September 2023.

ABSTRACT

Objective: To evaluate the efficacy of wearing a mask to prevent COVID-19 infection. **Methods:** This was a systematic review and meta-analysis of cohort and case-control studies, considering the best level of evidence available. Electronic databases (MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, and Clinical Trials.gov) were searched to identify studies that evaluated the effectiveness of wearing masks compared with that of not wearing them during the COVID-19 pandemic. Risk of bias and quality of evidence were assessed using the Cochrane risk of bias tool and the Grading of Recommendations Assessment, Development, and Evaluation. **Results:** Of the 1,028 studies identified, 9 met the inclusion criteria (2 cohort studies and 7 case-control studies) and were included in the analysis. The meta-analysis using cohort studies alone showed statistically significant differences, wearing a cloth mask decreased by 21% [RD = −0.21 (95% CI, −0.34 to −0.07); I^2 = 0%; p = 0,002] the risk of COVID-19 infection, but the quality of evidence was low. Regarding case-control studies, wearing a surgical mask reduced the chance of COVID-19 infection [OR = 0.51 (95% CI, 0.37-0.70); I^2 = 47%; p = 0.0001], as did wearing an N95 respirator mask [OR = 0.31 (95% CI, 0.20-0.49); I^2 = 0%; p = 0.00001], both with low quality of evidence. **Conclusions:** In this systematic review with meta-analysis, we showed the effectiveness of wearing masks in the prevention of SARS-CoV-2 infection regardless of the type of mask (disposable surgical mask, common masks, including cloth masks, or N95 respirators), although the studies evaluated presented with low quality of evidence and important biases.

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

INTRODUCTION

After the first case of COVID-19 in November of 2019, the pandemic has widely spread worldwide, causing numerous deaths from SARS-CoV-2-related ARDS. The transmission of respiratory viruses such as SARS-CoV-2 can occur through saliva droplets, person-to-person contacts, or contaminated surfaces,[1,2] and it can be avoided by barriers and social distancing protection.

At the beginning of the pandemic, there was a sudden and marked increase in the consumption of personal protective equipment (PPE), which, in association with social distancing, were the only methods to prevent the spread of the virus before vaccine availability. With the advent of vaccines, there was a marked reduction in infection and mortality rates, but those were still high. Nowadays, the use of PPE is adaptive considering the recommendations of local health agencies and COVID-19 incidence rates. The WHO[3] and the U.S. Centers for Disease Control and Prevention[4] recognize that wearing well-fitted masks and maintaining social distancing, such as avoiding crowded or closed-contact settings, as well as cleaning hands regularly and covering sneezes and coughs, reduce COVID-19 transmission. Masks can be used to protect healthy people or to prevent onward transmission. On the other hand, there is a concern related to the real effectiveness of the different types of masks in reducing the transmission of COVID-19. Commercially, there are three types of masks commonly sold in order to protect against aerial contamination: cloth face masks, worn by the general population; medical face masks (surgical face masks), worn by health care agents; and N95 respirators or equivalents, worn by health care professionals in the presence of aerosol contaminants.

Previous systematic reviews in the literature on this topic[5-7] did not take into consideration the relationship between the type of respiratory viruses and their respiratory infection rate, and this directly impacted on the results. Moreover, those studies had different study designs, creating bias and reducing the quality and reliability of the data obtained. To improve the information regarding the effectiveness of masks used during the COVID-19 pandemic, this systematic review was carried out with a selection of studies published

Correspondence to:
Idevaldo Floriano. Rua Marcos Vedovello, 89. CEP 13840-221. Mogi-Guaçu, SP, Brasil.
Tel.: 55 19 3981-4992. Email: idfloriano@hotmail.com
Financial support: None.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

during the COVID-19 pandemic, which were stratified according to the types of masks (cloth masks, surgical masks, and N95 respirators) used around the world, as well as the types of study design.

METHODS

This systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses recommendations.[8]

Eligibility criteria

The protocol of this study was based on the PICO methodology (**P**atients of interest, **I**ntervention to be studied, **C**omparison of intervention, and **O**utcome of interest). Therefore, the PICO framework in the present study was as follows: **P**atients: adults at risk of being infected with SARS-CoV-2; **I**ntervention: use of face masks; **C**omparison: individuals who did not wear face masks; and **O**utcome: COVID-19 infection. Observational (cohort or case-control) studies were included in this study, and no restrictions regarding the date of publication, language, or full-text availability were imposed.

Information sources and search strategy

Two 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, as well as gray literature. The main search strategy used was the following: "(mask OR masks OR N95 OR (Respiratory Protective Devices OR Respiratory Protective Device) OR face shield) AND (COVID OR COV OR CORONAVIRUS OR SARS) AND (random*) OR therapy/broad[filter] OR comparative study OR comparative studies)." The search strategy included studies published by November 1, 2022.

Study selection

Two independent researchers selected and extracted the data from the studies included. First, the studies were selected based on their titles and abstracts. Second, full texts were evaluated to be included or excluded, and disagreements were resolved by consensus or following a discussion with a third researcher.

Data collection and investigated outcomes

Data regarding authorship, year of publication, patient description, interventions (wearing masks 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 cohort and case-control studies was assessed using the current tool recommended by the Cochrane Collaboration to estimate the effectiveness and safety of nonrandomized interventional studies, designated Risk of Bias in Non-randomized Studies of Interventions.[9] This tool assesses seven domains of bias, classified by the time of occurrence, as were other fundamental elements, and are expressed as low risk, moderate risk, serious risk, critical risk, or no information.

The assessment of the 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 using the Grading of Recommendations Assessment, Development and Evaluation terminology[10,11] as very low, low, moderate, or high; the quality of evidence was described by the GRADEpro Guideline Development Tool (McMaster University, Hamilton, ON, Canada) for meta-analyses.

Synthesis of results and statistical analysis

Categorical outcomes were expressed by group (wearing masks or control): number of events and calculated risk in percentage (by dividing the number of events by the total number of individuals in each group) for cohort and case-control studies. The effectiveness of wearing a face mask for preventing transmission of COVID-19 respiratory infections in community settings was assessed using ORs and their respective 95% CIs for case-control studies. For cohort studies, the effects of meta-analyses were reported as risk differences (RDs) or ORs and corresponding 95% CIs. The use of RDs shows the absolute effect size in the meta-analysis when compared with the relative risk or the OR, and this technique can be used when the binary outcome is zero in both study arms. We used the fixed-effect or the random-effect model in the meta-analysis to evaluate the effect of intervention vs. control on the outcome when these data were available in at least two studies. The heterogeneity of effects among studies was quantified using the I^2 statistic ($I^2 > 50\%$ indicating high heterogeneity). For the meta-analysis, we used the Review Manager software, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, United Kingdom).[12] Results were expressed using a methodological (observational cohort study) design.

RESULTS

A flow diagram of the literature search and related screening process is shown in Figure 1. The search strategy identified 1,367 studies, and, after screening titles and abstracts, we identified 57 potentially eligible citations. After applying inclusion and exclusion criteria, we retrieved 18 citations for full-text analysis, and 9 studies[13-21] were included in this systematic review, 2 of those being cohort studies[13,14] and 7 being case-control studies.[15-21] The list of excluded studies and the reasons for their exclusion are available in the supplementary material. The characteristics of the studies included are described in Table 1. The

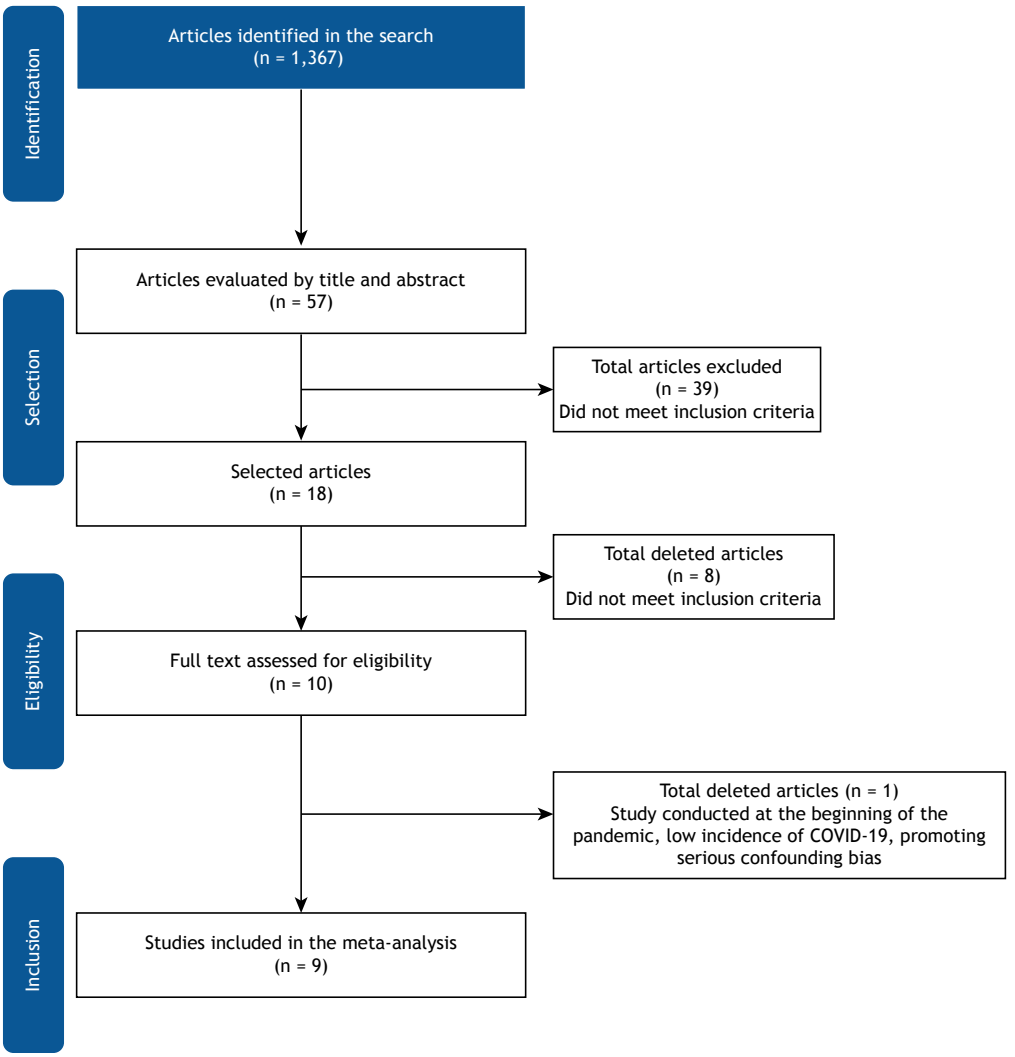


Figure 1. Flow chart of study selection process.

risk of bias and the quality of evidence are described in Tables 2 and 3, respectively. No publication bias was identified.

A total of 2,803 participants (192 in the cohort studies and 2,611 in the case-control studies) were included in the analysis (wearing a mask or not) in terms of effectiveness to decrease the indices of COVID-19 infection.

Regarding the risk of bias, all of the studies included showed high or critical biases due to confusion, selection of participants, or missed dates. Overall, the studies were considered to have a high risk of bias (Table 2): a serious risk in 5 studies and a moderate risk in 3 studies.

The cohort studies evaluated 192 participants on the effectiveness of wearing a mask (disposable surgical masks or common masks, including cloth masks) in preventing COVID-19 infection. The wearing of masks was associated with an important reduction (by 21%) in the risk of COVID-19 infection [RD = −0.21 (95% CI, −0.34 to −0.07); I^2 = 0%; p = 0.002], which indicated that it was necessary that 5 participants should wear a mask to avoid 1 COVID-19 case, with a low quality of evidence (Figure 2).

Six case-control studies included 729 subjects in the intervention group and 1,074 in the control group. The meta-analysis showed that the chance of contracting COVID-19 infection was 0.49 times lower in those who wore masks [OR = 0.51 (95% CI, 0.37-0.70); I^2 = 47%, p = 0.0001] when compared with the control group, with a low quality of evidence (Figure 3). The specific use of the N95 respirator masks was assessed in 4 case-control studies, which included 414 participants in the N95 mask group and 395 in the control group. The N95 mask group showed to have a 0.69 lower chance of acquiring COVID-19 infection in comparison with those who did not wear a mask [OR = 0.31 (95% CI, 0.20-0.49); I^2 = 0%, p = 0.00001], with a low quality of evidence (Figure 3).

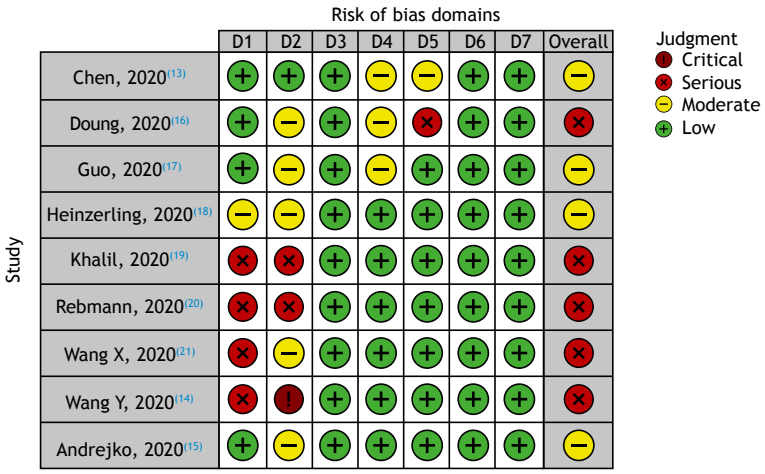
Summary of evidence

- The use of masks (disposable surgical masks or common masks, including cloth masks) caused a

Table 1. Description of the studies included in the systematic review.

Study	Design	Population	Intervention	Comparator	Outcome	Follow-up
Andrejko et al.[15]	Case-control	2,749 participants from the state of California, USA, were evaluated between February 18 and December 1, 2021. All participants reported having been in indoor public settings 14 days before SARS-CoV-2 testing	Wearing masks (cotton, surgical, or N95/KN95.	Not wearing masks	COVID-19 infection	14 days
Chen et al.[13]	Cohort	Risk factors were evaluated in 105 healthcare workers having had contact with 4 individuals positive for COVID-19 in nursing homes in China	Wearing masks (disposable nonsurgical face masks, surgical masks, or N95)	Not wearing masks	Demographic characteristics, clinical symptoms, and COVID-19 infection	14 days
Doung-Ngern et al.[16]	Case-control	1,050 people who attended public companies, nightclubs, and boxing stadiums in Thailand between March 1st and May 30, 2020 were interviewed via telephone	Wearing surgical masks	Not wearing masks	COVID-19 infection	21 days
Guo et al.[17]	Case-control	72 orthopedic surgeons working at hospitals in Wuhan, China, between December 31, 2019 and February 24, 2020	Wearing N95 masks	Not wearing masks	COVID-19 infection	N/A
Heinzerling et al.[18]	Case-control	37 hospital workers, contacting the first case of SARS-CoV-2 in California, USA.	Wearing surgical masks	Not wearing mask	COVID-19 infection	N/A
Khalil et al.[19]	Case-control	190 physicians who worked in hospitals in Bangladesh between May and June of 2020	Wearing community masks and N95 masks	Not wearing masks	COVID-19 infection	N/A
Rebmann et al.[20]	Case-control	9,335 students from the University of St. Louis, USA. were tested by PCR, resulting in 265 positive cases for COVID-19, and 378 students who had close contacts with positive cases between January and May of 2021 (26 cases and 352 controls)	Wearing surgical masks	Not wearing masks	COVID-19 infection	N/A
Wang et al.[14]	Retrospective Cohort	124 families with cases of COVID-19 infection in family members; hygiene behaviors, individual protection, and social distancing were evaluated	Wearing community masks	Not wearing masks	COVID-19 infection	14 days
Wang et al.[21]	Case-control	493 physicians and nurses working at the Zhongnan University Hospital, Wuhan, China, between January 2 and 22, 2020	Wearing N95 masks	Not wearing N95 masks	COVID-19 infection	N/A

Table 2. Risk of bias of the studies included in the analysis.



Domains:
D1: Bias due to confounding
D2: Bias due to selection of participants
D3: Bias in classification of interventions
D4: Bias due to deviations from intended interventions
D5: Bias due to missing data
D6: Bias in measurement of outcomes
D7: Bias in selection of the reported result

In accordance with Sterne et al.[9]

Table 3. Summary of results and analysis of certainty of evidence (GRADE) of the use masks during the COVID-19 outbreak.

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Certainty of evidence
	Risk of not wearing masks	Risk of wearing masks			
Wearing surgical masks during SARS-CoV-2 pandemic Case-control	Lower		RR 0.63 (0.51 to 0.79)	729 cases 1,074 controls (6 observational studies)	⊕⊕OO Low[a]
	0 per 1,000	0 per 1,000 (0 to 0)			
Wearing N95 masks during SARS-CoV-2 pandemic Case-control	Lower		RR 0.54 (0.42 to 0.69)	414 cases 391 controls (4 observational studies)	⊕⊕OO Low[a]
	0 per 1,000	0 per 1,000 (0 to 0)			
Wearing disposable surgical masks or common masks, including cloth masks during SARS-CoV-2 pandemic Cohort	368 per 1,000	154 per 1,000 (92 to 268)	RR 0.42 (0.25 to 0.73)	192 (2 observational studies)	⊕⊕OO Low[b]

GRADE: Grading of Recommendations Assessment, Development, and Evaluation; and RR: risk ratio. *The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
Explanations
a. Case-control studies with severe biases in confounding and patient selection domains.
b. Cohort studies with bias due to confounding, deviation from intended intervention, missing data, and participant selection domains.

reduction of 21% in the risk of COVID-19 infection [RD = −0.21 (95% CI, −0.34 to −0.07); I^2 = 0%, p = 0.002] in the cohort studies included, with a low certainty of evidence

- The use of surgical masks decreased the chance of COVID-19 infection by 49% [OR = 0.51 (95% CI, 0.37-0.70); I^2 = 47%, p = 0.00001] in the case-control studies included, with a low certainty of evidence
- The use of N95 respirator masks demonstrated a significant protective effect in decreasing (by 69%) the chance of COVID-19 infection [OR =

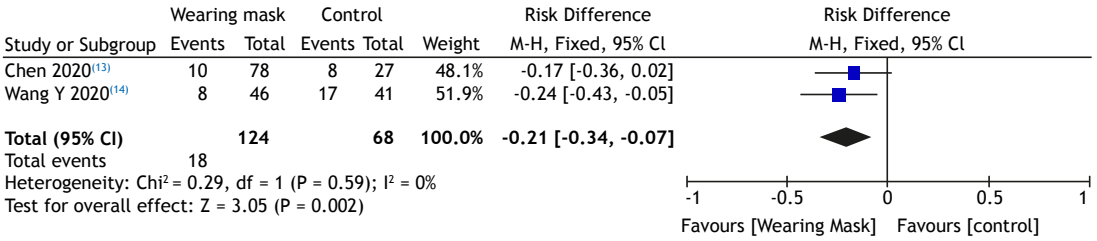


Figure 2. Forest plot of comparison: wearing disposable surgical masks or common masks, including cloth masks vs. control group regarding COVID-19 infection (cohort studies).

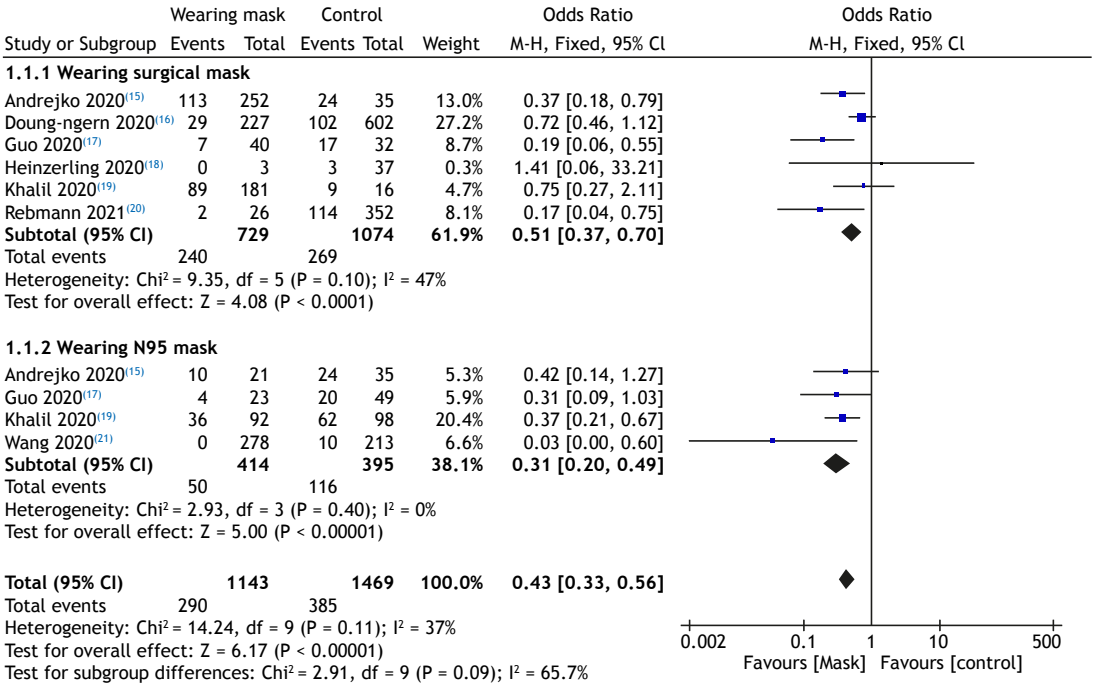


Figure 3. Forest plot of comparison: wearing surgical masks or N95 respirator masks vs. control group regarding COVID-19 infection (case-control studies).

0.31 (95% CI, 0.20-0.49); $I^2 = 0\%$; p = 0.00001] in the case-control studies included, with a low certainty of evidence

DISCUSSION

Our systematic review demonstrates a reduction in the risk of COVID-19 infection. By evaluating different subgroups of study designs (cohort studies whose intervention was the use of disposable surgical masks, common masks, including cloth masks, or N95 respirators; and case-control studies whose intervention was wearing surgical masks or N95 respirator masks), we obtained a relevant reduction in the risk of COVID-19 infection, regardless of the type of mask, but the certainty of evidence was low.

Comparing our results with those of other systematic reviews, we can claim that wearing masks can contribute to reducing COVID-19 infection. The previous literature studied the effect of wearing masks in different scenarios, different types of infectious aerosols, and different rates of infection. It is important to promote reliable knowledge and education to society regarding the use of facial masks as an instrument of individual protection. Japan is one of the countries that culturally educated its population to wear masks to protect others when they present respiratory symptoms. Nevertheless, this is not the only instruction that we can provide to protect against COVID-19 infection. We need to remember to maintain social distancing, hand hygiene, and other essential measures.

Xu et al.[22] have shown that indoor environments can contain high rates of aerosol dispersants, which may promote high rates of viral transmission; however, when wearing an N95 respirator or a surgical mask, the level of aerosols can be reduced significantly. Likewise, Araújo et al.[5] demonstrated that wearing face masks in a community scenario can significantly decrease viral infections. Moreover, surgical masks offer higher protection when compared with cloth masks. On the other hand, to achieve a significant reduction in COVID-19 transmission, more than half of

the population needs to be wearing masks. Therefore, the rate of infection transmission is important to be considered by public health recommendations regarding the use of masks. Nowadays, when we observe a new and more transmissible SARS-CoV-2 strain, a low rate of vaccination, and/or no use of facial masks, we may await more critical outcomes, such as increases in the number of hospitalizations and deaths again.

When we evaluated the use of masks without stratifying the specific type of mask or study design, there was a 57% reduction in the chance of COVID-19 infection (Figure 3). Regarding the comparison between surgical masks and N95 respirators, regardless of the study design, we found a 49% and 69% reduction in the chance of COVID-19 infection, respectively The difference in protection between surgical masks and N95 respirators is due to the difference in the permeability of the material used in their manufacture, because the material used in N95 respirator masks is less impermeable than that used in surgical masks, offering greater protection. However, there are biases, such as time of use, training for use, and number of times of exposure to contaminants and to places with a higher chance of contamination, that are determining factors in greater or lesser protection when using PPE.

This systematic review had some limitations: the first and major limitation is the huge variability in viral incidence (i.e., lack of preliminary estimates of the basic reproduction number [R_0] of SARS-CoV-2); the assessment of the effectiveness of wearing a mask can directly correlate to adherence, time of use, type of location of exposure, incidence of COVID-19 infection at the study site, type of mask, social distancing, and other factors. In addition, the studies included in this review were performed during the COVID-19 pandemic; however, the R_0 of each study was probably different, a fact that can cause largely different results. Moreover, most of the studies included were considered to have a serious risk of bias and a low certainty of evidence.

Because of the difficulty in conducting good-quality randomized controlled trials during a pandemic that has spread around the world rapidly, we needed to work with the best evidence available.

FINAL CONSIDERATIONS

The use of masks showed effectiveness in the prevention of SARS-CoV-2, regardless of the mask type (disposable surgical masks, common masks, including cloth masks, or N95 respirators). However, the certainty of evidence was low.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Canini L, Andréoletti L, Ferrari P, D'Angelo R, Blanchon T, Lemaitre M, et al. Surgical mask to prevent influenza transmission in households: a cluster randomized trial. PLoS One. 2010;5(11):e13998. https://doi.org/10.1371/journal.pone.0013998
2. Cowling BJ, Zhou Y, Ip DK, Leung GM, Aiello AE. Face masks to prevent transmission of influenza virus: a systematic review. Epidemiol Infect. 2010;138(4):449-456. https://doi.org/10.1017/S0950268809991658
3. World Health Organization [homepage on the Internet]. Geneva: World Health Organization; c2020 [cited 2020 Apr 8]. Coronavirus disease (COVID-19) advice for the public: When and how to use masks. Available from: https://www.who.int/emergencies/diseases/novel-coronavirus-2019/advice-for-public/when-and-how-to-use-masks
4. Centers for Disease Control and Prevention (CDC) [homepage on the Internet]. Atlanta: CDC; c2019 [cited 2020 Apr 8]. Recommendation regarding the use of cloth face coverings, especially in areas of significant community-based transmission. Available: https://www.cdc.gov/coronavirus/2019-ncov/prevent- getting- sick/cloth-facecover html
5. Araujo CM, Guariza-Filho O, Gonçalves FM, Basso IB, Schroder AGD, Cavalcante-Leão BL, et al. Front lines of the COVID-19 pandemic: what is the effectiveness of using personal protective equipment in health service environments?-a systematic review. Int Arch Occup Environ Health. 2022;95(1):7-24. https://doi.org/10.1007/s00420-021-01775-y
6. Coclite D, Napoletano A, Gianola S, Del Monaco A, D'Angelo D, Fauci A, et al. Face Mask Use in the Community for Reducing the Spread of COVID-19: A Systematic Review. Front Med (Lausanne). 2021;7:594269. https://doi.org/10.3389/fmed.2020.594269
7. Chou R, Dana T, Jungbauer R, Weeks C, McDonagh MS. Masks for Prevention of Respiratory Virus Infections, Including SARS-CoV-2, in Health Care and Community Settings : A Living Rapid Review. Ann Intern Med. 2020;173(7):542-555. https://doi.org/10.7326/M20-3213
8. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71. https://doi.org/10.1136/bmj.n71
9. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919. https://doi.org/10.1136/bmj.i4919
10. GRADE Working Group [homepage on the Internet]. c2021 [cited 2021 Aug 1]. GRADE. Available from: https://www.gradeworkinggroup.org/
11. GRADEpro GDT [homepage on the Internet]. Hamilton, Canada: McMaster University and Evidence Prime; c2021. GRADEpro Guideline Development Tool [Software]. Available from: https://www.gradepro.org/
12. Review Manager (RevMan) [Computer Program]. version 5.4. The Cochrane Collaboration; 2020.
13. Chen Y, Tong X, Wang J, Huang W, Yin S, Huang R, et al. High SARS-CoV-2 antibody prevalence among healthcare workers exposed to COVID-19 patients. J Infect. 2020;81(3):420-426. https://doi.org/10.1016/j.jinf.2020.05.067
14. Wang Y, Tian H, Zhang L, Zhang M, Guo D, Wu W, et al. Reduction of secondary transmission of SARS-CoV-2 in households by face mask use, disinfection and social distancing: a cohort study in Beijing, China. BMJ Glob Health. 2020;5(5):e002794. https://doi.org/10.1136/

bmjgh-2020-002794

15. Andrejko KL, Pry JM, Myers JF, Fukui N, DeGuzman JL, Openshaw J, et al. Effectiveness of Face Mask or Respirator Use in Indoor Public Settings for Prevention of SARS-CoV-2 Infection - California, February-December 2021. MMWR Morb Mortal Wkly Rep. 2022;71(6):212-216. https://doi.org/10.15585/mmwr.mm7106e1
16. Doung-Ngern P, Suphanchaimat R, Panjangampatthana A, Janekrongtham C, Ruampoom D, Daochaeng N, et al. Case-Control Study of Use of Personal Protective Measures and Risk for SARS-CoV 2 Infection, Thailand. Emerg Infect Dis. 2020;26(11):2607-2616. https://doi.org/10.3201/eid2611.203003
17. Guo X, Wang J, Hu D, Wu L, Gu L, Wang Y. Survey of COVID-19 Disease Among Orthopaedic Surgeons in Wuhan, People's Republic of China. J Bone Joint Surg Am. 2020;102(10):847-854. https://doi.org/10.2106/JBJS.20.00417
18. Heinzerling A, Stuckey MJ, Scheuer T, Xu K, Perkins KM, Resseger H, et al. Transmission of COVID-19 to Health Care Personnel During Exposures to a Hospitalized Patient - Solano County, California, February 2020. MMWR Morb Mortal Wkly Rep. 2020;69(15):472-476. https://doi.org/10.15585/mmwr.mm6915e5
19. Khalil MM, Alam MM, Arefin MK, Chowdhury MR, Huq MR, Chowdhury JA, et al. Role of Personal Protective Measures in Prevention of COVID-19 Spread Among Physicians in Bangladesh: a Multicenter Cross-Sectional Comparative Study. SN Compr Clin Med. 2020;2(10):1733-1739. https://doi.org/10.1007/s42399-020-00471-1
20. Rebmann T, Loux TM, Arnold LD, Charney R, Horton D, Gomel A. SARS-CoV-2 Transmission to Masked and Unmasked Close Contacts of University Students with COVID-19 - St. Louis, Missouri, January-May 2021. MMWR Morb Mortal Wkly Rep. 2021;70(36):1245-1248. https://doi.org/10.15585/mmwr.mm7036a3
21. Wang X, Pan Z, Cheng Z. Association between 2019-nCoV transmission and N95 respirator use. J Hosp Infect. 2020;105(1):104-105. https://doi.org/10.1016/j.jhin.2020.02.021
22. Xu H, Gan Y, Zheng D, Wu B, Zhu X, Xu C, et al. Relationship Between COVID-19 Infection and Risk Perception, Knowledge, Attitude, and Four Nonpharmaceutical Interventions During the Late Period of the COVID-19 Epidemic in China: Online Cross-Sectional Survey of 8158 Adults. J Med Internet Res. 2020;22(11):e21372. https://doi.org/10.2196/21372

J Bras Pneumol. 2023;49(6):e20230210
https://dx.doi.org/10.36416/1806-3756/e20230210

Radon exposure: a major cause of lung cancer in nonsmokers

Marilyn Urrutia-Pereira[1], José Miguel Chatkin[2], Herberto José Chong-Neto[3], Dirceu Solé[4]

1. Departamento de Medicina, Universidade Federal do Pampa – UNIPAMPA – Uruguaiana (RS) Brasil.
2. Disciplina de Medicina Interna e Pneumologia, Escola de Medicina, Pontifícia Universidade Católica do Rio Grande do Sul – PUCRS – Porto Alegre (RS) Brasil.
3. Departamento de Pediatria, Universidade Federal do Paraná – UFPR – Curitiba (PR) Brasil.
4. Disciplina de Pediatria, Escola Paulista de Medicina – EPM – Universidade Federal de São Paulo – UNIFESP – São Paulo (SP) Brasil.

Submitted: 18 June 2023.
Accepted: 6 September 2023.

ABSTRACT

Exposure to radon can impact human health. This is a nonsystematic review of articles written in English, Spanish, French, or Portuguese published in the last decade (2013-2023), using databases such as PubMed, Google Scholar, EMBASE, and SciELO. Search terms selected were radon, human health, respiratory diseases, children, and adults. After analyzing the titles and abstracts, the researchers initially identified 47 studies, which were subsequently reduced to 40 after excluding reviews, dissertations, theses, and case-control studies. The studies have shown that enclosed environments such as residences and workplaces have higher levels of radon than those outdoors. Moreover, radon is one of the leading causes of lung cancer, especially in nonsmokers. An association between exposure to radon and development of other lung diseases, such as asthma and COPD, was also observed. It is crucial to increase public awareness and implement governmental control measures to reduce radon exposure. It is essential to quantify radon levels in all types of buildings and train professionals to conduct such measurements according to proven efficacy standards. Health care professionals should also be informed about this threat and receive adequate training to deal with the effects of radon on human health.

Keywords: Radon; Lung neoplasms; Risk factors.

INTRODUCTION

Radon is a colorless and odorless radioactive gas that has a half-life of 3.83 days. It is formed from the radioactive decay of uranium from groundwater, soil, or rocks, and Its products are also colorless, tasteless, and odorless.[1,2]

Indoor (houses and buildings) radon concentrations vary and are influenced by several conditions: (a) geological characteristics of the site (permeability of the rocks, uranium content, and type of soil where the building is located); (b) the pathways that radon finds to infiltrate residences and commercial or noncommercial buildings; (c) the emanation of radon from building materials and ornamentation (such as granite floors and walls); (d) air exchange rate between interior and exterior areas, which depends on the type of building, ventilation systems, and how airtight (sealed) the building is.[3]

Nonspecific symptoms experienced by occupants due to the time spent in a building with poor indoor air quality are collectively designated "sick building syndrome."[4] Radon is harmful to the health of individuals exposed to it. Knowing the risks of such exposure is essential to prevent health damage.[5]

Radon seeps into buildings through cracks in floors or wall joints, gaps around pipes or cables, small pores in walls made of hollow concrete blocks, and open walls or ceilings. It usually reaches higher concentrations in cellars and living spaces in direct contact with the ground, but significant concentrations can also be found above the ground floor.[3] These concentrations can vary between adjacent buildings and within the same structure from one day to the next, or even within hours.[3]

The unit of measurement of radon is the Becquerel per cubic meter (Bq/m³),[6] and the average concentration of radon in open air ranges from 5 Bq/m³ to 15 Bq/m³; however, it is higher in enclosed spaces, especially if they are poorly ventilated. In buildings such as schools, offices, and homes radon concentrations range from 10 Bq/m³ to over 10,000 Bq/m³.[7,8]

The WHO recommends that indoor radon concentrations should not be higher than 100 Bq/m³.[4] It is adivisible that the reference level should not be higher than 300 Bq/m³.[7,8] According to the International Commission on Radiological Protection,[9] the global effective dose attributed to this type of radiation is estimated to be 2.4 mSv/year. The sum of equivalent doses in the tissues or organs is the effective dose.

The *Projeto Planalto de Poços de Caldas* (Poços de Caldas Plateau Project),[10] a pioneering initiative in Brazil, aims to provide reliable, technically accurate, and ethically safe information to alert health professionals and the population about the effects of radon radiation on health. The study identified three sites with average doses above 10 mSv/year, namely: Morro do Ferro (in the rural zone in the city of Poços de Caldas), Morro do Taquari, and in a uranium mine (both in the rural area in the city of Caldas).[10]

Correspondence to:
Herberto José Chong-Neto. Rua Padre Camargo, 453, Alto da Glória, CEP 80060-240, Curitiba, PR, Brasil.
Tel.: 55 41 3208-6500. E-mail: h.chong@uol.com.br
Financial support: None.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

The second part of that project (2004-2013) identified that 21% of the households surveyed had a radon concentration higher than 200 Bq/m³, pointing to the need for the implementation of a permanent model for surveillance of exposure to natural radiation.[11]

In many countries, drinking water is obtained from underground sources, such as springs and wells. Often, these sources have higher concentrations of radon than does surface water from reservoirs, rivers, or lakes. Radon dissolved in drinking water is released into the indoor air; thus, the amount inhaled by breathing is more significant than that ingested from drinking water.[3]

These data are confirmed by a study carried out in Porto Alegre, Brazil, that determined the concentrations of radon in water samples obtained from (precambrian fractured and cenozoic porous) aquifers that feed that city; it was found that more than half of the samples analyzed reached up to 500 BqL,[12] which is above the maximum limit determined as safe by the WHO.[3]

According to radon properties, all buildings are potential sources of this gas, and its concentration is unique to each environment. People living or working in these buildings might be exposed to very high levels, which makes the problem more complex and difficult to address.[6]

IMPACTS OF RADON EXPOSURE ON HUMAN HEALTH

Exposure to radon inside the home can potentially lead to serious health problems. Lopez et al. have shown that radon concentrations can be higher in residential than in public buildings.[13]

Indoor air renewal in residential buildings may only occur for a short period of time since poor ventilation might occur at night, during winter, or during the day when people are away on business. This was confirmed when determining radon concentrations in Canadian homes: they were up to three times higher than in school buildings, 4.7 times higher than in other public buildings and indoor workplaces, and 12 times higher than in the air outdoors.[14]

School children exposed to median concentrations equal to, or greater than the recommended concentrations of fine particulate matter, benzene, limonene, ozone, and radon in a school environment significantly had more frequent systemic, ocular, and upper/lower airway symptoms (sick school syndrome) when compared with unexposed subjects.[4,15]

In children's schools, indoor radon concentrations are also influenced by ventilation types, attendance regime, and building characteristics.[16] Davis et al. found that classroom radon concentrations decreased when school ventilation systems were on.[17] Branco et al. reported that radon concentrations in daycare centers and elementary schools in Portugal were related to the year of construction of the buildings.[18]

Several factors have been identified as capable of interfering with indoor radon concentrations: number of occupants, ventilation, room location in the building,[19] and construction-related factors, since constructions located on the same geological substrate but with different types of building materials may present different indoor radon concentrations.[20,21] In addition, the duration of exposure to radon also has essential relevance. Children, for having a longer life expectancy, if exposed continuously, have a higher lifetime risk of developing cancer.[22,23]

Another topic recently highlighted is the occupancy bias within the residential environment. Newly built houses are mainly inhabited by younger people, who appear to be exposed to higher radiation rates (5.01 mSv/year). In contrast, homes built many years ago are occupied by older people who are exposed to lower radiation rates (3.45-4.22 mSv/year).[24] This observation is important and reinforces the previous citation that exposure to radon at a younger age may represent an increased lifetime risk of health problems.[22,23]

A study conducted in the metropolitan region of Recife, Brazil, found that radon concentrations ranged from 2 to 1,174 Bq/m³ in residences in areas of uraniferous phosphorite outcrops, increasing by 10-16% the risk of developing radon-related pulmonary neoplasia.[25] The authors found that most households evaluated had habits that contributed to indoor gas accumulation, such as keeping windows closed for many hours during the day.[25]

High levels of radon have also been documented in large cities, leading to greater exposure for a broader population.[8] A survey by Petroni & Lima[26] in 35 air-conditioned commercial and residential buildings in the city of São Paulo, Brazil, indicated that 3% of those had radon concentrations above the WHO recommendations.[3] That study found the presence of radon (above 4 mSv/year) in some buildings.

The population must be aware of the health impacts related to home exposure to radon. Health professionals must encourage access to information about the health hazards resulting from such exposure and inform about the monitoring of home radon levels provided by public agencies.[27]

LUNG CANCER AND RADON

Lung cancer is the leading cause of death from cancer in the world, as well as a public health problem. Smoking is identified as the main risk factor for pulmonary cancer and accounts for about 80% of cases, while radon is the main factor among nonsmoker individuals, affecting between 10% and 15% of this population, and increases the 25-fold risk among active smokers when compared with nonsmokers.[8,28,29]

Studies on cancer have classified radon as a grade-1 human carcinogen, also called low grade or well differentiated, because it causes cancerous cells to be a little different from normal cells, which makes the neoplasm slowly progress. A relationship between exposure to radon and increased risk of pulmonary cancer in the general population has been

established.[8,30] However, the consequences of this contribution vary among different studies.[31,32]

Inhaled radon decay products emit radiation associated with high cytotoxic and genotoxic effects, causing lesions in the respiratory epithelium, damaging DNA, and potentially causing lung cancer.[33]

Mechanisms of action

Carcinogenesis by radiation is a complicated process and subject to the effects of different environmental agents, as well as genetic factors.[34] The carcinogenic effect induced by inhaled radon, particularly for the bronchial epithelium and especially in the bifurcations of the airways, is mainly due to the progenies of radon, mainly polonium 214 and 218, which emit high-energy alpha particles as the predominant form of radiation. Despite their limited ability to penetrate tissues, alpha particles can damage exposed tissues due to their high biological efficacy through various cytogenetic effects.[34]

Some of these effects include expression of pathogenic variants, chromosomal aberrations, generation of reactive oxygen species, modification of cell cycles, and increased production of proteins associated with cell cycle regulation and carcinogenesis.[35] In addition, there is evidence suggesting that residential exposure to radon is capable of inducing the expression of pathogenic *EGFR* variants, *ALK* translocations,[31] and an increased risk of small cell lung cancer among all histological types.[36,37]

Non-small cell lung cancer shows molecular alterations, such as somatic mutations (*EGFR*, *BRAF*, *HER2*, *MET*) or chromosomal rearrangements (*ALK*, *ROS1*, *RET*, *NTRK*) mainly in nonsmokers, suggesting an association between radon exposure and non-small cell lung cancer in nonsmokers.[29]

Epidemiology

Epidemiological studies have established an important association between exposure to radon and pulmonary cancer,[33,38-40] confirmed by the higher frequency of pulmonary cancer among uranium miners exposed to radon.[41,42]

A recent meta-analysis of 13 studies documented a direct relationship between the level of radon in households and the risk of developing lung cancer. Based on this information, the authors estimated that exposure to radon could be responsible for up to 2% of deaths from lung cancer in Europe.[43]

The risk of pulmonary cancer increases with the level of exposure to radon. An association was documented between exposure to radon above 50 Bq/m^3 and lung cancer.[44] Individuals exposed to concentrations greater than 200 Bq/m^3 had a 2.06-fold higher risk (95% CI, 1.61-2.64) than did those exposed to concentrations ≤ 50 Bq/m^3. Among active smokers, the risk increased more markedly with increasing exposures to radon, reaching up to 29.3 times higher (95% CI, 15.4-55.7) for heavy smokers exposed to concentrations greater than 200 Bq/m^3.[44]

A meta-analysis evaluated indoor exposure to radon and its effects on health and showed an increase in the relative risk for pulmonary cancer in China of 1.01 (95% CI, 1.01-1.02) for each increment of 10 Bq/m^3 in indoor radon concentrations.[45]

A systematic review followed by a meta-analysis[34] evaluated the association between residential radon exposure and lifetime risk of pulmonary cancer in never smokers. Those exposed to radon concentrations ≥ 100 Bq/m^3 presented with an excess relative risk of 15% of developing lung cancer, especially men.

Another meta-analysis studied the relationship between residential exposure to radon and histological types of pulmonary cancer.[46] High residential exposure to radon was associated with an increased risk of pulmonary cancer (OR = 1.48; 95% CI, 1.26-1.73). All histological types of pulmonary cancer were associated with residential radon exposure. The strongest association was observed with small cell lung cancer (OR = 2.03; 95% CI, 1.52-2.71), followed by adenocarcinoma (OR = 1.58, 95% CI, 1.31-1, 91), other histological types (OR = 1.54, 95% CI, 1.11-2.15), and squamous cell carcinoma (OR = 1.43, 95% CI, 1.18-1.74). With the elevation of residential levels of radon above 100 Bq/m^3, the risk of pulmonary cancer, small cell lung carcinoma, and adenocarcinoma increased by 11%, 19%, and 13%, respectively.[46]

Home exposure

Residential exposure to radon is a major contributor to pulmonary cancer mortality, although this contribution is highly variable across different countries, indicating the need for targeted prevention policies. The correction of estimates for dwelling height is essential to provide reliable estimates of mortality attributable to radon.[31]

In Canada there are no "radon-free" areas, and radon is responsible for 16% of deaths from lung cancer, 20% of homes exceed the guideline of 200 Bq/m^3, and 47.5% exceed the reference level recommended by the WHO (100 Bq/m^3).[47-49]

Long-term inhalation of alpha particles increases the risk of pulmonary cancer by 16% for each 100 Bq/m^3 increment and has a synergistic effect with other risk factors for pulmonary cancer.[47] When levels reach the limit set by the Canadian guideline, that is, above 200 Bq/m^3, the lifetime risk of pulmonary cancer is 17% for active smokers and 2% for nonsmokers.[47,50] These data reinforce those observed by a North American study in which a 3% increase in the incidence of pulmonary cancer was observed for each increase of 100 Bq/m^3 in radon exposure.[51]

Kurkela et al.[52] estimated that (at least) 3% to (at most) 8% of all pulmonary cancers were attributable to residential radon exposure. The proportion of small cell carcinoma cases attributable to radon was 8-13%. Among smokers, most radon-related cases were attributable to the combined effect of radon and

smoking, and the authors concluded that reducing radon exposure to an action level of 100 Bq/m³ would eliminate approximately 30% of radon-attributable lung cancer cases.[52]

Hadkhale et al.[53] observed an increased risk of pulmonary cancer in a population-based study in Finland in hospital districts with high radon exposure when compared with those with lower exposure. The authors reported that exposure to radon from groundwater would also be associated with an increased risk of pulmonary cancer.[53]

One study in Thailand reported significant differences in household levels of radon between lung cancer patients and healthy controls and estimated that 26% and 28% of deaths from lung cancer in men and women, respectively, were attributable to indoor radon exposure in that country. Other factors were identified as capable of interfering with the indoor radon levels, such as characteristics of the residence and its ventilation. The window-to-wall ratio was negatively associated with indoor radon levels.[54]

An ecological study evaluated the increased risk of pulmonary cancer mortality due to exposure to radon indoors in Mexico.[55] The mean indoor radon concentrations ranged from 51 to 1,863 Bq/m³, the highest mean exposure dose found was 3.13 mSv/year in the north of the country (Chihuahua), and the excess mortality from pulmonary cancer in the country was 10.0 ± 1.5 deaths per 10^5 population. The highest values were found in the north of the country, where there are numerous uranium deposits, followed by Mexico City, the most populous and polluted area in the country.[55]

Torres-Durán et al.[56] evaluated 829 patients with lung cancer, 56.7% of whom were smokers or former smokers. There was no association of indoor radon concentrations with age, sex, histological type, or tumor staging at diagnosis. Median indoor radon concentrations increased with age at diagnosis in men but not in women. When analyzing participants exposed to more than 1,000 Bq/m³, a predominance of small cell lung cancer and a more significant presence of advanced stages (IIIB and IV) were observed.[56]

Rodríguez-Martínez et al.[37] evaluated, in a multicenter case-control study, the effect of residential exposure to radon on the risk of small cell lung cancer in the general population. There was a statistically significant association for those exposed to concentrations above the permitted level (OR = 2.08; 95% CI, 1.03-4.39) in relation to those exposed to concentrations below 50 Bq/m³.[37]

Maggiore et al.[57] assessed the risk of radon exposure and lung cancer incidence/mortality in southeastern Italy. In that study the authors pointed out that the risk of exposure to radon should be better studied to evaluate the causes of the higher lung cancer mortality and incidence rates in the Salento area as compared with national average rates. For these reasons, the Local Health Authority of Lecce, in cooperation with the Regional Agency for Protection and Prevention of the Environment in Puglia and the National Research Council Institute of Clinical Physiology, has included the monitoring of individual concentrations of radon indoors in the protocol of a case-control study intended to investigate the role of different personal and environmental risk factors for lung cancer in the Salento area.[57]

According to the *Instituto Nacional do Câncer* (Brazilian National Cancer Institute) data, lung cancer was responsible for 28,620 deaths in Brazil in 2020, has been one of the leading causes of preventable death, and is, respectively, the third and fourth most common type of cancer in men (17,760 new cases) and women (12,440 new cases).[58] In addition, lung cancer is the first and third most common type regarding incidence among men and women worldwide, respectively.[59]

Cigarette smoking is the most critical risk factor for developing pulmonary cancer. Other risk factors cited by the *Instituto Nacional do Câncer*, besides radon, are occupational exposure to chemical or physical agents (asbestos, silica, uranium, chromium, alkylating agents, among others); drinking water containing arsenic, and high doses of beta-carotene supplements in smokers and former smokers. Radon is the main factor for pulmonary cancer in people who are nonsmokers (around 10-15%, with small variations).[58]

Lorenzo-González et al.[60] claimed that health professionals neglect residential radon and that it is rarely considered a variable in lung cancer risk scoring. Discussions with young adults can be valuable as they make long-term plans to settle into a home and work.[47] Family physicians play a crucial role in informing their patients about the health risks of radon exposure and in recommending proactive actions to reduce their exposure.[61]

From a clinical point of view, when nonsmokers are diagnosed with pulmonary cancer, radon should be considered as a potential cause.[34,62] From a public health point of view, residential radon should be considered an important factor for predicting the risk of pulmonary cancer, especially among smokers due to the synergistic effect of radon and tobacco smoke. Smoking cessation should be one of the main health priorities.[34]

There is a need to raise awareness among health professionals, legislators, policymakers, and the population so that necessary measures can be taken to reduce this harmful exposure, particularly in radon-prone areas, thus preventing a significant proportion of cancer deaths.[63]

Tables 1 and 2 show the risk of pulmonary cancer according to the level of radon exposure and smoking habit.[64]

PREVENTION AND MITIGATION

The following measures should be observed so that exposure to radon has a less destructive potential or even does not occur[3,65]:

a. For risk reduction in the general population, strategies are needed both for the prevention of

radon release (in new housing) and mitigation (in preexisting housing)
b. Periodic radon measurements should be carried out so that the effectiveness of the measures adopted for radon prevention and mitigation can be verified
c. Professionals in the construction sector are key players in preventing and mitigating radon exposure. They need to be trained to ensure their competence in this area

IDEAL RADON CONTROL PROGRAM

The following are characteristics and needs that a national radon exposure control program should have to be effective[3]:

a. National radon control programs should aim to reduce the risk for the general population, especially for individuals living in environments with high concentrations of this gas
b. To limit the risk, a national reference exposure level of 100 Bq/m³ should be established. If it is not possible to use this reference level, levels ≥ 300 Bq/m³ should be avoided
c. To reduce the risk to the general population, building codes should be implemented to require radon measurements in houses under construction
d. Radon measurements are necessary because building codes alone cannot guarantee that concentrations will be below the reference level
e. An effective national radon control program requires input from multiple agencies in the same country. One agency should lead implementation and coordination and ensure linkage with tobacco control, and one should lead health promotion programs

EXAMPLES OF ACTIONS

National Radon Action Plan—2021-2025

The U.S. National Radon Action Plan—2021-2025[66] goals are to find, correct, and prevent elevated levels of radon in eight million buildings by 2025 and to prevent 3,500 lung cancer deaths annually. Under this plan, leaders from various sectors work together to plan, guide, and sustain national actions to prevent radon exposure[66]:

a. To eliminate preventable lung cancer from radon by expanding protections for all communities and buildings
b. The only way to determine home radon levels is through testing
c. Qualified professionals can install a system that informs when high levels of radon are accumulating inside the building
d. New buildings should be designed and constructed using radon-resistant construction techniques in order to save lives now and in the future
e. Since low-income individuals and families are less likely to have their homes tested for radon levels, government awareness of this type of problem is needed
f. Some people do not know that indoor radon exposure can cause lung cancer, so there is a dire need for more disclosure
g. Some renters, or even homeowners, may challenge these provisions to protect their homes because they cannot afford the cost of radon testing and mitigation
h. Because reducing high radon concentrations in homes and other buildings is expected to result in important health benefits, access to life-saving radon protections should be more equitable across social groups

NEW SPANISH REGULATIONS FOR PROTECTION FROM RADON EXPOSURE

The Spanish Royal Decree No. 1029/2022 of December 20, 2022, establishes that the reference level for radon concentration in indoor areas is 300 Bq/m³ in terms of the annual average concentration of radon in the air in residences, public access buildings, and workplaces.[67]

Table 1. Risk of cancer from radon exposure for smokers.

Radon level	If 1,000 people who smoked were exposed to this level over a lifetime[a]. . .	The risk of cancer from radon exposure compares to[b]. . .	What to do: stop smoking and. . .
20 pCi/L	About 260 people could get lung cancer	< 250 times the risk of drowning	Fix your home
10 pCi/L	About 150 people could get lung cancer	< 200 times the risk of dying in a home fire	Fix your home
8 pCi/L	About 120 people could get lung cancer	< 30 times the risk of dying in a fall	Fix your home
4 pCi/L	About 62 people could get lung cancer	< 5 times the risk of dying in a car crash	Fix your home
2 pCi/L	About 32 people could get lung cancer	< 6 times the risk of dying from poison	Consider fixing your home if levels are 2-3.9 pCi/L
1.3 pCi/L	About 20 people could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L	-	(Average outdoor radon level)	

Adapted from the U.S. Environmental Protection Agency.[64] [a]If you are a former smoker, your risk may be lower. [b]Comparison data calculated using the 1999-2001 National Center for Injury Prevention and Control Report by the Centers for Disease Control and Prevention.

Table 2. Risk of cancer from radon exposure for never smokers.

Radon level	If 1,000 people who never smoked were exposed to this level over a lifetime[a]. . .	The risk of cancer from radon exposure compares to[b]. . .	What to do:
20 pCi/L	About 36 people could get lung cancer	35 times the risk of drowning	Fix your home
10 pCi/L	About 18 people could get lung cancer	20 times the risk of dying in a home fire	Fix your home
8 pCi/L	About 15 people could get lung cancer	4 times the risk of dying in a fall	Fix your home
4 pCi/L	About 7 people could get lung cancer	< the risk of dying in a car crash	Fix your home
2 pCi/L	About 4 people could get lung cancer	< the risk of dying from poison	Consider fixing your home if levels are 2-3.9 pCi/L
1.3 pCi/L	About 2 people could get lung cancer	(Average indoor radon level)	(Reducing radon levels below 2 pCi/L is difficult)
0.4 pCi/L	-	(Average outdoor radon level)	

Adapted from the U.S. Environmental Protection Agency.[64] Note: If you are a former smoker, your risk may be higher. [a]Lifetime risk of lung cancer deaths according to the U.S. Environmental Protection Agency Assessment of Risks from Radon in Homes (EPA 402-R-03-003). [b]Comparison data calculated using the 1999-2001 National Center for Injury Prevention and Control Report by the Centers for Disease Control and Prevention.

The new Spanish regulation establishes the obligation to perform radon measurements in all public access buildings, businesses, and residences, especially in areas with high radon levels. If high levels of this gas are detected, measures must be taken to reduce and mitigate exposure (for example, installation of radon reduction systems).[67]

FINAL CONSIDERATIONS

According to Stanifer et al.,[68] home radon testing is a primary lung cancer prevention strategy. Due to the high prevalence of smoking in adults and the high incidence of lung cancer, this measure can benefit these populations by providing more preventive interventions and adopting smoke-free and radon control policies. Thus, reducing the risk of radon exposure will be integrated with smoking cessation messages and lung cancer screening programs.

The key steps to reduce lung cancer deaths induced by radon exposure are to increase the awareness of population and health professionals of this threat, measure radon levels in all types of new buildings, build a workforce of qualified professionals who can solve radon-related problems using proven standards, and ensure that adequate funding is available to cover the costs of testing and repair.

AUTHOR CONTRIBUTIONS

All authors equally contributed to this work and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Shakoor H, Jehan N, Khan S, Khattak NU. Investigation of Radon Sources, Health Hazard and Risks assessment for children using analytical and geospatial techniques in District Bannu (Pakistan). Int J Radiat Biol. 2022;98(6):1176-1184. https://doi.org/10.1080/09553002.2021.1872817
2. Ngoc LTN, Park D, Lee YC. Human Health Impacts of Residential Radon Exposure: Updated Systematic Review and Meta-Analysis of Case-Control Studies. Int J Environ Res Public Health. 2022;20(1):97. https://doi.org/10.3390/ijerph20010097
3. Zeeb H, Shannoun F, editors. Manual da OMS sobre radônio em ambientes internos: uma perspectiva de saúde. 1st Ed; 2016. [Adobe Acrobat document, 122p.]. Available from: https://www.gov.br/ird/pt-br/central-de-conteudo/publicacoes/ManualdaOMSsobreradonioemambientesinternos.pdf
4. Gawande S, Tiwari RR, Narayanan P, Bhadri A. Indoor Air Quality and Sick Building Syndrome: Are Green Buildings Better than Conventional Buildings?. Indian J Occup Environ Med. 2020;24(1):30-32. https://doi.org/10.4103/ijoem.IJOEM_148_19
5. Nunes LJR, Curado A, Graça LCCD, Soares S, Lopes SI. Impacts of Indoor Radon on Health: A Comprehensive Review on Causes, Assessment and Remediation Strategies. Int J Environ Res Public Health. 2022;19(7):3929. https://doi.org/10.3390/ijerph19073929
6. Chapter 42. Radon. In: Etzel RA, Balk SJ, editors. Pediatric Environmental Health. 4th ed. Itasca, IL: American Academy of Pediatrics; 2018. p.739-746.
7. U.S. Environmental Protection Agency (EPA) [homepage on the Internet]. Washington, DC: EPA; c2023 [cited 2023 Feb 1]. Available from: https://www.epa.gov
8. Corrales L, Rosell R, Cardona AF, Martín C, Zatarain-Barrón ZL, Arrieta O. Lung cancer in never smokers: The role of different risk factors other than tobacco smoking. Crit Rev Oncol Hematol. 2020;148:102895. https://doi.org/10.1016/j.critrevonc.2020.102895
9. International Commission on Radiological Protection (ICRP) [homepage on the Internet]. Ottawa, ON: ICRP; c2023 [updated 2014; cited 2023 Mar 1]. Radiological Protection against Radon Exposure. Available from: https://www.icrp.org/publication.asp?id=ICRP%20Publication%20126
10. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA) [homepage on the Internet]. Rio de Janeiro: INCA. Projeto Planalto de Poços de Caldas: Pesquisa câncer e radiação natural: Minas Gerais-Brasil: 2004 a 2009, vol.1. Belo Horizonte: SES-MG; 2009. Available from: https://www.inca.gov.br/publicacoes/livros/projeto-planalto-pocos-de-caldas-pesquisa-cancer-e-radiacao-natural
11. Antoniazzi BN, Silva NC, Cunha TN, Otero UB. Projeto Planalto de Poços de Caldas: Pesquisa câncer e radiação natural: incidência e comportamento de risco: Minas Gerais - Brasil 2004 a 2013. Belo Horizonte: SES-MG; 2013.

12. Fianco ACB. Concentrações de randônio nas águas subterrâneas, rochas e solos de Porto Alegre, RS [dissertation]. Porto Alegre: Universidade Federal do Rio Grande do Sul; 2011. 99p. Available from: https://lume.ufrgs.br/handle/10183/32667
13. Lopes SI, Nunes LJR, Curado A. Designing an Indoor Radon Risk Exposure Indicator (IRREI): An Evaluation Tool for Risk Management and Communication in the IoT Age. Int J Environ Res Public Health. 2021;18(15):7907. https://doi.org/10.3390/ijerph18157907
14. Chen J. RISK ASSESSMENT FOR RADON EXPOSURE IN VARIOUS INDOOR ENVIRONMENTS. Radiat Prot Dosimetry. 2019;185(2):143-150. https://doi.org/10.1093/rpd/ncy284
15. Baloch RM, Maesano CN, Christoffersen J, Banerjee S, Gabriel M, Csobod É, et al. Indoor air pollution, physical and comfort parameters related to schoolchildren's health: Data from the European SINPHONIE study. Sci Total Environ. 2020;739:139870. https://doi.org/10.1016/j.scitotenv.2020.139870
16. Zhukovsky M, Vasilyev A, Onishchenko A, Yarmoshenko I. REVIEW OF INDOOR RADON CONCENTRATIONS IN SCHOOLS AND KINDERGARTENS. Radiat Prot Dosimetry. 2018;181(1):6-10. https://doi.org/10.1093/rpd/ncy092
17. Davis EA, Ou JY, Chausow C, Verdeja MA, Divver E, Johnston JD, et al. Associations Between School Characteristics and Classroom Radon Concentrations in Utah's Public Schools: A Project Completed by University Environmental Health Students. Int J Environ Res Public Health. 2020;17(16):5839. https://doi.org/10.3390/ijerph17165839
18. Branco PT, Nunes RA, Alvim-Ferraz MC, Martins FG, Sousa SI. Children's Exposure to Radon in Nursery and Primary Schools. Int J Environ Res Public Health. 2016;13(4):386. https://doi.org/10.3390/ijerph13040386
19. Curado A, Silva JP, Lopes SI. Radon risk assessment in a low energy consumption school building: A dosimetric approach for effective risk management. Energy Rep. 2020;6(Suppl 1):897-902. 10.1016/j.egyr.2019.11.155 https://doi.org/10.1016/j.egyr.2019.11.155
20. Sabbarese C, Ambrosino F, D'Onofrio A. Development of radon transport model in different types of dwellings to assess indoor activity concentration. J Environ Radioact. 2021;227:106501. https://doi.org/10.1016/j.jenvrad.2020.106501
21. Khan SM, Pearson DD, Rönnqvist T, Nielsen ME, Taron JM, Goodarzi AA. Rising Canadian and falling Swedish radon gas exposure as a consequence of 20th to 21st century residential build practices. Sci Rep. 2021;11(1):17551. https://doi.org/10.1038/s41598-021-96928-x
22. Shergill S, Forsman-Phillips L, Nicol AM. Radon in Schools: A Review of Radon Testing Efforts in Canadian Schools. Int J Environ Res Public Health. 2021;18(10):5469. https://doi.org/10.3390/ijerph18105469
23. Taylor BK, Smith OV, Miller GE. Chronic Home Radon Exposure Is Associated with Higher Inflammatory Biomarker Concentrations in Children and Adolescents. Int J Environ Res Public Health. 2022;20(1):246. https://doi.org/10.3390/ijerph20010246
24. Simms JA, Pearson DD, Cholowsky NL, Irvine JL, Nielsen ME, Jacques WR, et al. Younger North Americans are exposed to more radon gas due to occupancy biases within the residential built environment. Sci Rep. 2021;11(1):6724. https://doi.org/10.1038/s41598-021-86096-3
25. Ramos MOS. Radônio-222 e a Ocorrência de Câncer de Pulmão em Municípios da Região Metropolitana de Recife com Afloramentos de Fosforito Uranífero [thesis]. -Recife: Universidade Federal de Pernambuco; 2020.
26. Petroni R, Lima SC. Os perigos associados a concentração de radônio (222Rn) em ambientes climatizados. Conforlab Engenharia Ambiental. Available from: https://conforlab.com.br
27. Huntington-Moskos L, Rayens MK, Wiggins A, Hahn EJ. Radon, Secondhand Smoke, and Children in the Home: Creating a Teachable Moment for Lung Cancer Prevention. Public Health Nurs. 2016;33(6):529-538. https://doi.org/10.1111/phn.12283
28. Neri A, McNaughton C, Momin B, Puckett M, Gallaway MS. Measuring public knowledge, attitudes, and behaviors related to radon to inform cancer control activities and practices. Indoor Air. 2018;28(4):604-610. https://doi.org/10.1111/ina.12468
29. Riudavets M, Garcia de Herreros M, Besse B, Mezquita L. Radon and Lung Cancer: Current Trends and Future Perspectives. Cancers (Basel). 2022;14(13):3142. https://doi.org/10.3390/cancers14133142
30. Kang JK, Seo S, Jin YW. Health Effects of Radon Exposure. Yonsei Med J. 2019;60(7):597-603. https://doi.org/10.3349/ymj.2019.60.7.597
31. Ruano-Ravina A, Varela Lema L, García Talavera M, García Gómez M, González Muñoz S, Santiago-Pérez MI, et al. Lung cancer mortality attributable to residential radon exposure in Spain and its regions. Environ Res. 2021;199:111372. https://doi.org/10.1016/j.envres.2021.111372
32. Thandra KC, Barsouk A, Saginala K, Aluru JS, Barsouk A. Epidemiology of lung cancer. Contemp Oncol (Pozn). 2021;25(1):45-52. https://doi.org/10.5114/wo.2021.103829
33. Reddy A, Conde C, Peterson C, Nugent K. Residential radon exposure and cancer. Oncol Rev. 2022;16(1):558. https://doi.org/10.4081/oncol.2022.558
34. Cheng ES, Egger S, Hughes S, Weber M, Steinberg J, Rahman B, et al. Systematic review and meta-analysis of residential radon and lung cancer in never-smokers. Eur Respir Rev. 2021;30(159):200230. https://doi.org/10.1183/16000617.0230-2020
35. Robertson A, Allen J, Laney R, Curnow A. The cellular and molecular carcinogenic effects of radon exposure: a review. Int J Mol Sci. 2013;14(7):14024-14063. https://doi.org/10.3390/ijms140714024
36. Barros-Dios JM, Ruano-Ravina A, Pérez-Ríos M, Castro-Bernárdez M, Abal-Arca J, Tojo-Castro M. Residential radon exposure, histologic types, and lung cancer risk. A case-control study in Galicia, Spain. Cancer Epidemiol Biomarkers Prev. 2012;21(6):951-958. https://doi.org/10.1158/1055-9965.EPI-12-0146-T
37. Rodríguez-Martínez Á, Ruano-Ravina A, Torres-Durán M, Provencio M, Parente-Lamelas I, Vidal-García I, et al. Residential Radon and Small Cell Lung Cancer. Final Results of the Small Cell Study. Arch Bronconeumol. 2022;58(7):542-546. https://doi.org/10.1016/j.arbres.2021.01.027
38. Krewski D, Lubin JH, Zielinski JM, Alavanja M, Catalan VS, Field RW, et al. Residential radon and risk of lung cancer: a combined analysis of 7 North American case-control studies. Epidemiology. 2005;16(2):137-145. https://doi.org/10.1097/01.ede.0000152522.80261.e3
39. Zhang ZL, Sun J, Dong JY, Tian HL, Xue L, Qin LQ, et al. Residential radon and lung cancer risk: an updated meta- analysis of case-control studies. Asian Pac J Cancer Prev. 2012;13(6):2459-2465. https://doi.org/10.7314/APJCP.2012.13.6.2459
40. Darby S, Hill D, Deo H, Auvinen A, Barros-Dios JM, Baysson H, et al. Residential radon and lung cancer–detailed results of a collaborative analysis of individual data on 7148 persons with lung cancer and 14,208 persons without lung cancer from 13 epidemiologic studies in Europe [published correction appears in Scand J Work Environ Health. 2007 Feb;33(1):80]. Scand J Work Environ Health. 2006;32 Suppl 1:1-83.
41. Leuraud K, Schnelzer M, Tomasek L, Hunter N, Timarche M, Grosche B, et al. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. Radiat Res. 2011;176(3):375-387. https://doi.org/10.1667/RR2377.1
42. Dubin S, Griffin D. Lung Cancer in Non-Smokers. Mo Med. 2020;117(4):375-379.
43. Darby S, Hill D, Auvinen A, Barros-Dios JM, Baysson H, Bochicchio F, et al. Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. BMJ. 2005;330(7485):223. https://doi.org/10.1136/bmj.38308.477650.63
44. Lorenzo-Gonzalez M, Ruano-Ravina A, Torres-Duran M, Kelsey KT, Provencio M, Parente-Lamelas I, et al. Lung cancer risk and residential radon exposure: A pooling of case-control studies in northwestern Spain. Environ Res. 2020;189:109968. https://doi.org/10.1016/j.envres.2020.109968
45. Su C, Pan M, Liu N, Zhang Y, Kan H, Zhao Z, et al. Lung cancer as adverse health effect by indoor radon exposure in China from 2000 to 2020: A systematic review and meta-analysis. Indoor Air. 2022;32(11):e13154. https://doi.org/10.1111/ina.13154
46. Li C, Wang C, Yu J, Fan Y, Liu D, Zhou W, et al. Residential Radon and Histological Types of Lung Cancer: A Meta-Analysis of Case-Control Studies. Int J Environ Res Public Health. 2020;17(4):1457. https://doi.org/10.3390/ijerph17041457
47. Mema SC, Baytalan G. Radon and lung cancer risk. CMAJ. 2023;195(24):E850. https://doi.org/10.1503/cmaj.230110
48. MitigAir [homepage on the Internet]. Ottawa: Health Canada; 2021 [cited 2023 Jul 1]. Radon - what you need to know. Available from: https://www.mitigair.com/?gclid=Cj0KCQjwk96IBhDHARIsAEKO4xaCBSksmnEahL8pga2yXcqu_cregLx_KBAm4FoBdk2lFSSCqPbQF84aAl8dEALw_wcB
49. Khan SM, Pearson DD, Rönnqvist T, Nielsen ME, Taron JM, Goodarzi AA. Rising Canadian and falling Swedish radon gas exposure as a consequence of 20th to 21st century residential build practices. Sci Rep. 2021;11(1):17551. https://doi.org/10.1038/s41598-021-96928-x
50. Government of Canada [homepage on the Internet]. Ottawa: Health Canada; c2019 [cited 2023 Jul 1]. Radon: Is it in your home? Information for health professionals. Available from: https://www.canada.ca/en/health-canada/services/environmental-workplace-health/reports-publications/radiation/radon-is-it-in-you-home-information-health-professionals.html
51. Messier KP, Serre ML. Lung and stomach cancer associations with groundwater radon in North Carolina, USA. Int J Epidemiol. 2017;46(2):676-685. https://doi.org/10.1093/ije/dyw128
52. Kurkela O, Nevalainen J, Pätsi SM, Kojo K, Holmgren O, Auvinen A. Lung cancer incidence attributable to residential radon exposure

in Finland. Radiat Environ Biophys. 2023;62(1):35-49. https://doi.org/10.1007/s00411-022-01004-1

53. Hadkhale K, Atosuo J, Putus T. Groundwater radon exposure and risk of lung cancer: A population-based study in Finland. Front Oncol. 2022;12:935687. https://doi.org/10.3389/fonc.2022.935687
54. Somsunun K, Prapamontol T, Pothirat C, Liwsrisakun C, Pongnikorn D, Fongmoon D, et al. Estimation of lung cancer deaths attributable to indoor radon exposure in upper northern Thailand. Sci Rep. 2022;12(1):5169. https://doi.org/10.1038/s41598-022-09122-y
55. Ponciano-Rodríguez G, Gaso MI, Armienta MA, Trueta C, Morales I, Alfaro R, et al. Indoor radon exposure and excess of lung cancer mortality: the case of Mexico-an ecological study. Environ Geochem Health. 2021;43(1):221-234. https://doi.org/10.1007/s10653-020-00662-8
56. Torres-Durán M, Casal-Mouriño A, Ruano-Ravina A, Provencio M, Parente-Lamelas I, Hernández-Hernández J, et al. Residential radon and lung cancer characteristics at diagnosis. Int J Radiat Biol. 2021;97(7):997-1002. https://doi.org/10.1080/09553002.2021.1913527
57. Maggiore G, DE Filippis G, Totaro T, Tamborino B, Idolo A, Serio F, et al. Evaluation of radon exposure risk and lung cancer incidence/mortality in South-eastern Italy. J Prev Med Hyg. 2020;61(1):E31-E38.
58. Brasil. Ministério da Saúde. Instituto Nacional do Câncer (INCA) [homepage on the Internet]. Rio de Janeiro: INCA; c2022 [updated 2022 Jul 18; cited 2023 Feb 1]. Câncer de Pulmão. Available from: https://www.gov.br/inca/pt-br/assuntos/cancer/tipos/pulmao
59. Huang J, Deng Y, Tin MS, Lok V, Ngai CH, Zhang L, et al. Distribution, Risk Factors, and Temporal Trends for Lung Cancer Incidence and Mortality: A Global Analysis. Chest. 2022;161(4):1101-1111. https://doi.org/10.1016/j.chest.2021.12.655
60. Lorenzo-González M, Torres-Durán M, Barbosa-Lorenzo R, Provencio-Pulla M, Barros-Dios JM, Ruano-Ravina A. Radon exposure: a major cause of lung cancer. Expert Rev Respir Med. 2019;13(9):839-850. https://doi.org/10.1080/17476348.2019.1645599
61. Field RW. Radon: A Leading Environmental Cause of Lung Cancer. Am Fam Physician. 2018;98(5):280-282.
62. Ruano-Ravina A, Fernández-Villar A, Barros-Dios JM. Residential Radon and Risk of Lung Cancer in Never-Smokers. Arch Bronconeumol. 2017;53(9):475-476. https://doi.org/10.1016/j.arbres.2017.01.004
63. Gaskin J, Coyle D, Whyte J, Krewksi D. Global Estimate of Lung Cancer Mortality Attributable to Residential Radon. Environ Health Perspect. 2018;126(5):057009. https://doi.org/10.1289/EHP2503
64. U.S. Environmental Protection Agency (EPA) [homepage on the Internet]. Washington, DC: EPA; A Citizen's Guide to Radon: the Guide TO Protecting Yourself and Your Family from Radon; 2016. Available from: https://www.epa.gov/sites/default/files/2016-12/documents/2016_a_citizens_guide_to_radon.pdf
65. Khan SM, Gomes J, Krewski DR. Radon interventions around the globe: A systematic review. Heliyon. 2019;5(5):e01737. https://doi.org/10.1016/j.heliyon.2019.e01737
66. Radonleaders.org [homepage on the Internet]; c2022 [updated 2022 Jan; cited 2023 Feb 1]. The National Radon Action Plan 2021-2025. Available from: http://www.radonleaders.org/sites/default/files/2022-01/NRAP-2021-2025-Action-Plan-508.pdf
67. Instituto para la Salud Geoambiental [homepage on the Internet]. Madrid: Instituto para la Salud Geoambiental; c2022 [cited 2023 Feb 1]. Nueva ley de protección frente al radón. Disponível em: https://www.saludgeoambiental.org/nueva-ley-de-proteccion-frente-al-rado
68. Stanifer SR, Rayens MK, Wiggins A, Hahn EJ. Social Determinants of Health, Environmental Exposures and Home Radon Testing. West J Nurs Res. 2022;44(7):636-642. https://doi.org/10.1177/01939459211009561

COVID-19: clinical factors associated with functional capacity of hospitalized patients at admission and discharge

Raiany Franca Guimarães[1], Marcela Cangussu Barbalho-Moulim[1], Veronica Lourenço Wittmer[1], Lais Mello Serafim[1], Elizângela Kuster[1], Jenaine Rosa Godinho Emiliano[2], Juliana Baroni Cordeiro[2], Michele Coutinho Maia da Silva[2], Rozy Tozetti Lima[2], Juliana Zangirolami-Raimundo[3], Rodrigo Daminello Raimundo[3], Luiz Carlos Abreu[1], Flavia Marini Paro[1]

TO THE EDITOR:

At the beginning of COVID-19 pandemic, saving lives was the most urgent aim. However, a few months later, health care services started to face another huge challenge, the so-called long COVID-19, which may induce long-term or even permanent disabilities and may impact in disability-adjusted life years and quality-adjusted life years.[1]

Among the COVID-19 patients who need hospitalization, the length of the hospital stay and need for ICU is widely variable. Some individuals may require a long length of ICU stay and, consequently, are at a higher risk of developing post-intensive care syndrome.[2]

In addition to the functional loss resulting from hospitalization, COVID-19 mechanisms include pulmonary and extrapulmonary manifestations, affecting neurological, cardiovascular, renal, and musculoskeletal systems, among others,[3] and such dysfunctions might directly interfere with functional capacity.

Although some studies addressing the evolution of hospitalized COVID-19 patients have been published,[1-4] there are still gaps in knowledge about the factors associated with functional capacity impairment in these patients during hospitalization.

The present study aimed to describe the functional capacity of patients hospitalized for COVID-19 and its correlation with other clinical variables. This was an analytical longitudinal study involving all adult patients with COVID-19 admitted to the *Hospital Universitário Cassiano Antônio Moraes* between July and December of 2020. The Research Ethics Committee of the hospital approved this project (CAAE: 33373820,6,0000,5071; approval #4227571).

Demographic, clinical, and functional (ability to sit on the bed, to stand, and to walk) data were collected from the day of hospital admission to the day of discharge.

Statistical analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). Categorical variables were reported in their absolute and relative frequencies, and continuous numerical variables as means and standard deviations. Correlations were evaluated using the Spearman's correlation coefficient, adopting the significance level of 5%.

The sample consisted of 60 patients, with a mean age of 63.0 ± 15.7 years. The mean length of hospital stay was 19.3 ± 20.5 days. During the in-hospital period, 41 (68.3%) of the patients needed oxygen supplementation; however, only 2 (3.3%) continued to require it at discharge. Noninvasive ventilation was used in 12 patients (20%), and so was invasive mechanical ventilation, in 7 patients (11.7%) during a mean period of 17.3 ± 11.5 days. Almost half of the patients required ICU admission (mean length of ICU stay = 6.2 ± 13.2 days), 7 of whom (25%) requiring mechanical ventilation.

Regarding functional capacity, 41 (68.3%) of the patients were able to sit on the bed at admission, and this percentage increased to 85% at discharge. The ability to stand up was observed in 60.0% of the patients at admission, whereas it increased to 81.7% at discharge. On the day of admission, 61.7% of patients were able to walk, and this percentage increased to 76.7% at discharge.

On admission day, a moderate negative correlation was found between Spo_2 and inability to walk. This means that the lower saturation was, the greater the inability to walk was. Other clinical variables did not present significant correlations with the ability to walk at admission (Table 1). We also found a moderate negative correlation between Spo_2 and the inability to walk on the day of discharge (Table 1).

The number of days in ICU showed a moderate positive correlation with the inability to sit and a weak positive correlation with the inability to stand up at discharge (Table 1).

Our results showed that patients with lower Spo_2 had more difficulties in walking both at admission and discharge. Hypoxemia seems to have a negative effect on the functional performance in COVID-19 patients even after disease resolution. A study that evaluated COVID-19 patients after discharge reported worse performance in the six-minute walk test and impaired DL_{CO} in all hypoxemic patients, suggesting that this impairment was associated with vascular and pulmonary parenchymal phenomena resulting from COVID-19.[4]

1. Departamento de Educação Integrada em Saúde, Centro de Ciências da Saúde, Universidade Federal do Espírito Santo – UFES – Vitória (ES) Brasil.
2. Hospital Universitário Cassiano Antonio de Moraes – HUCAM – Vitória (ES) Brasil.
3. Laboratório de Delineamento de Estudos e Escrita Científica, Faculdade de Medicina do ABC, Santo André (SP) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

Table 1. Correlations between clinical variables and functional capacity of COVID-19 patients at hospital admission and discharge (N = 60).

Variable	Inability to sit				Inability to stand up				Inability to walk			
	Admission		Discharge		Admission		Discharge		Admission		Discharge	
	r	p	r	p	r	p	r	p	r	p	r	p
Spo_2, A	−0.128	0.377	−0.072	0.593	−0.212	0.14	−0.158	0.235	−0.3	0.034*	−0.122	0.36
Spo_2, D	–	–	−0.2	0.164	–	–	−0.259	0.07	–	–	−0.369	0.008*
Pao_2, A	0.136	0.392	0.204	0.195	0.075	0.636	−0.193	0.22	−0.29	0.856	−0.207	0.188
Hb, A	−0.207	0.113	−0.25	0.852	−0.082	0.535	−0.42	0.751	−0.12	0.36	−0.014	0.918
Hct, A	−0.192	0.145	−0.046	0.727	−0.58	0.662	−0.054	0.686	−0.09	0.485	−0.02	0.881
LHS, days	–	–	0.149	0.256	–	–	0.128	0.329	–	–	0.89	0.497
IMV, days	–	–	0.207	0.694	–	–	0.207	0.694	–	–	0.207	0.694
ICU, days	–	–	0.366	0.004*	–	–	0.286	0.028*	–	–	0.238	0.07

A: admission day; D: discharge day; Hb: hemoglobin; Hct: hematocrit; LHS: length of hospital stay; IVM: invasive mechanical ventilation; and ICU: length of ICU stay. *p < 0.05 (Spearman's correlation coefficient).

Low Spo_2 reduces oxygen delivery to tissues due to lower oxyhemoglobin saturation. In addition, muscle activity increases peripheral oxygen extraction, reduces muscle oxygenation, and increases the need for oxygen delivery to maintain activity,[5] which is not possible in patients presenting impaired diffusion capacity.

Our study also showed that longer length of ICU stay negatively influenced the ability to sit and stand by the discharge day. Similarly, the decline in functional capacity was observed in almost all hospitalized COVID-19 patients who had been discharged from the ICU in a study that used the Barthel index to measure the level of functional dependence in patients.[6]

Although the benefits of early mobilization are well known, it was recommended only in specific situations for hospitalized patients at the onset of the pandemic, because COVID-19 was poorly known and in order to reduce the risk of disease dissemination.[7] Currently, due to the growth in knowledge about the disease, early mobilization and rehabilitation have increasingly been recommended for these patients.[2,8-10] The results found in the present study contribute to reinforcing this.

In conclusion, a high prevalence of limitations in functional capacity was identified at hospital admission and discharge of COVID-19 patients. In addition, functional capacity negatively correlated with Spo_2 and length of ICU stay. These findings may contribute to the development of more effective prevention and early rehabilitation strategies for COVID-19 patients during hospitalization.

ACKNOWLEDGMENTS

We thank the *Hospital Universitário Cassiano Antônio Moraes* for authorizing access to the data and the physical therapists for their collaboration.

FUNDING

Raiany Franca Guimarães received a scholarship from the *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development; Funding code 001) during her participation in this project.

AUTHOR CONTRIBUTIONS

MCBM, VLW, FMP, RFG, JRGB, MCMS, JBC, RTL, LMS, and EK: project conception and design. MCBM, VLWP, JRGB, MCMS, JBC, RTL, RFG, LMS, EK, and FMP: data collection planning. MCBM, FMP and VLW: data collection coordination. JRGB, MCMS, JBC, RTL, MCBM, LMS, EK, and RFG: data collection. LMS, EK, RFG, JZR, RDR, and LCA: data tabulation and review. JZR, RDR, LCA, FMP, and MCBM: data analysis and interpretation. JZR, RDR, and LCA: data analysis; RFG and FMP: drafting of the manuscript; MCBM, VLWP, LMS, EK, RFG, JZR, RDR, LCA, JRGB, MCMS, JBC, RTL, and FMP: support, review, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Briggs A, Vassall A. Count the cost of disability caused by COVID-19. Nature. 2021;593(7860):502-505. https://doi.org/10.1038/d41586-021-01392-2
2. Jaffri A, Jaffri UA, Post-Intensive care syndrome and COVID-19: crisis after a crisis? Heart Lung. 2020;49(6):883–884. https://doi.org/10.1016/j.hrtlng.2020.06.006
3. Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19,.Nat Med. 2020;26(7):1017-1032. http://dx.doi.org/10.1038/s41591-020-0968-3
4. Wong AW, López-Romero S, Figueroa-Hurtado E, Vazquez-Lopez S, Milne KM, Ryerson CJ, et al. Predictors of reduced 6-minute walk distance after COVID-19: a cohort study in Mexico. Pulmonology. 2021;27(6):563-565. https://doi.org/10.1016/j.pulmoe.2021.03.004
5. Bhambhani YN. Muscle oxygenation trends during dynamic exercise measured by near infrared spectroscopy. Can J Appl Physiol. 2004;29(4):504-523. https://doi.org/10.1139/h04-033
6. Domínguez Fleitas V, Peña García M, De la Fuente Escudero C, García Pérez F. Functional evolution and mood of patients after admission for COVID-19 to intensive care unit [Article in Spanish]. Rehabilitacion (Madr). 2022;56(3):182-187. https://doi.org/10.1016/j.rh.2021.09.002

7. Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: Recommendations to guide clinical practice, J Physiother. 2020;66(2):73-82. https://doi.org/10.1016%2Fj.jphys.2020.03.011
8. Wittmer VL, Paro FM, Duarte H, Capellini VK, Barbalho-Moulim MC. Early mobilization and physical exercise in patients with COVID-19: a narrative literature review. Complementary Ther Clin Pract. 2021;43:101364. https://doi.org/10.1016/j.ctcp.2021.101364
9. Eggmann S, Kindler A, Perren A, Ott N, Johannes F, Vollenweider R, et al. Early Physical Therapist Interventions for Patients With COVID-19 in the Acute Care Hospital: A Case Report Series. Phys Ther. 2021;101(1):pzaa194. http://doi.org/10.1093/ptj/pzaa194
10. Dias LMS, Guimaraes FS, Leite CF, Paro FM, Annoni R, Oliveira ACO, et al. Physiotherapy practice for hospitalized patients with COVID-19. J Bras Pneumol. 2022;48(4):e20220121. https://doi.org/10.36416/1806-3756/e20220121

Nephrobronchial fistula: a diagnostic challenge in a patient with IgG4-related disease

Glauco Cabral Marinho Plens[1], Guilherme das Posses Bridi[1], Ellen Caroline Toledo do Nascimento[2], Rodrigo Caruso Chate[3], Bruno Guedes Baldi[1], Fábio Eiji Arimura[1], Ronaldo Adib Kairalla[1,3]

TO THE EDITOR:

IgG4-related disease is an immune-mediated condition characterized by the infiltration of several organs, including the lungs, pancreas, bile ducts, kidneys, thyroid, and central nervous system. One of the main features of the disease is the abundance of IgG4 in the affected tissues, which initially present with an inflammatory phase and progress to subsequent local fibrosis.[1] Thoracic involvement and significant symptoms may occur in 10% of cases, with no specific signs and symptoms. Several changes can be found on chest CT, such as nodules, ground-glass opacities, and peribronchovascular infiltrate.[2]

The kidneys can be affected in up to 20% of cases, and tubulointerstitial nephritis is the most common manifestation.[3] Nephrobronchial fistulas are rare complications of kidney disease, occurring mainly in association with perinephric abscesses after infectious episodes.[4] We describe the case of a nephrobronchial fistula in a patient with IgG4-related disease. Free and informed consent was obtained from the patient.

A 51-year-old female presented with a 1-year history right thoracic pain and hemoptysis. Chest CT revealed a nephrobronchial fistula in the thoracoabdominal transition with migrated calculi in the right inferior lobe, associated with a 2.3-cm discontinuity defect in the right diaphragm and atrophic right kidney, along with diffuse urothelial thickening of the ureter (Figures 1A-1C). During investigation, a transbronchial biopsy showed a lymphoplasmacytic inflammatory reaction with a predominance of IgG4. After multidisciplinary discussion, lung segmentectomy, right nephrectomy, and partial hepatectomy were performed to confirm diagnosis and

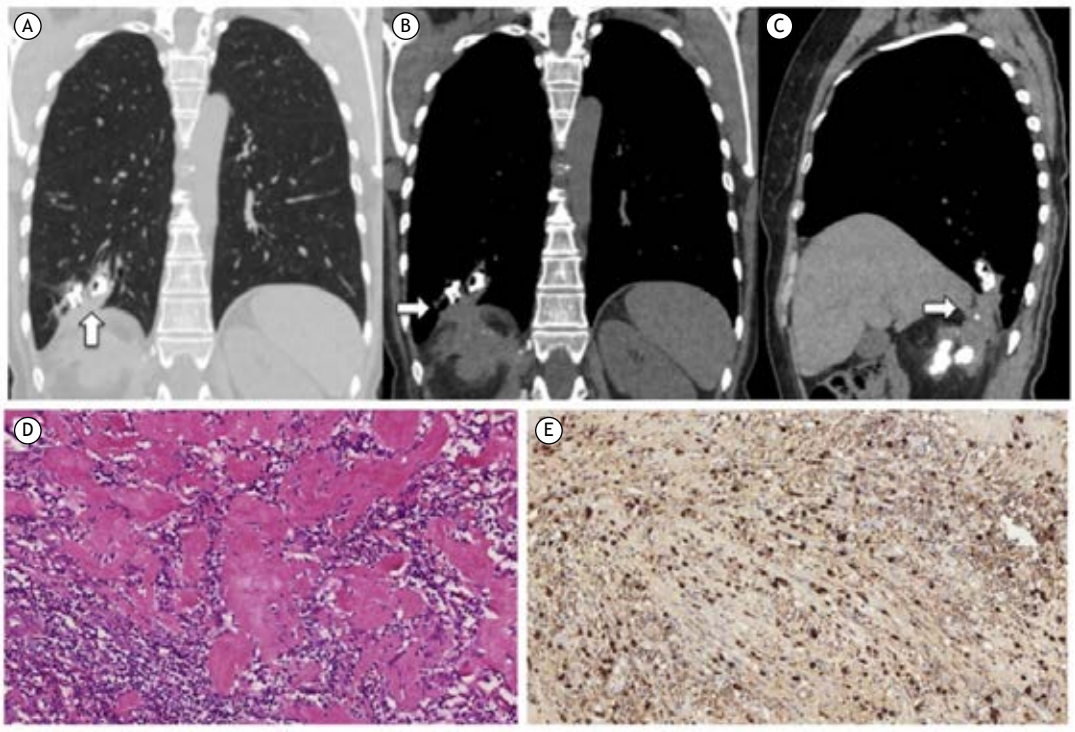


Figure 1. In A, a CT scan showing migrated calculi in the inferior right lobe (arrow). In B and C, coronal and sagittal reconstructions of CT scans showing diaphragmatic discontinuity and a nephrobronchial fistula with nephrolithiasis originated from the right kidney (arrows). Histopathological images showing the nephrobronchial fistula (H&E) with an intense area of fibrosis (in D) and positive IgG4 cells (in E).

1. Divisão de Pneumologia, Instituto do Coração – InCor – Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
2. Departamento de Patologia, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
3. Divisão de Radiologia, Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP) Brasil.
4. Núcleo de Tórax, Hospital Sírio-Libanês, São Paulo (SP) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

treat symptoms. Local excision of the fistula revealed intense lymphoplasmacytic infiltration, fibrosis, and vascular proliferation, which were present in the renal parenchyma as well. Specific IgG4 immunostaining showed > 100 positive cells per high-power field (Figures 1D and 1E). Nephrolithiasis was found in the fistulous tract with no signs of obstructive nephropathy. Autoantibodies were negative, serum IgG levels were unremarkable, and PET-CT scanning excluded signs of systemic activity.

A nephrobronchial fistula results from kidney inflammation that progresses to the respiratory system, most cases being mainly reported because of pyelonephritis.[4-6] We report the first case of a nephrobronchial fistula with calculi in a patient with histopathological results suggesting IgG4-related disease. The pathophysiology is uncertain, and we believe that local IgG4 inflammation could lead to the development of posterior fistulas in adjacent organs such as the diaphragm and kidneys, although there are no other systemic manifestations related to the disease.[7] After surgical treatment of the patient, symptoms improved with no signs of disease activity during follow-up. No additional treatment was necessary.

AUTHOR CONTRIBUTIONS

GCMP, GPB, and ECTN: data acquisition, analysis, and interpretation; drafting and revision of the manuscript. RCC, BGB, and FEA: study design; data analysis and interpretation; and revision of the manuscript. RAK: study design; data analysis and interpretation; drafting and revision of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Lanzillotta M, Mancuso G, Della-Torre E. Advances in the diagnosis and management of IgG4 related disease. BMJ. 2020;369:m1067. https://doi.org/10.1136/bmj.m1067
2. Muller R, Ebbo M, Habert P, Daniel L, Briantais A, Chanez P, et al. Thoracic manifestations of IgG4-related disease. Respirology. 2023;28(2):120-131. https://doi.org/10.1111/resp.14422
3. Boffa JJ, Esteve E, Buob D. Renal involvement in IgG4-related disease. Presse Med. 2020;49(1):104017. https://doi.org/10.1016/j.lpm.2020.104017
4. Tamburrini S, Fiorini V, Lugarà M, Napodano G, Del Biondo D, Squame F, et al. Nephrobronchial fistula a case report and review of the literature [published correction appears in Radiol Case Rep. 2023 Feb 24;18(5):2056]. Radiol Case Rep. 2021;16(11):3470-3477. https://doi.org/10.1016/j.radcr.2021.08.025
5. Rubin SA, Morettin LB. Nephrobronchial fistula: an uncommon manifestation of inflammatory renal disease. J Urol. 1982;127(1):103-105. https://doi.org/10.1016/s0022-5347(17)53628-9
6. Lee HP. Nephrobronchiai fistula with reports of two cases. J Urol. 1939;41:117.
7. Kawano M, Saeki T, Nakashima H. IgG4-related kidney disease and retroperitoneal fibrosis: An update. Mod Rheumatol. 2019;29(2):231-239. https://doi.org/10.1080/14397595.2018.1554321

Management and prognosis of malignant pleural effusions managed with indwelling pleural catheters

M Martins[1], M Serino[1], F Viana-Machado[1], H Novais-Bastos[1,2]

TO THE EDITOR:

Malignant pleural effusion (MPE) affects 15% of cancer patients, and the incidence of MPE is likely to rise as the global incidence of cancer increases and the overall survival improves.[1,2] Most patients with MPE are symptomatic, with dyspnea being the most common symptom. As MPE represents advanced or metastatic disease, survival is generally poor, ranging from a median of 3 months to 12 months depending on underlying patient factors and tumor-related factors.[1] An overall survival of 3 months has recently been reported in patients with MPE, regardless of lung expandability.[3] Indwelling pleural catheters (IPCs) are the primary modality of treatment in MPE patients with nonexpandable lung (NEL) and symptomatic recurrence. Multiple studies have established the effectiveness of IPCs in achieving the palliation of symptoms.[4]

We conducted a retrospective analysis of a cohort of adult patients with MPE managed with IPCs between August of 2014 and August of 2022 at a university hospital. The main objective of the analysis was to validate the PROMISE score in patients with MPE undergoing drainage with an IPC. The PROMISE score was developed and validated by Psallidas et al.[5] and is the first prognostic score for MPE to combine biological markers and clinical parameters to estimate 3-month mortality. Patients were assigned a 3-month mortality rate on the basis of their PROMISE scores, calculated at the time of IPC placement. The patients were divided into four groups: group 1 (a PROMISE score of 0-20)—a mortality rate of < 25%; group 2 (a PROMISE score of 21-27)—a mortality rate of 25-50%; group 3 (a PROMISE score of 28-35)—a mortality rate of 50-75%; and group 4 (a PROMISE score > 35)—a mortality rate > 75%. The PROMISE score includes parameters such as previous chemotherapy, previous radiation therapy, hemoglobin, serum white blood cell count, C-reactive protein, Eastern Cooperative Oncology Group (ECOG) performance status, cancer type, and tissue inhibitor of metalloproteinases 1 (an optional protein biomarker, used for calculating the biological PROMISE score).

Survival curves were generated by the Kaplan-Meier method and compared by the log-rank test. An independent sample t-test was used in order to evaluate differences between continuous variables with normal distribution, and Mann-Whitney U tests were used in order to evaluate differences between continuous variables with skewed distribution. Patient data were entirely anonymized, and the study protocol complied with the ethical principles of the Declaration of Helsinki. The study was approved by the Research Ethics Committee of the *Centro Hospitalar Universitário de São João*, located in the city of Porto, Portugal.

Of the 45 patients included in the present analysis, 68.9% were male (n = 31). The median age was 68 years (IQR, 60.5-74.5), and most (55.5%) of the patients were current or former smokers (n = 25). MPEs were mostly located on the right side (in 53.3% of the patients; n = 24), and the most common etiologies were lung adenocarcinoma (in 48.9% of the patients; n = 22), breast cancer (in 11.1%; n = 5), and pancreatic adenocarcinoma (in 8.9%; n = 4). Indications for IPC placement included NEL (in 44.4% of the patients; n = 20) and talc slurry pleurodesis failure (in 31.1%; n = 14). Most (73.3%) of the patients were hospitalized at the moment of IPC placement (n = 33). Thoracentesis had been performed a median of 59 days before IPC placement (IQR, 35.0-109.0), and immediate complications of IPC placement (subcutaneous emphysema and hemothorax) were observed in two cases. Pleural infection occurred in 22.2% of the patients (n = 10). Of those, 40% (n = 4) were identified within one week of IPC placement. Chemotherapy did not correlate with an increased risk of complications (p = 0.177), namely, pleural infection. In accordance with a protocol established in August of 2016, we shifted from Tenckhoff catheters to Rocket® catheters (Rocket Medical plc., Watford, UK), and the frequency of complications associated with IPCs decreased. IPCs were removed early in 24.4% of the patients (n = 11), because of pleural infection (in 36.4%; n = 4), because of spontaneous pleurodesis (in 36.4%; n = 4), or accidently (in 27.3%; n = 3).

The pleural fluid **l**actate dehydrogenase, **E**COG performance status, **n**eutrophil-to-lymphocyte ratio, and **t**umor type (LENT) score has been reported to be an easy-to-use, accessible tool to predict the survival of patients with MPE quite accurately. The LENT score can be useful in palliating the symptoms of advanced malignancies by modifying treatment strategies.[6] According to Psallidas et al.,[5] "the PROMISE score is the first prospectively validated prognostic model for MPE that combines biological and clinical parameters to accurately estimate 3-month mortality. It is a robust, clinically relevant prognostic score that can be applied immediately, provide important information on patient prognosis, and guide the selection of appropriate management strategies." In a recent study comparing

1. Departamento de Pneumologia, Centro Hospitalar Universitário de São João, Porto, Portugal.
2. Instituto de Investigação e Inovação em Saúde – i3S – Universidade do Porto, Porto, Portugal.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

the LENT and PROMISE scores, the latter was found to be more accurate in predicting survival.[7]

Approximately 30% of the 45 patients included in the present analysis (n = 13) were receiving palliative care at the time of IPC placement. Sixteen patients were later referred for symptom relief. The median waiting time until the first palliative care appointment was 53.5 days (IQR, 17.5-108.0). The patients were divided into four groups on the basis of their PROMISE scores (not including tissue inhibitor of metalloproteinases 1): group 1 (n = 21); group 2 (n = 18); group 3 (n = 6); and group 4 (n = 0). Half (51.1%) of the patients had an ECOG performance status > 2 (n = 23). Median survival was 63.0 days (IQR, 22.25-190.5), being significantly different among the groups ($p < 0.001$): 87.5 days (IQR, 20.5-184.5) in group 1; 76 days (IQR, 30.5-268.0) in group 2; and 22.5 days (IQR, 3.5-40.5) in group 3 (Figure 1). There was no significant difference among the groups regarding the frequency of pleural infection ($p = 0.171$).

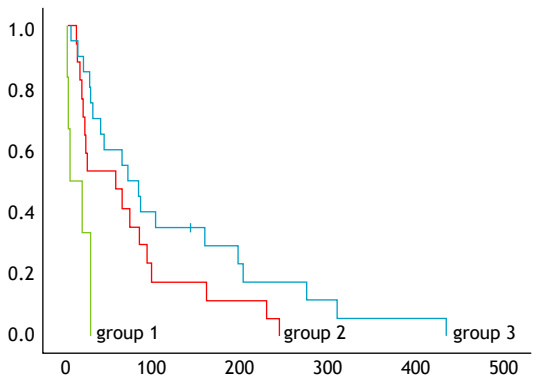


Figure 1. Kaplan-Meier survival curves based on the PROMISE score in individuals with malignant pleural effusion (MPE) requiring placement of an indwelling pleural catheter ($p < 0.001$). NOTE: group 1—MPE patients with a PROMISE score of 0-20; group 2—MPE patients with a PROMISE score of 21-27; and group 3—MPE patients with a PROMISE score of 28-35.

Although IPC can be a suitable first-line treatment option in patients with MPE, it is not exempt from adverse effects such as pleural infection, which, in our population, did not correlate with previous chemotherapy. The PROMISE score was found to be a valuable tool for predicting 3-month mortality in MPE patients undergoing IPC placement. The PROMISE score allows clinicians to reassess prognosis in this subset of patients and might have clinical implications as to whether or not to proceed with IPC placement, even in MPE patients without NEL. Furthermore, it is important to acknowledge that IPC placement is a treatment option that should be carefully discussed in frail patients. Application of the PROMISE score before IPC placement can identify those who are more likely to benefit from supportive measures alone rather than definitive treatment options such as IPC placement, which is not a risk-free therapeutic strategy. Thus, the PROMISE score is important in the decision-making regarding the use of IPCs in this population. We do not recommend IPC placement in group 3 and 4 patients and recommend a personalized evaluation in group 1 and 2 patients. Some of the limitations of the present analysis include its retrospective nature and limited sample size.

AUTHOR CONTRIBUTIONS

MM: conceptualization; methodology; investigation; data curation; software; resources; formal analysis; visualization; and writing, reviewing, and editing of the manuscript. MS and FVM: methodology; investigation; data curation; resources; formal analysis; and writing, reviewing, and editing of the manuscript. HNB: conceptualization; methodology; investigation; data curation; software; resources; formal analysis; visualization; writing, reviewing, and editing of the manuscript; and supervision. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

REFERENCES

1. Bedawi EO, Guinde J, Rahman NM, Astoul P. Advances in pleural infection and malignancy. Eur Respir Rev. 2021;30(159):200002. https://doi.org/10.1183/16000617.0002-2020
2. Bibby AC, Dorn P, Psallidas I, Porcel JM, Janssen J, Froudarakis M, et al. ERS/EACTS statement on the management of malignant pleural effusions. Eur Respir J. 2018;52(1):1800349. https://doi.org/10.1183/13993003.00349-2018
3. Trovisco R, Freitas C, Serino M, Ferreira P, Martins B, Coelho D, et al. Predictors of lung entrapment in malignant pleural effusion [published online ahead of print, 2022 Sep 27]. Pulmonology. 2022;S2531-0437(22)00199-4. https://doi.org/10.1016/j.pulmoe.2022.08.001
4. Kulandaisamy PC, Kulandaisamy S, Kramer D, Mcgrath C. Malignant Pleural Effusions-A Review of Current Guidelines and Practices. J Clin Med. 2021;10(23):5535. https://doi.org/10.3390/jcm10235535
5. Psallidas I, Kanellakis NI, Gerry S, Thézénas ML, Charles PD, Samsonova A, et al. Development and validation of response markers to predict survival and pleurodesis success in patients with malignant pleural effusion (PROMISE): a multicohort analysis. Lancet Oncol. 2018;19(7):930-939. https://doi.org/10.1016/S1470-2045(18)30294-8
6. Akram MJ, Khalid U, Ashraf MB, Bakar MA, Butt FM, Khan F. Predicting the survival in patients with malignant pleural effusion undergoing indwelling pleural catheter insertion. Ann Thorac Med. 2020;15(4):223-229. https://doi.org/10.4103/atm.ATM_289_20
7. Ermin S, Özdogan Y, Batum Ö, Yilmaz U. The role of LENT and PROMISE scores in predicting survival in malignant pleural effusion. Lung India. 2022;39(4):325-330. https://doi.org/10.4103/lungindia.lungindia_633_21

Not everything is disease progression—increased fluorodeoxyglucose uptake secondary to diaphragmatic paralysis

Felipe Marques da Costa[1], Augusto Kreling Medeiros[2], Marcos Aurélio Fonseca Magalhães Filho[3]

A 46-year-old female nonsmoker with metastatic lung cancer, who was currently on targeted therapy with lorlatinib, presented with a four-week history of progressive dyspnea.

Physical examination revealed reduced breath sounds in the left lung and an SpO_2 drop to 94%. Pulmonary function tests showed a restrictive ventilatory pattern. An FDG-PET/CT scan demonstrated increased FDG uptake in the right diaphragm, a finding that was absent on prior imaging. Given the manifest signs of cervical disease progression, a diagnosis was established of left phrenic nerve compression leading to left diaphragmatic elevation and a subsequent compensatory increase in the work of the functioning side and to increased FDG uptake in the right diaphragm (Figure 1).

Increased FDG uptake is generally attributable to muscle activity, surgical interventions, or inflammatory conditions.[1] In the context of pulmonary pathology, bilateral FDG uptake in the diaphragm is typically secondary to hyperventilation.[2] However, unilateral FDG uptake is predominantly indicative of contralateral diaphragmatic paralysis. Contralateral FDG uptake is a compensatory physiological response that should not be misdiagnosed as malignant, a condition that is notably rare.[1,3]

FINANCIAL SUPPORT

None.

AUTHOR CONTRIBUTIONS

FMC, MAFMF, and AKM: study conception, planning, and design; and data collection. FMC and MAFMF: writing of the preliminary drafts and final version of the manuscript. FMC, MAFMF, and AKM: revision of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

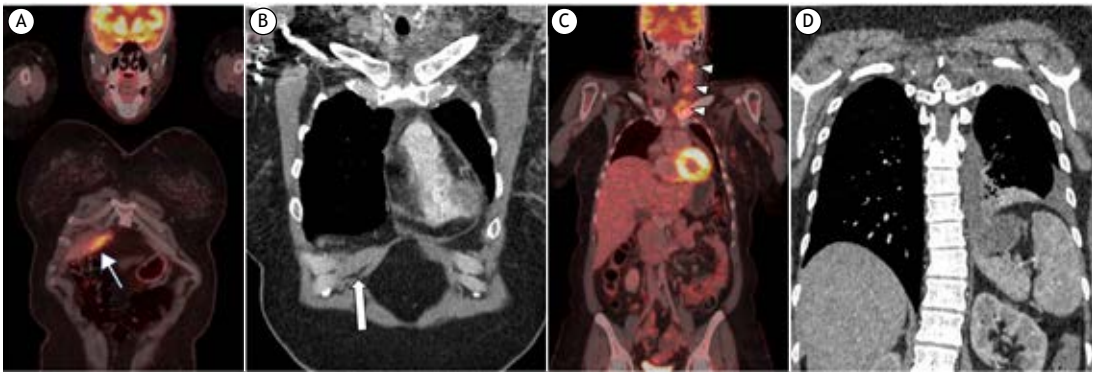


Figure 1. In A, a coronal PET/CT image reveals hypermetabolism in a small area of the anterior aspect of the right diaphragm (arrow), consistent with mechanical overexertion. In B, a coronal CT slice reinforces this observation, showing no evidence of any lesion in the diaphragm, particularly in its right anterior section (arrow). In C, a PET/CT scan taken a month later showed that signs of neoplastic progression became more pronounced in the neck, especially on the left side. This is evidenced by increased uptake in lymph nodes and by an infiltrative lesion adjacent to the left sternoclavicular joint and the scalene muscle (arrowheads). This is the typical location of the cervical portion of the phrenic nerve before it descends into the thorax. In D, a coronal CT slice shows elevation of the left diaphragm, which was not present on previous CT scans, suggesting left phrenic nerve paralysis.

REFERENCES

1. Joshi P, Lele V. Left is right and right is wrong: Fluorodeoxyglucose uptake in left hemi-diaphragm due to right phrenic nerve palsy. Indian J Nucl Med. 2013;28(1):32-33. 10.4103/0972-3919.116812
2. Cook GJ, Wegner EA, Fogelman I. Pitfalls and artifacts in 18FDG PET and PET/CT oncologic imaging. Semin Nucl Med. 2004;34(2):122-133. 10.1053/j.semnuclmed.2003.12.003
3. Benameur Y, Ait Sahel O, Nabih Oueriagli S, Doudouh A. Infection of implantable cardiac defibrillator [Article in French]. Rev Prat. 2020;70(3):235.

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

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia

Angioinvasive aspergillosis in a patient with acute myeloid leukemia and influenza B virus infection

Samuel Santos de Freitas[1], Ana Paula Zanardo[1,2], Rafael Domingos Grando[1,2]

A 32-year-old male patient was hospitalized for worsening symptoms of odynophagia, fever, and malaise. Laboratory tests confirmed acute myeloid leukemia. The patient then presented with severe hypoxemic respiratory failure caused by influenza B virus and rhinovirus infection, requiring mechanical ventilation and extracorporeal membrane oxygenation. The patient was then started on treatment with all-trans-retinoic acid, hydroxyurea, dexamethasone, and broad-spectrum antibiotics. Antifungal therapy was added because of persistent fever, worsening radiological findings, and galactomannan-positive BAL fluid. One week later, a follow-up chest X-ray showed an air crescent sign within a parenchymal consolidation. A CT scan of the chest confirmed cavitary lesions with solid content and an air component around them, characterizing the air crescent sign, which is consistent with angioinvasive aspergillosis in patients undergoing treatment for and in the recovery phase of hematologic malignancies, as a result of increased granulocytic activity. The differential diagnosis in this setting includes other invasive fungal diseases, pulmonary infarction, necrotizing pneumonia, and lung abscess.

Aspergillus infection is a life-threatening condition in immunosuppressed patients.[1] Aside from biological testing, CT is particularly useful because the finding of a halo sign together with a positive galactomannan test can allow early diagnosis and treatment. The air crescent sign is a finding that suggests good therapeutic response in these patients.[2,3]

AUTHOR CONTRIBUTIONS

SSF: conceptualization; investigation; and drafting and reviewing of the manuscript. APZ and RDG: conceptualization; investigation; and reviewing of the manuscript. All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

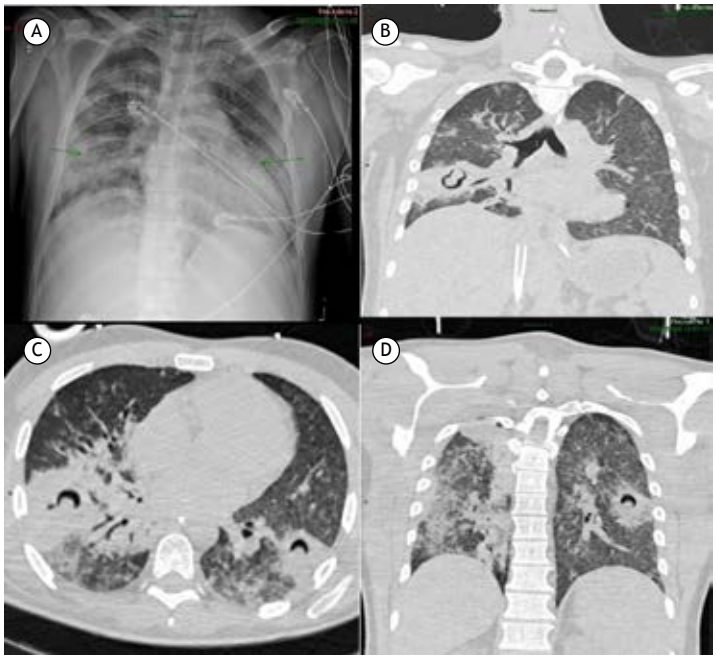


Figure 1. Air crescent sign on chest X-ray (in A) and chest CT scans (in B, C, and D).

REFERENCES

1. Sales Mda P. Chapter 5–Aspergillosis: from diagnosis to treatment. J Bras Pneumol. 2009;35(12):1238-1244. https://doi.org/10.1590/s1806-37132009001200012
2. Curtis AM, Smith GJ, Ravin CE. Air crescent sign of invasive aspergillosis. Radiology. 1979;133(1):17-21. https://doi.org/10.1148/133.1.17
3. Chong WH, Ibrahim A, Saha BK. The evolution of invasive pulmonary aspergillosis on chest imaging in response to antifungal therapy. BMJ Case Rep. 2021;14(3):e242576. https://doi.org/10.1136/bcr-2021-242576

1. Hospital Moinhos de Vento, Porto Alegre (RS) Brasil.
2. Programa de Pós Graduação em Ciências Pneumológicas, Universidade Federal do Rio Grande do Sul – UFRGS – Porto Alegre (RS) Brasil.

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

List of reviewers for volume 49 (1-6) 2023

A

Ada Clarice Gastaldi - Universidade de São Paulo - Ribeirão Preto - SP
Adriana Claudia Lunardi - Universidade da Cidade de São Paulo - São Paulo - SP
Adyleia Aparecida D Dalbo Conttrara - Universidade Estadual de Campinas - São Paulo - SP
Alberto Cukier - Universidade de São Paulo - São Paulo - SP
Alberto Ruano-Ravina - Universidade pública em Santiago de Compostela, Espanha
Alcindo Cerci Neto - Universidade Estadual de Londrina - Londrina - PR
Aldo Albuquerque Neto - Universidade Federal de São Paulo - São Paulo - SP
Alessandro Goncalves Campolina - Universidade de São Paulo - São Paulo - SP
Alessandro Wasum Mariani - Universidade de São Paulo - São Paulo - SP
Alexandre Kawassaki - Universidade de São Paulo - São Paulo - SP
Alexandre Melo Kawassaki - Universidade de São Paulo - São Paulo - SP
Alfésio Braga - Universidade Católica de Santos - Santos - SP
Aline Zaparte - Louisiana State University Internal Medicine - New Orleans - United States
Amanda Guimarães - Universidade Federal do Rio Grande do Sul - Rio Grande do Sul - RS
Ana Alice Amaral Ibiapina Parente - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Ana Paula Santos - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Ana Paula Santos - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Anderson Alves de Camargo - Universidade Nove de Julho - São Paulo - SP
Anderson José - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Andre Albuquerque - Universidade de São Paulo - São Paulo - SP
Arthur Souza Junior - Universidade de São Paulo - São Paulo - SP

B

Bianca Espíndula - Universidade de São Paulo - São Paulo - SP
Bogdan Moldoveanu - University of Louisville, Louisville, KY - USA
Bruno Valle Pinheiro - Universidade Federal de Juiz de Fora - Juiz de Fora - MG

C

Caio Morais - Universidade de São Paulo - São Paulo - SP
Carlos Almeida - Universidade Federal do Sul e Sudeste do Pará - Nova Marabá, Marabá - PA
Carmen Barbas - Universidade de São Paulo - São Paulo - SP
Célia Regina Moutinho de Miranda - Instituto Fernandes Figueira - Rio de Janeiro - RJ
Celso Ricardo Fernandes de Carvalho - Universidade de São Paulo - São Paulo - SP
Claudia Costa - Universidade Estadual do Rio de Janeiro - Rio Janeiro - RJ
Clemax Sant'Anna - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Concetta Esposito - Hospital Nereu Ramos - Florianópolis - Florianópolis - SC

D

Daniel Amaral - Universidade Nove de Julho - São Paulo - SP
Daniela Blanco - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Danielle Climaco - Hospital Otávio de Freitas - Recife - PE
Danilo Berton - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Dante Escuissato - Universidade Federal do Paraná - Curitiba - PR
Denise Rossato Silva - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Deniz Çelik - Alanya Alaaddin Keykubat University - Turkey
Dicle Kaymaz - Health Sciences University, Ankara, Ataturk - Turkey

E

Eanes Pereira - Universidade Federal do Ceará - Fortaleza - CE
Edson Marchiori - Universidade Federal Fluminense - Niterói - RJ
Eduardo Enrique Borsini - Hospital Britanico de Buenos Aires, Medicine Respiratory Unit - Buenos Aires - Argentina
Eduardo Vieira Ponte - Faculdade de Medicina de Jundiaí - São Paulo - SP
Eliseu Waldman - Universidade de São Paulo - São Paulo - SP
Eloara Vieira Machado Ferreira - - Universidade Federal de São Paulo - São Paulo - SP
Emílio Pizzichini - Universidade Federal de Santa Catarina - Florianópolis – SC
Erich Vidal Carvalho - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Ernesto Crisafulli - University of Verona - Italy
Eserval Rocha Junior - Universidade de São Paulo - São Paulo - SP
Evanirso da Silva Aquino - Hospital Infantil João Paulo II - Belo Horizonte - MG

F

Fabio Arimura - Universidade de São Paulo - São Paulo - SP
Fabio Dantas Filho - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS

BY-NC © 2023 Sociedade Brasileira de Pneumologia e Tisiologia
ISSN 1806-3756

Fabio Pitta - Universidade Estadual de Londrina - Londrina - PR
Fabrizio Luppi - Respiratory Disease, Fondazione IRCCS San Gerardo dei Tintori, Monza, Italy
Felipe von Ranke - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Fernanda Carvalho de Mello - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Fernanda Vendrusculo - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre - RS
Fernando Didier - Universidade de São Paulo - São Paulo - SP
Fernando Queiroga Júnior - Hospital Universitário Oswaldo Cruz - Recife - PE
Flávia Del Castanhel -Universidade Federal de Santa Catarina- Florianópolis - RS
Flávio Arbex - Universidade Federal de São Paulo - São Paulo - SP
Forest Arnold - University of Louisville, Louisville, KY
Frederico Leon Arrabal Fernandes - Universidade de São Paulo - São Paulo - SP

G

Giovana Rodrigues Pereira - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Guilherme das Posses Bridi - Universidade de São Paulo - São Paulo - SP
Gustavo Chatkin - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre- RS

H

Helaine Jacinta Salvador Mocelin - Universidade Federal do Espírito Santo Centro de Ciências da Saúde - Vitória - ES
Ho Yeh Li - Universidade de São Paulo - São Paulo - SP

I

Irma de Godoy - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Isabela Neves de Almeida - Universidade Federal de Ouro Preto - Ouro Preto - MG
Israel Silva Maia - Hospital Nereu Ramos - Florianópolis - SC

J

James Bradley - Respiratory Medicine at St George's, University of London University of Louisville - Kentucky -USA
Jessica Fonseca - Universidade Estadual de Londrina - Londrina - PR
João Aléssio Juliano Perfeito - Universidade Federal de São Paulo - São Paulo - SP
João Carlos Alchieri - Universidade Federal do Rio Grande do Norte - Natal - RN
Joao Papa - Universidade Estadual Paulista Júlio de Mesquita Filho - Bauru - SP
José Alberto Neder Serafini - Kingston Health Sciences Centre and Queen's University - Kingston - ON - Canada
José Angelo Rizzo - Universidade Federal de Pernambuco Recife - PE
Jose de Arimateia Araujo Filho - Hospital Sírio-libanesa Radiologia - São Paulo - SP
José Eduardo Delfini Cançado - Faculdade de Ciências Médicas da Santa Casa de Misericórdia de São Paulo - São Paulo - SP
José Leonidas Alves Júnior - Universidade de São Paulo - São Paulo - SP
José Roberto de Brito Jardim - Universidade Federal de São Paulo - São Paulo - SP
Jose Roberto Lapa e Silva - Universidade Federal Fluminense - Niterói - RJ
Juan Cascón Hernández - Hospital Universitario Central de Asturias - Oviedo - España
Juan Guardiola - Respiratory Medicine at St George's, University of London University of Louisville - Kentucky -USA
Juliana Brandão Folador Morellato - A.C.Camargo Cancer Center - São Paulo - SP
Juliana Carvalho Ferreira - Universidade de São Paulo - São Paulo - SP

K

Kaifeng Xu - Universidade de Pequim (Peking University) - China
Karen D' Àvila - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Karin Mueller Storrer - Universidade Federal do Paraná - Curitiba - PR
Klaus Irion - Manchester University NHS Foundation Trust - Manchester - Grã-Bretanha
Konstantinos Chandolias - University of Thessaly - Lamia - Greece

L

Leandro Taniguchi - Universidade de São Paulo - São Paulo - SP
Leonardo Jönck Staub - Universidade Federal de Santa Catarina - Florianópolis - SC
Leticia Lauricella - Instituto do Câncer do Estado de São Paulo - São Paulo - SP
Lia Possuelo - Universidade de Santa Cruz do Sul - Rio Grande do Sul - RS
Lilian Serrasqueiro Ballini Caetano - Universidade Federal de São Paulo - São Paulo - SP
Linjie Zhang- Universidade Federal do Rio Grande - Rio Grande - RS
Lucia Sales - Universidade Federal do Pará - Belém - PA
Luis Carlos Maia Cardozo Junior -Universidade de São Paulo - São Paulo - SP
Luis Renato Alves - Universidade de São Paulo - Ribeirão Preto - SP
Luiz de Abreu Junior - Clínica Radiologia Saldanha Lisboa - Lisboa - Portugal
Luiz Felippe Judice - Universidade Federal Fluminense - Niterói - RJ

M

Magali Santos Lumertz - Pontifícia Universidade Católica do Rio Grande do Sul - Porto Alegre- RS
Marcela Bhering - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ
Marcelo Alcântara Holanda - Universidade Federal do Ceará - Fortaleza - CE
Marcelo Beraldo - Universidade de São Paulo - São Paulo - SP
Marcelo Gazzana - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Marcelo Gervilla Gregório - Clinica Clínica Respsono - São Paulo - SP
Marcio Valente Sawamura - Universidade de São Paulo - São Paulo - SP

Marcos Minicucci - Universidade Estadual Paulista Júlio de Mesquita Filho - Botucatu - SP
Marcos Oliveira - Unidade Local de Saude da Guarda EPE - Guarda - Portugal
Maria Angelica Pires Ferreira - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Mariana Araujo - Universidade Federal do Paraná - Curitiba - PR
Mariana Migliorini Parisi - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Mariangela Pimentel Pincelli - Universidade Federal de Santa Catarina - Florianópolis - SC
Mario Barreto - Università degli Studi di Roma La Sapienza - Roma - Italy
Martin Rainer Kolb -Universidade McMaster - Hamilton - ON - Canadá
Maycon Moura Reboredo - Universidade Federal de Juiz de Fora - Juiz de Fora - MG
Mônica Corso Pereira - Universidade Estadual de Campinas - São Paulo - SP
Morten Dahl - University of Copenhagen, Copenhagen, Denmark
Murilo Foppa - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS

N

Nataly Campos - Universidade Federal do Ceará - Fortaleza - CE
Neio Boechat - Universidade Federal do Rio de Janeiro - Rio de Janeiro - RJ

O

Oliver Nascimento - Universidade Federal de São Paulo - São Paulo - SP
Olivia Meira Dias - Universidade de São Paulo - São Paulo - SP
Ozge Ozalp - Cyprus International University - Nicosia, North Cyprus

P

Patricia Soarez - Universidade de São Paulo - São Paulo - SP
Paul O'Byrne - McMaster University - Ontario - Canada
Paulo de Tarso Dalcin - Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Paulo Duarte - Universidade de São Paulo - São Paulo - SP
Paulo Kussek - Faculdades Pequeno Príncipe - Curitiba - PR
Pedro Augusto Reck dos Santos - Hospital Marcelino Champagnat - Curitiba - PR
Philippe Figueiredo Braga Colares - Universidade de São Paulo - São Paulo - SP

R

Rafael Mizutani - Universidade de São Paulo - São Paulo - SP
Regina Maria Carvalho-Pinto - Universidade de São Paulo - SP
Regis Goulart Rosa - Hospital Moinhos de Vento - Porto Alegre - RS
Renata Cohen - Instituto Fernandes Figueira - Rio de Janeiro - RJ
Renata Ferrari - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Roberta Pulcheri Ramos - Universidade Federal de São Paulo - São Paulo - SP
Roberta Ribeiro De Santis Santiago - A.C.Camargo Cancer Center - São Paulo - SP
Roberto Mogami - Universidade do Estado do Rio de Janeiro - RJ
Rodolfo Augusto Bacelar Athayde - Universidade de São Paulo - São Paulo - SP
Rodrigo Abensur Athanazio - Universidade de São Paulo - São Paulo - SP
Rodrigo Cavallazzi - Respiratory Medicine at St George's, University of London University of Louisville - Kentucky -USA
Rodrigo Chate - Universidade de São Paulo - São Paulo - SP
Rogelio Pérez-Padilla - National Institute of Respiratory Diseases, Mexico City, Mexico
Rogerio Rufino - Universidade do Estado do Rio de Janeiro - Rio de Janeiro - RJ
Rong Yang - Cornell University - Ithaca, NY
Rosemeri Maurici - Universidade Federal de Santa Catarina - Florianópolis - SC
Rudolf Oliveira - Universidade Federal de São Paulo - São Paulo - SP

S

Samara Gouveia - Universidade Federal do Delta do Parnaíba - Parnaíba - PI
Sandra Eugenia Coutinho Brasil -Universidade Federal do Rio Grande do Sul - Porto Alegre - RS
Sara Moraes - Universidade de São Paulo - São Paulo - SP
Scott Bickel - University of Alabama at Birmingham - Birmingham - AL
Sergio Alberto Rupp Paiva - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Shriya Khurana - Respiratory Medicine at St George's, University of London University of Louisville - Kentucky -USA
Silvia Carla Sousa Rodrigues - Universidade Federal de São Paulo - São Paulo - SP
Silvia Terraneo - University of Milan - Milan - Italy
Sofia Sousa - Hospital de Braga - Braga - Portugal
Sonia Togeiro - Universidade Federal de São Paulo - São Paulo -SP
Stephan Philip Leonhardt Altmayer - Universidade Federal de Ciencias da Saude de Porto Alegre - Porto Alegre - RS
Stephen Furmanek - Norton Infectious Diseases Institute - Louisville - Kentucky
Suzana Erico Tanni - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP

T

Thiago André Fuscaldi Corrêa - Hospital Universitário de Brasília -Brasília - DF
Thomas Chandler - Norton Infectious Diseases Institute - Louisville - Kentucky

U

Ulysses Torres - Centro Diagnóstico do Grupo Fleury - São Paulo - SP

V

Valéria Maria Augusto - Universidade Federal de Minas Gerais - Belo Horizonte - MG
Vanessa Pereira Lima - Universidade Federal dos Vales do Jequitinhonha e Mucuri - Diamantina - MG
Vania Nogueira - Universidade Estadual Paulista "Júlio de Mesquita Filho" - Botucatu - SP
Veronica Moreira Amado - Universidade de Brasília - Brasília - DF
Viviane Rossi Figueiredo - Universidade de São Paulo - São Paulo - SP

W

Wolfgang Aguiar - Universidade Federal de Ciências da Saúde de Porto Alegre - Porto Alegre - RS

Y

Yekta Altemur Karamustafaoglu - Trakya University Faculty of Medicine - Turkey

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

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

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

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

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

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

Authorship criteria

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

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

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

Presentation and submission of manuscripts

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

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

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

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

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

Whenever the authors mention any substance or uncommon piece of equipment they must include the catalogue model/number, name of manufacturer, city and country of origin. For example:

"... ergometric treadmill (model ESD-01; FUNBEC, São Paulo, Brazil) ..."

In the case of products from the USA or Canada, the name of the state or province should also be cited. For example:

"... guinea pig liver tTg (T5398; Sigma, St. Louis, MO, USA) ..."

Manuscript preparation

Title Page: The title page should include the title (in Portuguese and in English); the full names, highest academic degrees and institutional affiliations of all authors; complete address, including telephone number, fax number and e-mail address, of the principal author; and a declaration of any and all sources of funding.

Abstract: The abstract should present the information in such a way that the reader can easily understand without referring to the main text. Abstracts should not exceed 250 words. Abstracts should be structured as follows: Objective, Methods, Results and Conclusion. Abstracts for review articles may be unstructured.

Abstracts for brief communications should not exceed 100 words.

Summary: An abstract in English, corresponding in content to the abstract in Portuguese, should be included.

Keywords: Three to six keywords in Portuguese defining the subject of the study should be included as well as the

corresponding keywords in English. Keywords in Portuguese must be based on the Descritores em Ciência da Saúde (DeCS, Health and Science Keywords), published by Bireme and available at: http://decs.bvs.br, whereas keywords in English should be based on the National Library of Medicine Medical Subject Headings (MeSH), available at: http://www.nlm.nih.gov/mesh/MBrowser.html.

Text:

Original articles: For original articles, the text (excluding the title page, abstracts, references, tables, figures and figure legends) should consist of 2000 to 3000 words. Tables and figures should be limited to a total of five. The number of references should not exceed 30. Original articles should be divided into the following sections: Introduction, Methods, Results, Discussion, Acknowledgments, and References. The Methods section should include a statement attesting to the fact the study has been approved by the ethics in human research committee or the ethics in animal research committee of the governing institution. There should also be a section describing the statistical analysis employed, with the respective references. In the Methods and Results sections, subheadings may be used, provided that they are limited to a reasonable number. Subheadings may not be used in the Introduction or Discussion.

Review and Update articles: Review and Update articles are written at the request of the Editorial Board, which may occasionally accept unsolicited manuscripts that are deemed to be of great interest. The text should not exceed 5000 words, excluding references and illustrations (figures or tables). The total number of illustrations should not exceed eight. The number of references should not exceed 60.

Pictorial essays: Pictorial essays are also submitted only at the request of the Editors or after the authors have consulted and been granted permission by the Editorial Board. The text accompanying such essays should not exceed 3000 words, excluding the references and tables. No more than 12 illustrations (figures and tables) may be used, and the number of references may not exceed 30.

Brief Communications: Brief communications should not exceed 1500 words, excluding references and tables. The total number of tables and figures should not exceed two, and the references should be limited to 20. The text should be unstructured.

Letters to the Editor: Letters to the Editor should be succinct original contributions, not exceeding 800 words and containing a maximum of 6 references. Comments and suggestions related to previously published materials or to any medical theme of interest will be considered for publication.

Correspondence: Authors may submit comments and suggestions related to material previously published in our journal. Such submissions should not exceed 500 words.

Imaging in Pulmonary Medicine: Submissions should not exceed 200 words, including the title, text, and references (no more than three). Authors may include up to three figures, bearing in mind that the entire content will be published on a single page.

Tables and Figures: All tables and figures should be in black and white, on separate pages, with legends and captions appearing at the foot of each. All tables and figures should be submitted as files in their original format. Tables should be submitted as Microsoft Word files, whereas figures should be submitted as Microsoft Excel, TIFF or JPG files. Photographs depicting surgical procedures, as well as those showing the results of exams or biopsies, in which staining and special techniques were used will be considered for publication in color, at no additional cost to the authors. Dimensions, units and symbols should be based on the corresponding guidelines set forth by the Associação Brasileira de Normas Técnicas (ABNT, Brazilian Association for the Establishment of Technical Norms), available at: http://www.abnt.org.br.

Legends: Legends should accompany the respective figures (graphs, photographs and illustrations) and tables. Each legend should be numbered with an Arabic numeral corresponding to its citation in the text. In addition, all abbreviations, acronyms, and symbols should be defined below each table or figure in which they appear.

References: References should be listed in order of their appearance in the text and should be numbered consecutively with Arabic numerals. The presentation should follow the Vancouver style, updated in October of 2004, according to the examples below. The titles of the journals listed should be abbreviated according to the style presented by the List of Journals Indexed in the Index Medicus of the National Library of Medicine, available at: http://www.ncbi.nlm.nih.gov/entrez/journals/loftext.noprov.html. A total of six authors may be listed. For works with more than six authors, list the first six, followed by 'et al.'

Examples: Journal Articles

1. Neder JA, Nery LE, Castelo A, Andreoni S, Lerario MC, Sachs AC et al. Prediction of metabolic and cardiopulmonary responses to maximum cycle ergometry: a randomized study. Eur Respir J. 1999;14(6):1204-13.

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

Other situations:

In other situations not mentioned in these author instructions, authors should follow the recommendations given by the International Committee of Medical Journal Editors. Uniform requirements for manuscripts submitted to biomedical journals. Updated October 2004. Available at http://www.icmje.org/.

All correspondence to the Jornal Brasileiro de Pneumologia should be addressed to:

Prof. Dr. Rogério Souza

Editor-Chefe do Jornal Brasileiro de Pneumologia

SCS Quadra 01, Bloco K, Salas 203/204 - Ed. Denasa. CEP: 70.398-900 - Brasília - DF, Brazil

Telefones/Fax: 0xx61-3245-1030, 0xx61-3245-6218

Jornal Brasileiro de Pneumologia e-mail address:

jpneumo@jornaldepneumologia.com.br

(Assistente Editorial - Luana Campos)

Online submission of articles:

www.jornaldepneumologia.com.br

CONHEÇA O NOVO APLICATIVO DA BAYER!

O aplicativo **Risco na HP** facilita a utilização das estratégias para estratificação de risco do seu paciente, de acordo com as diretrizes do **Registro Francês**[1, 2], **Registro COMPERA**[3,4], **REVEAL 2.0 e REVEAL Lite 2**

O aplicativo Risco na HP está disponível para download gratuito nas principais lojas de aplicativo.

Baixar na App Store

DISPONÍVEL NO Google Play

Google Play e o logo Google Play são marcas da Google LLC
e App Store é uma marca da Apple Inc.

O aplicativo Risco na HP foi desenvolvido com base em publicações científicas1-6 para realizar uma estimativa na estratificação de risco da Hipertensão Pulmonar.

A responsabilidade pela determinação da conduta terapêutica para cada paciente é do médico e sua equipe. O aplicativo apenas facilita a utilização das estratégias de avaliação de risco. As informações apresentadas pelo aplicativo não devem ser utilizadas isoladamente.

Referências:

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

Essa mensagem não deve ser compartilhada por se destinar somente a profissionais de saúde habilitados a prescrever ou dispensar medicamentos

PP-VEN-BR-0037-1 | Fevereiro 2022

Chegou: EGURINEL® (pirfenidona)

O primeiro similar de pirfenidona do Brasil!

Egurinel® (pirfenidona) é bioequivalente ao medicamento referência![1]

Referência: 1. Vespasiano CFP, Accennato VAC, Costa F, Riccio MF, Bernasconi G, et al. (2020) Bioequivalence between Two Capsules of Pirfenidona in Healthy Subjects under Fed Condition. J Bioeq Stud 6(1): 101.

EGURINEL® (pirfenidona) é apresentado em embalagem contendo 270 cápsulas. **Indicações**: EGURINEL® (pirfenidona) está indicado para tratamento de fibrose pulmonar idiopática (FPI). **Posologia**: Adultos: Ao iniciar o tratamento, a dose deve ser escalonada em um período de 14 dias até a dose diária recomendada de nove cápsulas por dia, como se segue: **Dias 1 a 7**: uma cápsula, três vezes por dia (801 mg/dia). **Dias 8 a 14**: duas cápsulas, três vezes por dia (1602 mg/dia). **Dias 15 em diante**: três cápsulas, três vezes por dia (2403 mg/dia). A dose diária recomendada de EGURINEL® para pacientes com FPI é de três cápsulas de 267 mg três vezes por dia com alimentos até um total de 2403 mg/dia. **Contraindicações**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Precauções e Advertências**: Função Hepática: lesão hepática induzida por medicamento (DILI) na forma de elevação transitória e clinicamente silenciosa de transaminases tem sido continuamente reportada em pacientes tratados com EGURINEL® (pirfenidona). Em casos raros, estas elevações foram associadas com elevação concomitante da bilirrubina e consequências clínicas sérias, incluindo casos isolados com desfecho fatal reportados pós-comercialização. Provas de função hepática (ALT, AST e bilirrubinas) devem ser realizadas antes do início do tratamento com EGURINEL® e subsequentemente em intervalos mensais nos 6 primeiros meses e depois a cada 3 meses a partir de então. Reação de hipersensibilidade e erupção cutânea: a exposição direta à luz solar (incluindo bronzeamento artificial) deve ser evitada ou reduzida durante o tratamento com pirfenidona. Os pacientes devem ser orientados a usar bloqueador solar eficaz diariamente, usar roupas que protejam contra a exposição solar e evitar outros medicamentos que reconhecidamente provoquem fotossensibilidade. Os pacientes devem ser orientados a reportar sintomas de fotossensibilidade ou erupção cutânea ao seu médico. Ajustes de dose ou descontinuação temporária de tratamento podem ser necessários no caso de reação de fotossensibilidade ou erupção. Tontura: tonturas têm sido relatadas em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mentais. Em estudos clínicos, a maioria dos pacientes que apresentaram tontura tinham um único evento, e a maioria dos eventos resolvidos, com uma duração média de 22 dias. Se a tontura não melhorar ou se agravar, pode ser necessário um ajuste da dose ou até mesmo a interrupção de pirfenidona. Fadiga: Fadiga tem sido relatada em pacientes tomando pirfenidona. Portanto, os pacientes devem saber como eles reagem a este medicamento antes de se envolver em atividades que exigem prontidão ou coordenação mental. Perda de peso: a perda de peso tem sido relatada em pacientes tratados com pirfenidona. Os médicos devem monitorar o peso dos pacientes, e, quando necessário, incentivar o desenvolvimento do consumo de calorias se a perda de peso for considerada de importância clínica. Distúrbios gastrintestinais: nos estudos clínicos, os eventos adversos gastrointestinais como náuseas, diarreia, dispepsia, vômitos, doença do refluxo gastresofágico e dor abdominal foram mais frequentemente relatados pelos pacientes nos grupos de tratamento com pirfenidona do que naqueles que receberam o placebo. **Interações**: EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® **Reações Adversas**: as reações adversas mais comuns, obtidas dos estudos pivotais foram: náuseas (36%); erupção cutânea (30,3%); tosse (27,8%); infecção do trato respiratório superior (26,8%) e diarréia (25,8%). VENDA SOB PRESCRIÇÃO MÉDICA. **Reg. MS- 1.2214.0114. SAC: 08000 016 6575 "Informações adicionais disponíveis aos profissionais de saúde mediante solicitação a Zodiac Produtos Farmacêuticos S.A – www.zodiac.com.br - Para informações completas, consultar a instrução de uso do produto. Contraindicação**: EGURINEL® (pirfenidona) está contraindicado nos casos de hipersensibilidade à substância ativa ou qualquer um de seus componentes; histórico de angioedema devido ao uso de pirfenidona; insuficiência hepática grave ou doença hepática terminal; insuficiência renal grave (CrCl < 30mL/min) ou doença renal terminal com necessidade de diálise. O uso concomitante de fluvoxamina e EGURINEL® está contraindicado. **Interação:** EGURINEL® é contraindicado para pacientes em uso concomitante de fluvoxamina. A coadministração de EGURINEL® e ciprofloxacino 750 mg (inibidor moderado e seletivo de CYP1A2) aumentou a exposição a pirfenidona em 81%. Se o uso de ciprofloxacino 750 mg duas vezes por dia não puder ser evitado, a dose de EGURINEL® deve ser reduzida para 1602 mg por dia (duas cápsulas, três vezes por dia). EGURINEL® deve ser usado com cautela quando o ciprofloxacino for utilizado em dose de 250 mg ou 500 mg, uma ou duas vezes por dia. No caso de indutores moderados de CYP1A2 (p.ex., omeprazol), o uso concomitante pode teoricamente resultar em redução dos níveis plasmáticos de pirfenidona. A coadministração de medicamentos que atuem como indutores potenciais tanto de CYP1A2 quanto de outras isoenzimas CYP envolvidas no metabolismo da pirfenidona (p.ex., rifampicina) pode resultar em redução significativa dos níveis plasmáticos de pirfenidona. Esses medicamentos devem ser evitados sempre que possível. O tabagismo tem o potencial para induzir a produção de enzimas hepáticas e por isso aumenta a depuração e reduz a exposição ao EGURINEL®. O uso concomitante de indutores potentes de CYP1A2, incluindo o fumo, deve ser evitado durante a terapia com EGURINEL® .

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

SE PERSISTIREM OS SINTOMAS, O MÉDICO DEVERÁ SER CONSULTADO.

30 ANOS Zodiac Produtos Farmacêuticos | ZODIAC