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HIGHLIGHT

Loss of response to calcium channel blockers in pulmonary hypertension

Handgrip strength for frailty risk assessment in older adults with asthma

Fat embolism syndrome causing a crazy-paving pattern on CT

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.
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Anti-alarmin asthma therapies: where do we go from here?

Ibrahim Sulaiman[1], Gail M Gauvreau[2]

Asthma is a chronic airway inflammatory disorder that is characterized by reversible airway obstruction, inflammation, and hyperresponsiveness. Stable control of asthma symptoms is achievable by using combinations of inhaled corticosteroids and β_2 agonists; however, severe asthma patients do not respond well to these combinations.[1] Improved understanding of the inflammatory pathways in the airways of asthma patients has led to tremendous progress in the development of effective biologics blocking the actions of type-2 (T2) cytokines (IL-4, IL-5, and IL-13). While these biologics reduce asthma exacerbation rates by approximately 50%, they are not as effective in uncontrolled asthma, especially in those with non-eosinophilic and non-allergic phenotypes.[2] Interventions targeting mediators further upstream in the inflammatory cascade have been under evaluation (Table 1).

Alarmins are a diverse group of endogenous danger signals and multifunctional host-defense peptides (or proteins) released by epithelial cells into the extracellular microenvironment upon exposure to pathogens and environmental insults, and they play a critical role in innate immunity, antigen presentation, and adaptive immune response.[3] Among the numerous constitutively expressed alarmins, thymic stromal lymphopoietin (TSLP), IL-33, and IL-25 are pivotal to the initiation of T2 inflammatory responses in the airways and have been implicated in the pathobiology of chronic inflammatory conditions such as asthma.[4] Targeting the alarmins may help address the unmet medical need of T2-low (and non-T2) inflammation, which constitutes approximately 50% of the asthma population.[2]

Developing an effective anti-alarmin for asthma therapy requires consideration of several factors including the downstream inflammatory pathways, the target molecule (cytokine versus receptor), and the route of administration.

TSLP is present in two different isoforms, signaling through a heterodimer receptor consisting of TSLPR and IL-7R-alpha. The comparative efficacy of targeting TSLP long versus short isoform, or TSLP versus TSLPR, is unknown. To date, blockade of the TSLP pathway with a human monoclonal antibody (mAb) that binds to TSLP (tezepelumab, also known as AMG 157) has been approved in several countries for the treatment of severe asthma. Despite the potentially redundant actions of TSLP, IL-33, and IL-25 in driving T2 immune responses, tezepelumab added to inhaled corticosteroid treatment successfully improved FEV_1, reduced asthma exacerbation rates by nearly 70%, and decreased airway inflammation in severe asthma patients, with efficacy demonstrated in both T2-high and T2-low asthma.[5] Numerous other anti-TSLP and anti-TSLPR drugs are being tested for safety and efficacy in asthma patients (Table 1). Although head-to-head comparisons of anti-TSLP mAbs have not been conducted, two proof-of-concept studies using identical methodology examined the effect of systemically administered tezepelumab mAb (700 mg, i.v.) and inhaled CSJ 117 mAb-fragment (4 mg once daily), compared to placebo, on allergen-induced early and late asthma responses, as well as on markers of airway and systemic inflammation.[6,7] Tezepelumab and CSJ 117 both inhibited allergen-induced late asthma responses, sputum eosinophils, and fractional exhaled nitric oxide at 12 weeks post-dosing; however, only tezepelumab inhibited all allergen-induced outcomes at 7 weeks post-dosing and consistently inhibited the early asthma response and circulating eosinophil levels. The faster onset of action by i.v. administration may occur via systemic suppression of cells involved in the allergic cascade.

IL-33 is a pleiotropic cytokine that interacts with the ST2 receptor and IL-1 receptor accessory protein (IL-1RAP) to modulate its activities. From the full-length IL-33 cytokine precursor, various mature isoforms are formed with varying efficacies depending on the site of proteolytic cleavage. It is not well understood whether the pathogenic effect of IL-33 is caused by the full-length IL-33 and/or its mature isoform, making IL-33 a challenging target. The IL-33 mAb, itepekimab, positively impacted asthma control and health-related quality of life,[8] while treatment with the IL-33 mAb etokimab had no effect on blood eosinophil counts or asthma exacerbation (NCT03469934). No additional studies with anti-IL-33 mAbs have been planned, probably due to the small effect size reported in these early clinical trials. However, blocking the ST2 receptor with astegolimab has shown more promising results, reducing asthma exacerbation rates, improving FEV_1, and enhancing asthma-related quality of life.[9] Anti-ST2 mAbs may be more effective than anti-IL-33 mAbs due to the broad expression of ST2 on relevant inflammatory cells in the airways and the prevention of signaling by all forms of IL-33. However, an improved understanding of IL-33 pathway blockade for asthma treatment will require trials with larger sample sizes. Other anti-ST2 therapies under investigation for the treatment of asthma include tozorakimab (MEDI3506), a potent inhibitor of reduced and oxidized forms of IL-33, acting via ST2 and non-ST2 pathways.[10]

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Table 1. Alarmin-targeted clinical trials in asthma.

#	Clinical trial number	Trial name	Trial phase	Asthma severity	Primary outcome	Intervention (route of administration)	Age of participants, years
				Bivalent anti-TSLP/IL-13			
1.	NCT05366764		1	Mild to moderate	Incidence of AEs and TEAEs	SAR443765	18 to 60
				Anti-TSLP			
2.	NCT05329194 (Recruiting as of 2023/06/23)	PASSAGE	4	Severe asthma	Annualized AER, asthma exacerbation days & proportions	Tezepelumab (s.c.)	12 to 130
3.	NCT05280418 (Recruiting as of 2023/06/23)		3	Uncontrolled moderate-to-severe	Pre-bronchodilator 129Xe MRI ventilation defect percent	Tezepelumab (s.c.)	18 and older
4.	NCT03927157 (Active as of 2023/06/23)		3	Severe uncontrolled Asthma	Annualized AER	Tezepelumab (s.c.)	18 to 80
5.	NCT05274815 (Active as of 2023/06/23)	WAYFINDER	3	Severe uncontrolled asthma	OCS discontinuation or reduction to ≤ 5 mg/day	Tezepelumab (s.c.)	18 to 80
6.	NCT05398263 (Recruiting as of 2023/06/23)	SUNRISE	3	Severe uncontrolled asthma - OCS-dependent asthma	Reduction from baseline in the daily maintenance of OCS dose	Tezepelumab (s.c.)	18 to 80
7.	NCT04048343		3	Severe uncontrolled asthma	Adverse events	Tezepelumab (s.c.)	12 to 80
8.	NCT03406078	SOURCE	3	Severe uncontrolled asthma - OCS-dependent asthma	Categorized reduction from baseline in the daily OCS dose	Tezepelumab (s.c.)	18 to 80
9.	NCT03706079	DESTINATION	3	Severe uncontrolled asthma	Exposure adjusted AEs and severe AEs	Tezepelumab (s.c.)	13 to 81
10.	NCT05740748 (Active as of 2023/06/23)		2	Mild allergic asthma	Methacholine PD20	Tezepelumab (s.c.)	18 to 65
11.	NCT05774340 (Active as of 2023/06/23)		2	Moderate to severe	Annualized AER	CM326 (s.c.)	18 to 75
12.	NCT05593250 (Enrolling as at 2023/06/23)		2	Severe uncontrolled asthma	Annualized AER	SHR-1905 (s.c.)	18 to 75
13.	NCT02054130	PATHWAY	2	Severe uncontrolled asthma	Annualized AER	Tezepelumab aka MEDI9929 (s.c.)	18 to 75
14.	NCT04410523 (Terminated: sponsor decision)		2	Severe uncontrolled asthma	Change in baseline FEV_1	Ecleralimab aka CSJ117 (inh)	18 to 75
15.	NCT02698501	UPSTREAM	2	Uncontrolled asthma	Change in baseline mannitol PD15	Tezepelumab aka AMG 157 (i.v.)	18 to 75
16.	NCT01405963		1	Mild allergic asthma	Allergen-induced change in FEV_1	Tezepelumab aka AMG 157 (i.v.)	18 to 60

Continue...▶

Table 1. Alarmin-targeted clinical trials in asthma. (Continued...)

#	Clinical trial number	Trial name	Trial phase	Asthma severity	Primary outcome	Intervention (route of administration)	Age of participants, years
17.	NCT03138811 (Terminated: met set objective without safety concern)		1	Mild allergic asthma	Allergen-induced change in FEV_1	Ecleralimab aka CSJ 117 (inh)	18 to 60
18.	NCT05110976 (Recruiting as of 2023/06/23)		1	Asthma patients on medium to high dose ICS/LABA	AEs and PK	AZD8630 (inh)	18 to 75
19.	NCT05171348		1	Healthy volunteers	Incidence of adverse events	CM326 (s.c.)	18 to 65
20.	NCT04673630	TRAILHEAD	1	Mild/moderate/severe	PK	Tezepelumab (s.c.)	05 to 11
21.	NCT02512900		1	Mild to moderate	PK	Tezepelumab aka MEDI9929 (s.c.)	12 to 17
22.	NCT04842201		1	Healthy volunteers	Number and severity of adverse events	CM326 (s.c.)	18 to 65
				Anti-TSLP receptor			
23.	NCT05448651 (Active as at 2023/06/23)		1	Mild asthma	AEs and severe AEs	UPB-101 (s.c.)	18 to 60
				Anti-IL-33			
24.	NCT03387852		2	Moderate to severe	Loss of asthma control	Itepekimab aka SAR440340 (s.c.)	18 to 70
25.	NCT03469934		2	Severe eosinophilic asthma	Safety and change in blood eosinophil count	Etokimab aka ANB020 (s.c.)	18 to 65
				Anti-ST2			
26.	NCT04570657	FRONTIER-3	2	Moderate to severe	Baseline FEV_1	Tozorakimab aka MEDI-3506	18 to 65
27.	NCT02918019		2	Severe uncontrolled asthma	Reduction in AER	Astegolimab aka MSTT1041A (s.c.)	18 to 75
28.	NCT03207243 (Terminated: high screen failure rate & low enrollment)		2	Moderate to severe	Loss of asthma control	Melrilimab aka GSK3772847 (i.v.)	18 and older
				Anti-IL-25			
29.	NCT01199289		2	Moderate to severe	Change in ACQ score from baseline	AMG 827 aka brodalumab (s.c.)	18 to 65

TSLP: tissue stromal lymphopoietin, AEs: adverse events, TEAEs: treatment-emergent adverse events, aka: also known as; PK: pharmacokinetic, AER: asthma exacerbation rate, OCS: oral corticosteroids, ICS: inhaled corticosteroids, LABA: long-acting β_2 agonist, Inh: inhaled; and ACQ: Asthma Control Questionnaire.

Despite strong evidence showing the upregulation of IL-25 and IL-17RA and B receptor subunits in asthma, as well as the role of IL-25 signaling in the development of cardinal asthma features,[2] the only clinical trial targeting this pathway using brodalumab to block IL-17RA reported no improvement on the primary outcome (FEV_1).[11] Although it is possible that the role of IL-25 in the pathobiology of human asthma may not be as crucial as that of IL-33 and TSLP, this cannot be concluded without first investigating the effects of blocking IL-17RB or IL-25 in clinical trials.

The anticipated higher efficacy of anti-alarmin therapies versus biologics targeting downstream inflammatory cytokines is based on the idea that regulation of alarmin signaling also broadly impacts multiple relevant downstream inflammatory pathways. In support, dual therapy with the anti-IL-33 mAb itepekimab plus dupilumab (inhibiting downstream IL-13) found no superior outcome from the combined therapy.[8] In contrast, however, a study of a bifunctional NANOBODY molecule (SAR443765) targeting both TSLP and IL-13 reported a greater reduction in fractional exhaled nitric oxide and T2 biomarker levels when compared with monovalent TSLP or IL-13 mAb (NCT05366764). Whether combining anti-alarmin therapy with blockade of downstream pathways such as IL-13 will be a more effective approach or not requires an improved understanding of asthma pathobiology and disease endotypes.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to the drafting, writing, and reviewing of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Could APO-varenicline and cytisine be solutions for the shortage of varenicline in Brazil?

Paulo César Rodrigues Pinto Corrêa[1], José Miguel Chatkin[2]

The presence of N-nitrosamines in pharmaceutical products gained notoriety in 2018, when the regulatory agencies European Medicine Agency and U.S. Food and Drug Administration (FDA) became aware of the presence of N-nitrosodimethylamine in angiotensin II receptor antagonists (known as belonging to the group of sartans).[1] After that, there has been a concomitant recall of these drugs in the United States, European countries, Australia, and New Zealand.

On June 9, 2021, Pfizer Brazil announced that its varenicline tartrate, marketed in Brazil as Champix®, in all its forms would undergo a temporary withdrawal.[2] No mention to a nitrosamine impurity was made. On July 16, 2021 Pfizer USA issued a voluntary recall for twelve lots of varenicline distributed in the United States and Puerto Rico between June of 2019 and June of 2021 due to the presence of a nitrosamine.[3] Over the next couple of months, both Pfizer USA and Pfizer Europe voluntarily recalled other lots of varenicline, also due to elevated amounts of N-nitroso-varenicline (NNV), and subsequently announced the interruption of production and distribution of the drug globally.[4]

There was a significant reduction of varenicline use by the limited delivery of the drug to pharmacies and its consequent withdrawal from all the world market. According to Lang et al.,[5] during the restriction period in the USA (between January of 2021 and June of 2022), no increase in the prescription/consumption of any form of nicotine replacement therapy (NRT) or prolonged-release bupropion was detected. The authors emphasized that a considerable number of smokers would probably have given up their smoking cessation treatment. That study did not take account of the consumption of the aforementioned drugs without medical prescription (over-the-counter NRT purchases), since the study was limited only to those with commercial insurance.[5]

In August of 2021, the FDA released its laboratory analysis of varenicline products available in the USA, informing NNV levels above FDA's acceptable intake limit in some samples.[6] In the same document, the Agency described the analytical methods to be used in laboratory testing.[6] Few months later, in November of 2021, the FDA published an update on risk mitigation strategies, encouraging manufacturers to explore the approaches to attenuate or prevent the formation of impurities.[7] After the detection of NNV, different approaches to control impurities could have been used. Safety-based limits, such as permissible daily exposure, acceptable intake, threshold of toxicological concern, and less-than-lifetime limits were all possibilities.[8]

FDA scientists stated that NNV might increase the risk of cancer if the exposure is above the acceptable intake limit and over a prolonged period.[6] However, a person taking a drug containing NNV at or below the acceptable intake limit every day for 70 years was not expected to have an increased risk of cancer. The FDA concluded that consuming up to 37 ng of NNV/day, the acceptable intake limit, was reasonably safe for humans.[6] The Agency also evaluated the risk of exposure to NNV at levels up to 185 ng per day and found a minimal additional cancer risk when compared with a lifetime of exposure to NNV.[6]

These movements and findings of international agencies had repercussions in the Brazilian *Agência Nacional de Vigilância Sanitária* (ANVISA, Health Regulatory Agency) and in Pfizer Brazil, the international manufacturer of this medication.

On July 6, 2021, the ANVISA issued Guide 50 version 1 to help "varenicline sponsors" further investigate and handle the issue of varenicline contamination with nitrosamine impurities. Later on, the ANVISA launched a public consultation on this subject to assess the risks of using the drug and how to control the potentially carcinogenic nitrosamines for human use.[9] On May 4, 2022, the ANVISA released the second version of Guide 50/2022[10] and published the Collegiate Directorate Resolution no. 677/2022 on the control of nitrosamines in acceptable intake limits.[11] The new version of the guide entered into force immediately and the Resolution established that pharmaceutical companies should develop a risk matrix clearly defining the sequence of evaluation of the products in their portfolio, contemplating the risk categories as "very high", "high", "medium", "low", and "very low".[11]

Pharmaceutical companies must meet the requirements set forth in that Resolution for risk assessment of products classified as at a "very high" risk by March 1, 2023: that was the deadline for Pfizer Brazil and its varenicline medication. A review on the development of the analytical methods for determining nitrosamine and N-nitroso impurities in pharmaceuticals has been published recently.[12]

The smoking cessation landscape in Brazil has been worrisome for quite a while. Apart from the continued shortage of varenicline since 2020,[13] there has been a scarcity of NRT in all its forms in several health care facilities of the Brazilian *Sistema Público de Saúde* (SUS, Unified Health Care System). Unfortunately, there are no resupply dates yet. As far as we know, the Brazilian Ministry of Health has not yet considered importing APO-varenicline, the generic varenicline tartrate product

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approved by international agencies as a generic equivalent to Champix® tablets.

An alternative to Pfizer's varenicline is the generic varenicline tartrate tablets produced by PAR Pharmaceutical (Woodcliff Lake, NJ, USA), which has already been approved by the FDA.[6] In addition there is also APO-varenicline® tablets (Apotex Corp, Toronto, Canada), which is available in North America and Australia. Both generic products contain levels of NNV impurity below the acceptable intake and could/should be imported to enable Brazilian smokers to be motivated to quit their drug addiction more easily.

Another possibility could be cytisine, an alkaloid that binds with high affinity to nicotinic acetylcholine alpha4-beta2 receptors, the very same mechanism of action of varenicline. Cytisine has been used in several countries in Eastern Europe since the 1960s as a low-cost alternative in smoking cessation. It is now available over the counter as a useful drug for smoking cessation in 18 European countries, including Italy, Poland, and Portugal.[14]

In 2014, Walker et al.[15] reported that, when combined with brief behavioral support, cytisine was superior to NRT in helping smokers quit smoking, but it was associated with a higher frequency of self-reported adverse events. The most common adverse events were gastrointestinal symptoms, comprising abdominal swelling, gastritis, and constipation. More recently, Walker et al.[14] conducted another study to determine whether cytisine was at least as effective as varenicline in supporting smoking abstinence for ≥ 6 months in New Zealand indigenous populations. Smokers received a prescription for 12 weeks of cytisine or varenicline, plus low-intensity cessation behavioral support from the prescribing doctor and community stop-smoking services or a research assistant. Continuous abstinence rates at 6 months post-cessation date were 12.1% in cytisine users vs. 7.9% in varenicline users (risk difference, 4.29%; relative risk = 1.55).[15] At the 12-month follow-up in the latter study, the smoking cessation rate was 32.1% in the intervention arm and 7.3% in the control arm).[14] The adjusted OR for continuous abstinence was 7.2 (95% CI, 4.6-11.2).[14] Self-reported adverse events over 6 months significantly occurred more frequently in the varenicline group (varenicline: 509 events in 138 participants vs. cytisine: 313 events in 111 participants), with incidence rate ratio of 0.56. Common adverse events were nausea, headache, and difficulty in sleeping. The authors concluded that cytisine, a very low-cost medication, is safe and at least as effective as varenicline in supporting smoking cessation.[14]

Courtney et al.[16] failed to demonstrate noninferiority of cytisine compared with varenicline regarding smoking cessation. It should be considered, however, that the authors adopted the standard 25-day treatment regimen for cytisine, which sets the cessation date at day 5 after initiation of the medication. At the end of the first month (at which point the cytisine treatment was finished), self-reported abstinence in the previous week were 42.5% and 32.3% with the use of cytisine and varenicline, respectively.[16] Another important point regarding that clinical trial was that the behavioral support was close to none: participants got only a referral to a telephone smoking cessation line.[16] Thus, it would be worth testing a longer treatment period with cytisine with appropriate behavioral support in future studies.

There has been some private research investment on cytisine following the commercialization and patent of cytisine succinate[16] and mesylate salts[17] as new drug products. A simplified dosing cytisine regimen (1.5 mg and 3 mg three times daily) with two administration schedules (commercial titration vs. simplified three times daily) within a 25-day treatment period was tested in the a multicenter, double-blind, randomized, placebo-controlled phase 2b trial conducted in the USA.[18] Patients received 12 behavioral support sessions by a qualified staff member plus supportive literature and online resources. The 3-mg dose/schedule three times a day (no titration)[18] was selected for further evaluation in a phase 3 program that was designed to evaluate the efficacy and safety of 3-mg dose three times daily when compared with placebo and also longer treatment schedules (like Courtney et al.[16] suggested) to reduce potential relapses in smoking. Both studies have been completed; the second study completion date was March 21, 2023.[19] Their results have not been published yet. Achieve Life Sciences intends to develop and commercialize cytisine (also known as cytisinicline) in the USA, and thereafter to target other markets such as Western Europe, Japan, and Latin America.[20]

There have been some interactions between regulators and industry to address how NNV should be controlled, but the FDA has not changed its 2020 update guidance yet. A "nitrites in excipients" database has been developed by the industry to facilitate risk assessment of drug products,[21,22] but there are still gaps in knowledge on novel nitrosamines and more research is needed to address nitrosamine impurities. Getting rid of NNV is a Herculean task: a number of factors are involved, including the chemical structure of varenicline, manufacturing processes, storage, and/or packaging conditions.

Pfizer's varenicline, the most effective smoking cessation drug, has been unavailable in Brazil since 2020 and will not be available in the near future (if it will ever be again). However, there are generic varenicline tartrate products in the global market that are available for quite some time in many countries. Law no. 12,401 created the Brazilian National Committee for Technology Incorporation, defining both the criteria and deadlines for technology incorporation in the SUS.[23] The committee is responsible for advising the Brazilian Ministry of Health regarding the incorporation or disinvestment of health technologies in the SUS and development of clinical guidelines.[23] The time has come for the Committee to start the process of incorporation of APO-varenicline within the SUS.

AUTHOR CONTRIBUTIONS

The authors equally contributed to this work.

CONFLICTS OF INTEREST

None declared.

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The MECOR program: almost three decades inspiring and improving respiratory clinical research in Brazil and across the globe

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Physicians and other healthcare workers can have several professional roles. Besides our core role as clinicians, many of us also have roles as researchers and/or educators. These roles have long been part of the practice of Medicine and are contemplated in the Hippocratic Oath, which includes the duty to share scientific knowledge and teach the next generation of physicians.[1] However, our formal training in medical school and residency is largely focused on clinical skills, while the necessary skills to design and conduct research or to teach residents and medical students is usually learned on the go, by imitation, leading to less than ideal performance and contributing to burnout and low self-confidence.[2]

In Brazil, clinical research is mainly conducted by investigators who have a PhD degree or a Master's degree in Science, and by graduate students enrolled in PhD's and Master's programs. Such programs last three to four years, require full-time dedication, are unevenly distributed across the country,[3] and scholarships are scarce and financially unattractive. As a result, many clinicians who wish to conduct research may be discouraged from doing so because of insufficient training, and there is a need to strengthen research capacity in the country.[4,5]

In this scenario, the American Thoracic Society (ATS) Methods in Epidemiologic, Clinical, and Operations Research (MECOR) program offers an opportunity to learn research methodology with a hands-on approach by providing an annual course, during which students from all Latin America spend an immersive week learning how to conduct research by designing, analyzing, and interpreting the results of their own research projects. The MECOR program is intended for clinicians, investigators, academicians, and public health care professionals, being created by the ATS to strengthen the capacity and leadership in epidemiological, clinical, and operational research related to respiratory diseases, intensive care medicine, and sleep medicine in low- and middle-income countries.

Since the initiation of the program in Latin America in 1994, the scope of the ATS MECOR program has grown tremendously. Today, the program's footprint is truly global, with courses running in seven regions/countries across the globe annually and involving more than 1,800 graduates. In Latin America, it is now jointly supported by the ATS, the *Asociación Latinoamericana de Tórax* (ALAT), and the respiratory society that hosts the annual meeting each year, including the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT). At the end of 2021, 621 Brazilian students had attended MECOR courses, comprising approximately 35% of the students from Latin America.[6]

One of the many strengths of the program is that it offers the opportunity to learn by doing, with the supervision of dedicated faculty and mentors, and feedback from peers. During the week, students work on their own projects, which they then conduct when they go home to their countries and institutions. This educational method is powerful because it incorporates many aspects of adult learning theory and active learning, and students report high rates of satisfaction with the program.[7] Beyond satisfaction, graduates report good outcomes with the publishing of the results of their projects,[8] and, since 2012, most of the faculty in Latin America have been graduates of the program, including course directors.

Throughout the 29 years of MECOR in Latin America, numerous SBPT members have actively participated in the program, many of them subsequently assuming leadership positions in their institutions and within the SBPT. The current and the past SBPT presidents, for example, have been MECOR students. The objective of the MECOR program aligns with the SBPT's mission to promote continuous professional growth and excellence, and to stimulate partnerships and scientific research.[9] This partnership has resulted in seven MECOR courses held in Brazil so far.

There is a need for research capacity building in Brazil, and the partnership between SBPT and the ATS MECOR program has impacted the careers of many researchers in Respiratory Science. As graduates of the program rise to leadership positions in their institutions and pass on their knowledge and skills learned during the MECOR program to their trainees, this virtuous cycle has the potential to make a difference in medical education and research careers, with the final goal of improving Respiratory Health in Latin America.

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The challenges of asthma care in low- and middle-income countries: what's next?

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Asthma is a global health concern that affects millions of people worldwide, placing a significant burden on individuals, families, and communities. This chronic respiratory condition can have a profound impact on the quality of life and productivity of the patients. Understanding the global burden of asthma and recognizing the importance of asthma care for all is crucial to address this widespread issue globally. Firstly, it is essential to acknowledge the scale of the problem. Asthma is estimated to affect over 300 million people globally, and its prevalence continues to rise steadily. This chronic disease knows no boundaries and affects people of all ages, races, and socioeconomic backgrounds. From high-income nations to low- and middle-income countries (LMICs), asthma is a universal health challenge that demands attention.[1] The burden of asthma extends beyond individual suffering. Families with asthma members often face emotional, financial, and practical challenges. Frequent visits to healthcare facilities, medical expenses, and the need for ongoing treatment can strain household budgets. Moreover, asthma-related emergencies and hospitalizations can disrupt daily routines, impact education and work, and diminish the overall quality of life for both patients and families.[1] For the 2023 World Asthma Day (May 2), the GINA chose the theme "Asthma Care for All", acknowledging the importance of initiatives for achieving the best diagnostic and management practices for all patients with asthma, regardless of the country economic development.[2] The majority of the burden of asthma morbidity and mortality occurs in LMICs.[3] Some LMICs report very high rates (up to 90%) of uncontrolled asthma.[4,5] The GINA strives to reduce this burden by encouraging healthcare leaders to ensure the availability of and access to effective, quality-assured medications.[2]

Inadequate access to asthma care exacerbates the burden experienced by the individuals affected. Disparities in healthcare resources and limited availability of affordable medications, particularly in LMICs, hinder the effective management of the condition. This lack of access can lead to uncontrolled asthma, as well as increased hospitalizations and deaths.[6] It is crucial to recognize that proper asthma care, including accurate diagnosis, appropriate medication, regular monitoring, and patient education, can significantly improve outcomes and reduce the burden of the disease.[2] Addressing the burden of asthma requires a comprehensive and collaborative approach. Governments, healthcare systems, policymakers, and communities must prioritize asthma as a public health concern, especially in regard to severe asthma.[1,7] Increased investment in asthma research, improved access to affordable medications, particularly those for severe asthma, and enhanced healthcare infrastructure are necessary steps toward achieving effective asthma management on a global scale.[6] Education and awareness also play a pivotal role in reducing the burden of asthma. Promoting asthma education among healthcare professionals, patients, and their families is vital for early detection of the disease, proper self-management, and prevention of exacerbations. By globally empowering individuals with knowledge and skills, we can foster a proactive approach to asthma care that improves health outcomes and reduces the burden on individuals and societies.[1,2,6,7]

In LMICs, the lack of disease awareness and that of access to adequate asthma treatment pose a significant challenge and exacerbate the burden of this chronic respiratory condition in these populations. Several factors contribute to the difficulties faced by individuals in LMICs when seeking asthma care, as follows: 1) healthcare infrastructure (limited healthcare infrastructure, including a shortage of healthcare facilities, medical professionals, and essential medical supplies); 2) affordability (the cost of asthma medications and limited financial resources); 3) limited availability (inadequate availability of asthma medications); 4) lack of awareness and education about the disease (from patients and health professionals); and 5) cultural and social factors (cultural beliefs and social stigmas surrounding chronic illnesses).[1,2,6,7] Addressing the challenges of accessing the best asthma management in LMICs requires a multifaceted approach. Efforts should focus on improving healthcare infrastructure, including expanding the number of healthcare facilities, training healthcare professionals, and ensuring the availability of essential medications at affordable prices. Public health campaigns aimed at increasing awareness and education about asthma, its management, and the importance of seeking medical care timely are also crucial. Collaboration between governments, healthcare organizations, medical societies, and international agencies is essential to mobilize resources and develop sustainable strategies for improving asthma care access in LMICs.[1,2,6] The difficulties to raise resources for interventional studies addressing important unanswered questions on asthma focusing on LMICs populations are also a challenge to be overcome.[1]

In conclusion, the burden of asthma is a significant global challenge that affects millions of people worldwide, particularly in LMICs. Recognizing the importance of "asthma care for all" is crucial for addressing this issue. Only by empowering all the stakeholders (patients, patients' nongovernmental organizations, healthcare organizations,

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governments, policymakers, and medical societies) to address all barriers to asthma management, increasing access to affordable medications, education, and awareness, as well as prioritizing asthma as a public health concern, we will be able to alleviate the burden on individuals, families, and communities, ultimately improving the quality of life for those living with asthma in these populations.

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Multiple vascular nodules

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

A 17-year-old man presented with complaints of sudden-onset hemoptysis. Chest CT showed bilateral pulmonary nodules (Figure 1A), which were opacified after injection of iodinated contrast medium (Figure 1B).

Unenhanced CT showed multiple nodules with partially defined borders, predominantly in the lower lobes. The differential diagnosis of multiple nodular lesions is wide, including neoplastic and infectious diseases, among others. However, this patient had two findings—a clinical finding (hemoptysis) and a CT finding (all nodules were adjacent to bronchi)—that raised the possibility of vascular origin, which mandatorily led to the intravenous injection of contrast medium. Contrast-enhanced imaging demonstrated that the nodules corresponded to pulmonary artery aneurysms.

Pulmonary artery aneurysms may be due to numerous causes, such as congenital, infectious, and neoplastic diseases, as well as vasculitis, iatrogenic and traumatic causes, among others. Multiple bilateral lesions are most commonly associated with vasculitis. The two major types of vasculitis that cause this finding are Hughes-Stovin syndrome and Behçet's disease. Hughes-Stovin syndrome is characterized by the combination of multiple pulmonary artery aneurysms and deep vein thrombosis. Since the radiological findings of Hughes-Stovin syndrome are indistinguishable from those of Behçet's disease, some researchers have suggested that this syndrome is part of a spectrum, along with Behçet's disease.[1-3]

In our case, because of the finding of aneurysms, the patient underwent clinical reassessment, which detected painful, recurrent oral and genital ulcerations, thus characterizing the diagnosis of Behçet's disease. The diagnosis of Behçet's disease is based on the presence of recurrent oral ulcerations together with two of the following criteria: genital ulcerations, eye lesions (uveitis or retinal vasculitis), skin lesions, or a positive skin pathergy test. On the basis of the findings of oral and genital ulcerations and pulmonary artery aneurysms, our patient met the criteria for the diagnosis of Behçet's disease.

Pulmonary vascular changes, such as aortic and pulmonary artery aneurysms, are rare complications of Behçet's disease, suggest a poor prognosis, and are the main cause of mortality due to the possibility of rupture. Hemoptysis is the most common presenting symptom of pulmonary artery aneurysms. More than half of patients die from pulmonary hemorrhage within three years.[1-3] Our patient has been followed on an outpatient basis for six months, and there have been no complications.

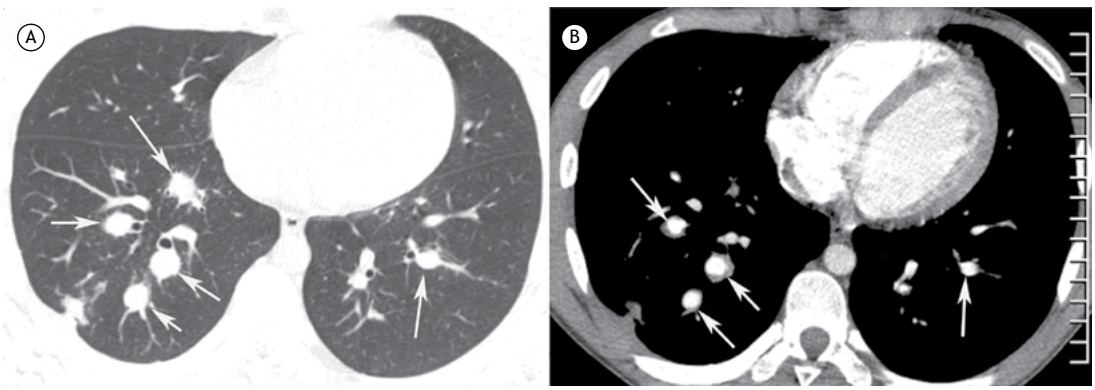

Figure 1. In A, unenhanced CT scan of the chest (lung window) showing multiple nodules (arrows) in the lower lobes, adjacent to the bronchi. In B, iodinated contrast-enhanced CT image (lung window) showing contrast opacification of the nodules (arrows), characterizing pulmonary artery aneurysms.

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Losing your fear of using R for statistical analysis

Iara Shimizu[1,2], Juliana Carvalho Ferreira[2,3]

WHAT IS R?

R is a programming language widely used in health research, as it provides a vast collection of software packages that encompass a wide range of data analysis techniques to conduct from simple to complex statistical analyses, to create graphics and figures, and to design websites and apps.

Because it is a programming language, it requires input through a command line, which may seem intimidating to nonprogrammers. However, even if you have never programmed before, there are several tips to get started and gradually learn how to use R, including preset software packages that extend the capabilities of basic R and allow users to perform specialized tasks without having to write all of the code from scratch.

ADVANTAGES OF R

Being an open-source program, R facilitates changes in analyses and ensures reproducibility of results in new datasets, allowing you to document and share your analyses in a systematic and organized way, in addition to the possibility of creating reproducible reports that combine code, text, and visualizations in a single document.

For researchers who do not want to use commercial statistical software, R is an option because it is free and adaptable to different operating systems.

One of the greatest advantages of R is its online support, since it has a very extensive and active community of users around the world, who continually develop new functionalities for the program and offer solutions to the various questions that may arise.

GETTING STARTED WITH R AND RSTUDIO

To get started with R programming for statistical analysis in health research, you can follow these steps, summarized in Figure 1.

1. Installing R and RStudio—Install R and RStudio on your computer. R is a programming language used for statistical computing and graphics, and RStudio is a program designed for working with R programming language, providing a user-friendly interface. Visit the official R website[1] and download the appropriate version for your operating system. There is also the possibility of using an online version that does not require installation of any software.[2]
2. Importing data into R—This involves extracting data from a file or database and importing them into an R data frame. You can import data into R from various sources, such as CSV files, Excel files, or databases, and manage the data by filtering, sorting, merging, or transforming datasets. If you do not have data of your own, R has a list of open data sets that can be used to gain hands-on experience and improve programming skills.
3. Learning R coding basics—Get familiar with the basic language of R. There are several free online tutorials, books, and resources available for learning R, such as the "Hands-On Programming with R"[3] for programming beginners. To use the R program, you enter the instructions, known as commands, which direct R to perform a specific task, such as calculate the mean of a variable or perform a t-test to compare two groups. If you type a command that R does not recognize, it will return an error message. If that happens, do not panic! Read the error message to understand the problem, review the command that you have typed for any mistakes or syntax errors, or search for solutions online using help pages in R or in communities and forums.
4. Statistical analysis—R has a system with a varied number of packages designed specifically for statistical analysis, such as basic R functions, stats package, survival analysis package, and more specialized packages; packages not included in

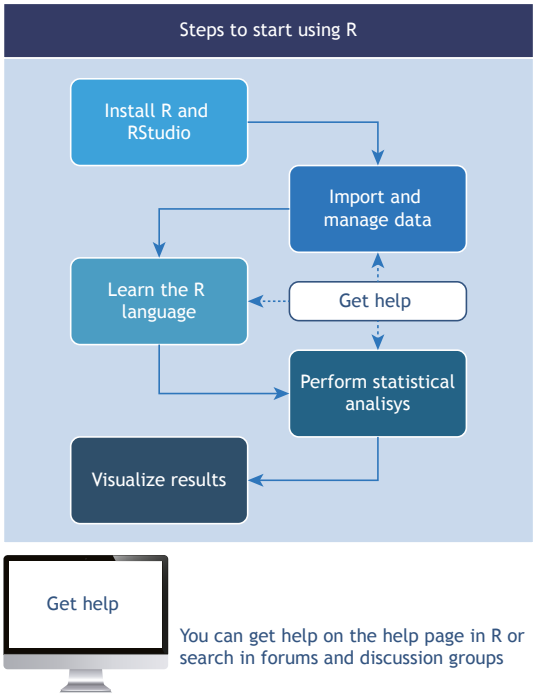

Figure 1. Steps to start using R.

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the basic software need to be installed. However, basic statistical analysis can be performed with a few simple and easy-to-learn commands.

5. Visualization of results—R provides a diverse range of packages that enable the generation of high-quality figures and charts. Researchers can create figures and charts that facilitate a deeper understanding of the data and aid in the communication of key results.
6. Getting help—Each R function comes with its own help page that you can access by typing the name of the function preceded by a question mark. R community forums and discussion groups allow you to submit a question or search through previously answered questions. Participating in the community will expose you to different perspectives, new techniques, and useful resources.

In conclusion, learning R programming for statistical analysis is like learning a new language: it may seem somewhat difficult in the beginning, but as you learn, it becomes easier. We recommend that, as a new user, you start with small projects to gradually build your skills and explore advanced techniques as you go.

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Using the pulmonary function laboratory to assist in disease management: COPD

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BACKGROUND

This is the first of a series of concise manuscripts focused on how best to use the pulmonary function laboratory for diagnosis, assessment of disease severity/risk estimation, and selection of treatment strategies in prevalent respiratory and nonrespiratory diseases. We start with a heterogeneous lung disease in which pulmonary function tests (PFTs) assume a pivotal role in each of these domains: COPD.[1]

OVERVIEW

A 61-year-old man with a smoking history of 21 pack-years was referred to Respirology because of "out-of-proportion" dyspnea (modified Medical Research Council dyspnea scale [mMRC] score = 2-3) relative to preserved FEV_1 and FEV_1/FVC ratio, and a non-significant volume (FVC) response to short-acting bronchodilator. Given the nonobstructive findings on spirometry and lack of improvement after treatment with two different long-acting muscarinic antagonists (LAMAs), the referring physician was uncertain of the diagnosis of COPD. Repeat PFTs showed low $FEF_{25-75\%}$, "scooping" of the expiratory flow-volume curve at low lung volumes, low inspiratory capacity (IC), a mild but consistent increase in residual volume and functional residual capacity (either absolute or relative to TLC), increased specific airway resistance, low DL_{co}, and low alveolar volume/TLC. Cardiopulmonary exercise testing showed excess ventilation and dynamic hyperinflation leading to inspiratory constraints and limiting dyspnea. COPD was confirmed, and treatment was escalated to dual therapy with long-acting β_2 agonist (LABA)/LAMA. A two-month course of dual LABA/LAMA therapy was associated with improvement in dyspnea (mMRC score = 1), allowing the patient to enroll in a structured reconditioning exercise program.

Regrettably, the role of PFTs in COPD management has been progressively devalued in influential guidelines. The 2023 GOLD report, for instance, confirms previous versions by recommending forced spirometry for diagnosis only.[2] Despite suggesting the grading of FEV_1 impairment, little emphasis is given to its use (or to the use of any other functional marker) in treatment choices. Simply sticking to a rigid FEV_1/FVC cutoff for diagnosis can lead to misinterpretation, requiring careful individualization.[3] Findings of decreased available volume for tidal expansion (i.e., low IC) and/or increased "static" lung volumes give unique insights into the genesis and severity of COPD-related dyspnea. There is a large variability in key determinants of breathlessness at a given FEV_1: the severity of lung mechanical impairment (as determined by measurements of lung volumes) and gas exchange inefficiency (as assessed by DL_{co} and carbon monoxide transfer coefficient) is much more informative.[4] As depicted in Chart 1, this knowledge may have important implications for pharmacological and nonpharmacological treatment. Simple tests of functional exercise capacity, such as the six-minute walk test, might prove useful in quantifying patient impairment, in determining the potential need for exertional oxygen supplementation, and in prognostic estimation in multiparametric indexes. As shown herein, incremental cardiopulmonary exercise testing might indicate that "the lungs" do contribute to exertional dyspnea, thereby prompting treatment optimization in equivocal cases.[5]

CLINICAL MESSAGE

It is unlikely that the clinical and surgical management of COPD will ever dispense with functional data. The pulmonologist should combine the information provided by PFTs with clinical data (e.g., dyspnea severity, exacerbation burden), blood workup data (e.g., eosinophil count, IgE and alpha-1 antitrypsin levels), and structural findings (e.g., emphysema burden and distribution, airway disease) to decide on the best clinical or surgical treatment approaches (Chart 1).

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Chart 1. Key pulmonary function test data that are more likely to influence COPD management in individual patients.*

Clinical scenario	Recommendations
Diagnosis	• ↓Post-BD FEV_1/FVC is virtually diagnostic of COPD in the right clinical context • Post-BD FEV_1/FVC ≥ LLN but < 0.7 requires a case-by-case approach to identify other markers of obstruction/airway disease: ↓FEV_1, ↓$FEF_{25-75\%}$ (corrected for FVC or not), ↓FEV_3/FEV_6, "scooping" of the expiratory flow-volume curve, ↑sRaw, ↑RV and/or FRC, ↓DL_{CO} and/or K_{CO}, or V_A/TLC < 0.80. The higher the number of abnormalities, the greater the likelihood of disease. Chest imaging correlation might also be helpful • ↓Post-BD FEV_1/slow VC alone should be used with caution, as it increases the number of false positives for obstruction in the elderly • Spirometry normalization after inhaled BD speaks against COPD but may occur in the initial stages of the disease in a patient with dominant chronic bronchitis • Mild to moderate, proportional decrements in FEV_1 and FVC with ↔ FEV_1/FVC and ↔ TLC (the "nonspecific pattern") may occur in COPD: a volume response to inhaled BD and/or other markers of obstruction might be helpful to confirm COPD in the right clinical context • ↔ DL_{CO} does not exclude COPD: although it speaks against substantial emphysema, it may occur in patients with dominant airway disease/chronic bronchitis • When V_A/TLC < 0.80, K_{CO} might be pseudo-normal despite ↓DL_{CO}. If K_{CO} is reduced despite a low V_A/TLC, extensive emphysema should be suspected • CPET might provide further confirmatory evidence of COPD in equivocal cases: excess ventilation ($\dot{V}_E/\dot{V}CO_2$ nadir ≥ 34 L/L), dynamic hyperinflation, inspiratory constraints, or↑dyspnea-work rate and ↑dyspnea-$\dot{V}_E$ slopes
Disease severity/ risk estimation	• Post-BD FEV_1 yields only a rough estimate of a patient's ventilatory capacity • ↓FVC and/or VC usually indicate more severe disease (↑RV/TLC, frequently ↓IC) • ↓IC and/or IC/TLC are strong predictors of exertional dyspnea. In those with ↔ IC, ↑FRC (and, consequently, ↑TLC) also predicts a greater dyspnea burden • Increased "static" lung volumes at a given FEV_1 provide a better insight into the mechanical abnormalities relevant to dyspnea genesis, the functional reserve required to face the consequences of an exacerbation, and the severity of negative cardiopulmonary interactions, all of which have prognostic implications • Regardless of underlying mechanisms, the severity of DL_{CO} impairment predicts morbidity and mortality • 6MWD independently predicts poorer outcome, being used in multiparametric indexes of disease severity/prognosis • Hypoxemia and, in particular, hypercapnia indicate more extensive disease and poorer prognosis • In patients with dyspnea that is out of proportion (as per the mMRC score) to the severity of FEV_1 impairment, an increased resting and exercise physiological dead space may uncover a key determinant of breathlessness • Excess ventilation and early critical inspiratory constraints during CPET provide important clues regarding disease severity and daily life dyspnea, being associated with poorer survival • Short-term decreases in FEV_1 or FVC of ≥ 20% are considered "significant," although less pronounced decrements might be relevant in patients with greater impairment. Thresholds for year-to-year decrease are not well established and should be considered on a case-by-case basis • Decreases in DL_{CO} of > 4 units or > 15% (whichever is greater) indicate a fast decline, usually associated with progressive emphysema

Continue...▶

Chart 1. Key pulmonary function test data that are more likely to influence COPD management in individual patients.* (Continued...)

Clinical scenario	Recommendations
Clinical management	• A "negative" response to inhaled BD during spirometry should *not* be used as evidence against its use on a long-term basis • A volume response to inhaled BD (i.e., an increase in FVC and/or VC of ≥ 10%, or an increase in IC ≥ 0.2 L) is more relevant to dyspnea improvement than are changes in FEV_1 • A large volume response to inhaled BD (i.e., a large increase in FVC) might be associated with similar improvement in FEV_1: the latter finding should not be unrestrictedly used as evidence of associated asthma • Increased longitudinal variability in FEV_1—particularly when FVC varies little—may suggest associated asthma in the right clinical context, thereby prompting a more liberal use of ICS • Severe lung hyperinflation and/or gas trapping indicate worse abnormalities in the "slow" compartment (small airways): BDs/inhalers with greater distal deposition might be particularly effective • Inspiratory muscle weakness (e.g., MIP < 70% predicted) might prompt inspiratory muscle training in dyspneic, maximally treated patients—particularly if dyspnea is out of proportion (as per the mMRC score) to only mild to moderate gas trapping • BiPAP may be considered for those with pronounced daytime hypercapnia ($Paco_2$ > 50-55 mmHg) and/or recent/frequent hospitalization for acute-on-chronic respiratory failure; conversely, CPAP should be offered to those with comorbid OSA • Resting oxygen supplementation targeting Sao_2 > 90% (88-92% in hypercapnic patients) should be offered to those with Pao_2 ≤ 55 mmHg or Sao_2 < 88% or Pao_2 of 56-59 mmHg and right heart failure or erythrocytosis on room air • Some dyspneic patients do derive symptomatic benefit from exertional oxygen supplementation when Sao_2/Spo_2 < 88% on room air • Patients with FEV_1 of 15-45% predicted, TLC ≥ 100% predicted, severe gas trapping (RV ≥ 175%), and DL_{co} > 20% of predicted are more likely to report benefit after bronchoscopic lung volume reduction • Noninvasive mechanical ventilation during acute exacerbations is indicated in the presence of respiratory acidosis ($Paco_2$ ≥ 45 mmHg, pH ≤ 7.35) • Persistent or worsening hypoxemia (Pao_2 < 40 mmHg) and/or severe/worsening respiratory acidosis ($Paco_2$ ≥ 60 mmHg and increasing, pH ≤ 7.25 and decreasing) despite supplemental oxygen (via Venturi mask or requiring Fio_2 > 0.4) and noninvasive ventilation during exacerbations should prompt admission to intensive care for life-threatening acute respiratory failure
Surgical management	• TLC > 100% predicted, severe gas trapping (RV > 150% predicted), pronounced decrement in VA/TLC, ↔ or near normal DL_{co}, and ↔ arterial blood gases are useful to predict which patients are prone to derive greater symptomatic benefit from giant bullectomy • Post-BD FEV_1 < 45% predicted, RV > 150% predicted, and TLC > 100% predicted help in identifying adequate candidates for lung volume reduction surgery among those with reduced exercise capacity and dominant upper-lobe-predominant emphysema; conversely, the risk of perioperative death increases in those with FEV_1 and/or DL_{co} < 20% predicted • Patients who are not candidates for lung volume reduction and have a homogeneous distribution of emphysema, post-BD FEV_1 and/or DL_{co} < 20% of predicted, and a history of exacerbations associated with moderate to severe hypercapnia ($Paco_2$ > 50 mmHg), pulmonary hypertension, and/or cor pulmonale despite oxygen therapy are potential candidates for lung transplantation

BD: bronchodilator; LLN: lower limit of normal; FEV_3: forced expiratory volume in three seconds; FEV_6: forced expiratory volume in six seconds; sRaw: specific airway resistance; FRC: functional residual capacity; K_{co}: carbon monoxide transfer coefficient; V_A: alveolar volume; CPET: cardiopulmonary exercise testing; $\dot{V}_E$: minute ventilation; $\dot{V}co_2$: carbon dioxide output; IC: inspiratory capacity; 6MWD: six-minute walk distance; ICS: inhaled corticosteroids; mMRC: modified Medical Research Council dyspnea scale; and OSA: obstructive sleep apnea. *Unless otherwise indicated, ↑, ↔, and ↓ values are relative to the statistical limits of normal.

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ORIGINAL ARTICLE

Handgrip strength as a diagnostic tool for frailty risk in elderly patients with moderate to severe asthma

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Study carried out at the Fundação Programa para o Controle da Asma na Bahia – ProAR – Salvador (BA) Brasil.

ABSTRACT

Objective: To evaluate handgrip strength (HGS) as a diagnostic tool for frailty risk in elderly patients with asthma, as well as to investigate the prevalence of frailty in this population. **Methods:** This was a cross-sectional study including 96 patients ≥ 60 years of age diagnosed with moderate to severe asthma and treated at a tertiary referral center in Brazil. We measured HGS using a calibrated hydraulic hand dynamometer. We used a frailty scale and the AUC to assess the diagnostic accuracy of the HGS test. **Results:** The median age of participants was 67 years. Most (78%) were women and non-White (91%) of low socioeconomic status. HGS identified those at risk for frailty, with an AUC of 71.6% (61.5-80.4%; $p < 0.002$), as well as a sensitivity of 73.58% and a specificity of 67.53%, on the basis of a cutoff of ≤ 19 kgf. **Conclusions:** HGS appears to be a simple, reliable tool for clinicians to determine frailty risk in older asthma patients in a point-of-care setting.

Keywords: Hand strength; Frailty; Asthma; Aged.

INTRODUCTION

Aging promotes physiological changes related to increased proinflammatory cytokine activity, resulting in peripheral muscle dysfunction and declining lung function.[1] With the global increase in life expectancy, asthma in the elderly has become an emerging public health issue worldwide. Notably, asthma prevalence in this population ranges from 7.0% to 10.6%, with unexpectedly high asthma-related mortality.[2] Elderly asthma patients are also more likely to present with airway remodeling and noneosinophilic asthma, as well as being more likely to have a poor perception of symptoms.[3,4] Accumulating evidence indicates that frailty is a critical prognostic factor in chronic respiratory diseases and impacts asthma control.[5,6] Therefore, assessing frailty risk is critical in the clinical management of elderly asthma patients.

Frailty, a cornerstone in geriatric medicine, is a multidimensional syndrome with complex physical, psychosocial, and economic associations.[7-9] It has been reported that the prevalence of frailty among noninstitutionalized adults ≥ 60 years of age in Brazil is 13.5%.[10] The frailty phenotype, first described by Fried et al.,[11] has a substantial clinical impact because these individuals experience a three-fold increased mortality when compared with robust older adults.[12] Although frail elderly individuals experience several apparent physiological dysfunctions, early recognition of frailty can be challenging. Despite the lack of agreement regarding the best methodology to identify frailty in older adults, several screening instruments have been validated for evaluating frailty risk in clinical practice.[9] The handgrip strength (HGS) test measures the maximum static muscular force of the dominant hand using a dynamometer. Given that muscle strength is a component of the frailty phenotype, HGS has been validated as a reliable tool for frailty syndrome screening in older adults.[13,14] Moreover, HGS is a predictor of a wide range of health outcomes, including mortality, disability, and hospitalization.[15,16]

Frailty is not a static condition and can be modified by targeted clinical interventions. Identifying elderly asthma patients at an increased frailty risk is paramount, given that this condition can increase asthma morbidity.[17-19]

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We hypothesized that HGS is a reliable and easy-to-use method for frailty risk assessment in older patients with asthma. Moreover, given its ease of use, this tool could be part of a comprehensive evaluation of comorbidities among asthma patients with advanced age.

METHODS

This was a cross-sectional study performed between 2020 and 2021 and designed to evaluate the diagnostic accuracy of HGS for frailty risk assessment in elderly patients with asthma. A consecutive sample of 96 older patients was included in the study (Figure 1). All of the patients were treated at a tertiary outpatient clinic located in the city of Salvador, Brazil. Inclusion criteria were as follows: having been diagnosed with asthma by a chest physician and being ≥ 60 years of age. We excluded former or current smokers with a smoking history > 10 pack-years; patients with other pulmonary diseases or extrapulmonary diseases that could interfere with asthma evaluation; and patients with a history of asthma exacerbation in the week before enrollment.

We collected data on demographic characteristics (age, sex, race, household income, and BMI), as well as clinical data on smoking (current smoking, past smoking, and smoking history, in pack-years), comorbidities, current asthma treatment, medication adherence, inhaler technique, use of oral corticosteroids, history of exacerbations, and history of hospitalizations. The definition of asthma and severity classification followed the 2020 recommendations of the GINA.[20] We objectively assessed inhaler technique errors such as errors in dose preparation, placing the inhaler in the mouth, exhaling normally before use, incorrect inhalation technique, and failure to hold the breath after inhaling.[20] The 5-item Asthma Control Questionnaire was used in order to assess asthma control.[21] Spirometry and flow-volume curves were performed before and after bronchodilator administration, with the use of a computerized spirometer (KoKo PFT, Longmont, CO, USA), in accordance with the American Thoracic Society recommendations.[22]

We evaluated HGS (in kgf) using a calibrated hydraulic dynamometer (Baseline®; Fabrication Enterprises Inc., White Plains, NY, USA).[23] Trained research staff collected three consecutive measurements from the dominant hand, with a minimum interval of 1 min between measurements, with the patient in a sitting position and with the elbow flexed at 90°. The best of the three measurements was used for analysis. The research staff that performed the HGS test was blinded to the frailty status of patients.

To determine the diagnostic accuracy of the HGS test, we used s frailty scale developed by Fried et al., previously translated to Portuguese and validated for use in Brazil.[12] The scale is the instrument of choice for characterizing frailty on the basis of the following clinical criteria: unintentional weight loss, weakness, slow gait speed, self-reported exhaustion, and a low level of physical activity. Unintentional weight loss was defined as self-reported loss of 4.5 kg or 5% of

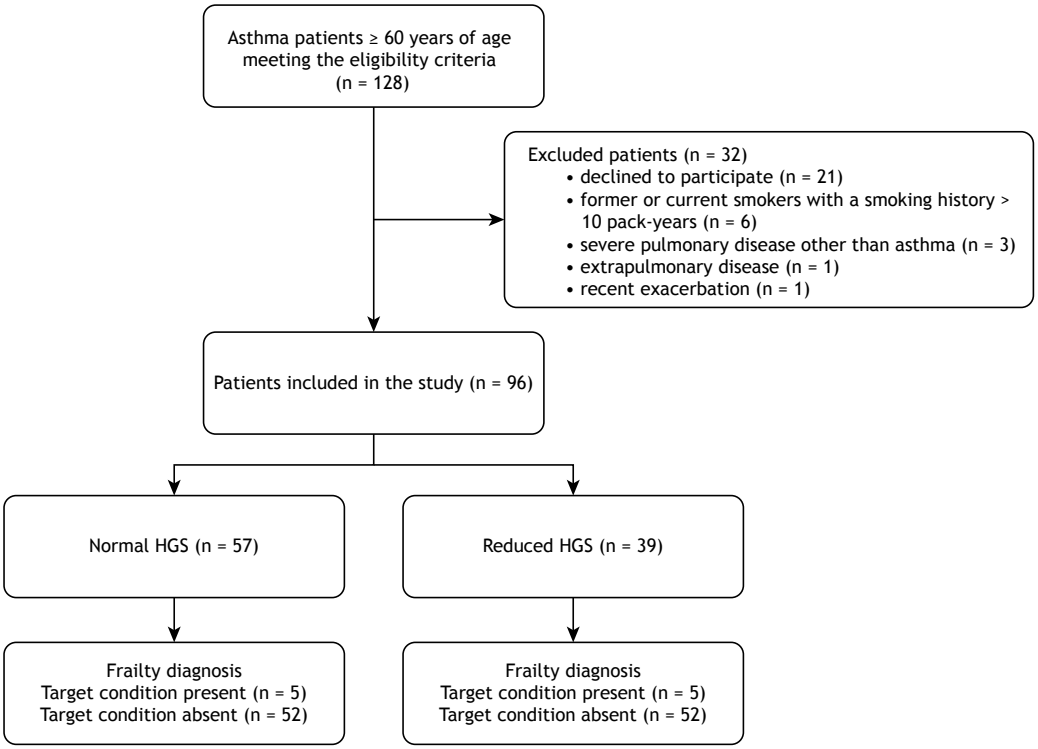

Figure 1. Flow chart of the study population. HGS: handgrip strength.

normal body weight in the last 12 months. Weakness (HGS) was measured with a hand dynamometer on the dominant hand. Muscle weakness was defined by an inability to perform an HGS maneuver or HGS within the lower quintile of the normal range. A stopwatch was used in order to monitor the gait speed over three meters. Slow gait speed was determined on the basis of performance in the highest quintile of time or inability to perform the test. Exhaustion was defined by affirmative responses (most or almost all of the time) to the items on the Center for Epidemiological Studies-Depression Scale. We used the Minnesota Leisure Time Physical Activity Questionnaire in order to assess the level of physical activity. A combination of 3 or more frailty criteria defined frailty; the presence of 1 or 2 frailty criteria characterized prefrail individuals; and the absence of any frailty criteria characterized the nonfrail or robust group.[11]

Likelihood ratios (LRs) are a measure that incorporates both sensitivity and specificity and is used in order to determine the impact of a new diagnostic test on the probability of a disease. The formula for calculating the LR for a positive test result (LR+) is LR+ = sensitivity/(1 − specificity), whereas the formula for calculating the LR for a negative test result (LR−) is LR− = (1 − sensitivity)/specificity. Specifically, we employed LRs to assess the pretest probability for frailty at different proposed cutoff points for HGS, considering the prevalence of the disease in the study population.

The study was conducted in accordance with the 2015 Standards for Reporting of Diagnostic Accuracy Studies guidelines[24] and was approved by the local institutional review board (CAAE no. 3.505.830 - 07/29/2019). All participating patients gave written informed consent. The data obtained were stored in real time on the Research Electronic Data Capture (REDCap; Vanderbilt University, Nashville, TN, USA) platform. We intend to make research data freely available to other researchers (and study participants) upon request.

Statistical analysis

We summarized quantitative variables using medians and interquartile ranges. We expressed categorical and qualitative variables as numbers and proportions. We used the chi-square test in order to compare categorical variables and the Student's t-test or the Mann-Whitney test in order to compare continuous data. To measure the global accuracy of the index test, we used the AUC. An HGS of ≤ 19 kgf was the cutoff point that showed the best diagnostic accuracy. We considered a p value < 0.05 as statistically significant. We conducted the statistical analysis using the GraphPad Prism software, version 9.0.3 (GraphPad Software, Inc., San Diego, CA, USA).

RESULTS

Between 2020 and 2021, 128 patients ≥ 60 years of age with a diagnosis of moderate to severe asthma were assessed for eligibility and invited to participate in the study. A total of 32 patients were excluded for the following reasons: failure to provide written informed consent; being a current or former smoker with a smoking history > 10 pack-years; having severe pulmonary or extrapulmonary diseases; and having experienced an acute exacerbation in the past four weeks (Figure 1). Ninety-six patients were included in the analysis. The median age of participants was 67 (64-73) years. Most (78%) were women and non-White (91%) of low socioeconomic status.

Nineteen patients fulfilled the criteria for the frailty phenotype, with a 19.79% prevalence of frailty in our sample. HGS identified those at risk for frailty, with an AUC of 71.6% (61.5-80.4%; p < 0.002). An HGS cutoff of ≤ 19 kgf showed a sensitivity of 73.58% and a specificity of 67.53% (Figure 2). No significant adverse events occurred because of the HGS test or gait speed assessment.

We assessed the diagnostic properties of the index test at different cutoffs to define low muscle strength. Figure 3 illustrates positive predictive values (PPVs) and the respective LRs. For an HGS cutoff of ≤ 19 kgf, we obtained an LR+ of 2.27, with a PPV of approximately 40%, and an LR− of 0.39, with a PPV of approximately 6%.

We conducted a sensitivity analysis of the accuracy of the index test, adjusted by sex. Table 1 shows a distribution of sensitivity, specificity, LR+, and LR− for different HGS cutoffs for females and males. For females, the sensitivity of the index test was highest for a cutoff of ≤ 27 kgf (93.75%), with an LR− of 1.23, and the specificity of the test was highest for a cutoff of ≤ 12 kgf (86.44%). An HGS of ≤ 11 kgf showed an LR+ of 3.69, with a PPV of approximately 48%, and an HGS of ≤ 20 kgf showed an LR+ of 1.08, with a PPV of 21%. We obtained an LR− of 0.29, with a

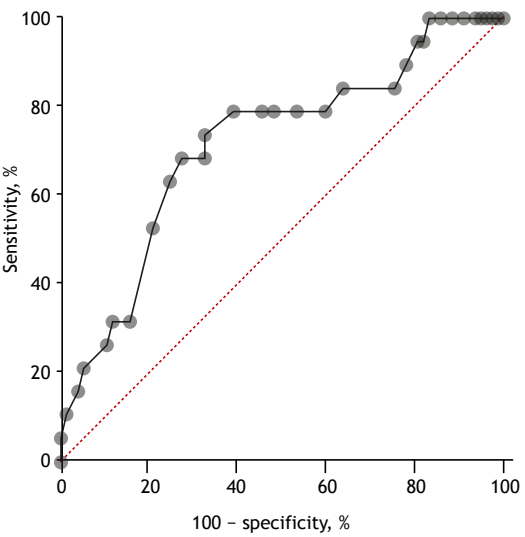

Figure 2. Diagnostic accuracy of the handgrip strength test, as determined by the AUC. A cutoff point of ≤ 19 kgf showed the best diagnostic accuracy, with a sensitivity of 73.58% and a specificity of 67.53%.

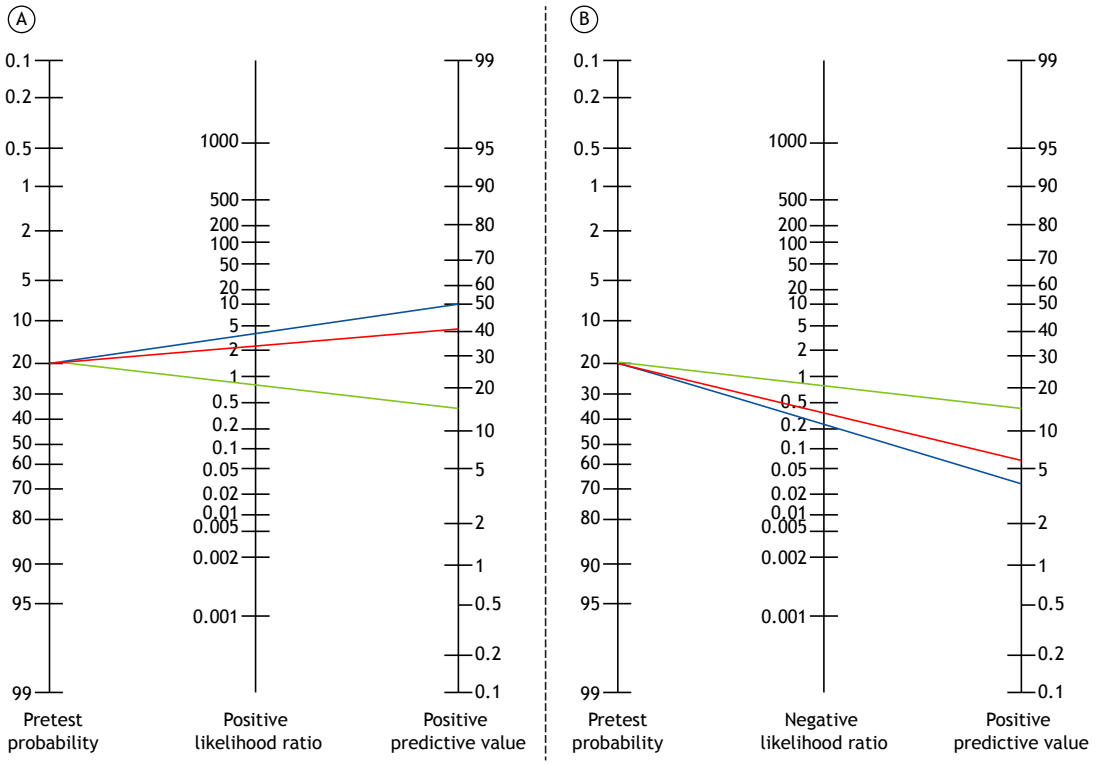

Figure 3. Fagan's nomogram showing the positive predictive values (PPVs) for several cutoffs and positive likelihood ratios (LR+), in A, and negative likelihood ratios (LR−), in B. In A, PPVs for a diagnosis of frailty based on handgrip strength (HGS) cutoffs of ≤ 11 kgf, ≤ 19 kgf, and ≤ 28 kgf (pretest probability of frailty, 19.79%). For an HGS cutoff of ≤ 19 kgf (red line), we obtained an LR+ of 2.27, with a PPV of approximately 40%; for an HGS cutoff of ≤ 11 kgf (green line), we obtained an LR+ of 4.05, with a PPV of 50%; and for an HGS cutoff of ≤ 28 kgf (blue line), we obtained an LR+ of 1.08, with a PPV of 16%. In B, LR− and PPVs for a diagnosis of frailty based on the same HGS cutoffs. For an HGS cutoff of ≤ 19 kgf (red line), we obtained an LR− of 0.39, with a PPV of approximately 6%; for an HGS cutoff of ≤ 11 kgf (green line), we obtained an LR− of 0.83, with a PPV of approximately 16%; and for an HGS cutoff of ≤ 28 kgf (blue line), we obtained an LR− of 0.27, with a PPV of approximately 4%.

Table 1. Diagnostic properties of the index test for frailty risk assessment in females and males.

Females					Males				
HGS cutoff, kgf	Sensitivity, %	Specificity, %	LR+	LR−	HGS cutoff, kgf	Sensitivity, %	Specificity, %	LR+	LR−
≤ 9	12.50	98.31	7.38	0.89	≤ 20	0.0	100	0.0	1.0
≤ 12	31.25	86.44	2.30	0.80	≤ 25	33.33	83.33	2.0	0.8
≤ 19	87.50	57.63	2.06	0.22	≤ 27	66.67	77.78	3.0	0.43
≤ 24	93.75	27.12	1.29	0.23	≤ 32	100	66.67	3.0	0.0

HGS: handgrip strength; LR+: positive likelihood ratio; and LH−: negative likelihood ratio.

PPV of 5%, for an HGS cutoff of ≤ 17 kgf. Regarding the diagnostic proprieties of the index test for males, an HGS of ≤ 27 kgf showed an LR+ of 3.00, with a PPV of 45%, and an LR− of 0.43, with a PPV of 5%.

Comparative analysis of asthma outcomes, comorbidities, and lung function by frailty status

Frail patients were significantly older (p = 0.04) than nonfrail patients (Table 2). Regarding comorbidities, most of the patients reported rhinitis (74%) and gastroesophageal reflux (60%); depression was less common, and dementia was rare.

Most of the patients reported high treatment adherence and correct inhaler technique. Adherence to up to 80% of the prescribed doses was self-reported by 83% and 79% of the patients in the nonfrail and frail groups, respectively. Approximately 90% of the patients in both groups demonstrated correct inhalation technique, without any critical errors. Regarding asthma control, most of the study participants were receiving treatment with medium-dose long-acting β_2 agonists and inhaled corticosteroids or high-dose inhaled corticosteroids, in accordance with the GINA recommendations for step 4 asthma treatment. There

was no significant difference in median 5-item Asthma Control Questionnaire scores between the groups, although 31% of the frail patients had uncontrolled disease, whereas 23% of the nonfrail patients had uncontrolled disease.

Lung function parameters did not differ significantly between the groups. Median FEV_1 values (in L and in % predicted, respectively) were 2.06 L (73%) in the nonfrail group and 1.89 L (72%) in the frail group. It should be noted that spirometry was not performed in 10 (10%) of the patients, because of biosafety issues during the COVID-19 pandemic. There were missing data for 7 (9%) of the patients in the nonfrail group and 3 (16%) of those in the frail group (Table 2).

We also analyzed the cumulative corticosteroid exposure in the previous year. We observed a higher frequency of use of corticosteroids in the frail group, although the difference was not significant. Notably, 68% of the patients in the frail group needed at least one oral corticosteroid course and 16% needed at least one parenteral corticosteroid course in the previous year. Both groups reported no hospital admissions for asthma in the previous year. There was no significant difference in muscle strength between the groups in relation to their cumulative corticosteroid exposure, with median HGS values of 23.00 (15-26) kgf and 21.00 (16-27) kgf in the frail and nonfrail groups, respectively (p = 0.869).

DISCUSSION

We investigated the diagnostic accuracy of the HGS test for assessing frailty risk in patients ≥ 60 years of age with moderate to severe asthma treated at a tertiary referral center in Brazil. Our findings suggest that HGS is a simple, reliable tool for clinicians to determine frailty risk in a point-of-care setting. There is minimal observer effect when assessing muscle strength with a hand dynamometer,[14] and any trained multidisciplinary team member can perform this procedure. Therefore, an easy-to-use, accurate diagnostic tool facilitates screening programs for frailty in elderly asthma patients.

In Brazil, the ongoing process of aging takes place in wide social inequality, often in precarious health and socioeconomic conditions.[25] Environments highly influence individual behavior and exposure to health risks. According to the WHO, an older person is someone over 60 years of age.[26] Indeed, life expectancy may vary in developed and developing countries because environments influence individual behavior, exposure to risks, and access to health services.[27]

HGS has historically been reliably used in the assessment of frailty.[13,14] We found a prevalence of frailty of approximately 20% in our sample. The predominance of moderate-to-severe asthma patients can partially explain this prevalence rate, which is higher than those reported in similar studies of older patients with asthma. In a study conducted in France, adult asthma patients were found to have a two-fold increased prevalence of frailty when compared with individuals without asthma (13% vs. 6%).[28] In a study conducted in Japan, the prevalence of frailty in outpatients with asthma was reported to be 14.5%.[6] Esophageal dysmotility and chronic aspiration are

Table 2. Baseline characteristics of the study population, stratified by the presence or absence of frailty.[a]

Variable	Group		p
	Nonfrail (n = 77)	Frail (n = 19)	
Age, years	67 [60-90]	69 [61-88]	0.04
Female sex	59 (76.6)	16 (84.2)	0.55
Non-White	71 (92.2)	17 (89.5)	0.65
Household income, number of times the Brazilian national minimum wage	1.9 [0.96-2.44]	1.0 [0.96-2.0]	0.20
BMI, kg/m^2	29.5 [26.5-33.1]	28.8 [23.7-33.7]	0.58
Spirometry[b]			
FEV_1, L	2.06 [1.7-2.5]	1.8 [1.3-2.2]	0.79
FEV_1, % predicted	72.6 [66.5-81.5]	80.5 [69.3-88.4]	0.17
FVC, L	1.3 [1.1-1.6]	1.3 [0.7-1.5]	0.22
FVC, % predicted	61.2 [47.3-69.2]	58.2 [45.4-80.7]	0.76
FEV_1/FVC	0.63 [0.51-0.83]	0.63 [0.47-0.84]	
ACQ-5 score	0.80 [0.2-1.6]	1.2 [0.2-1.6]	0.96
Oral corticosteroid tapers in the last year	34 (44.16)	13 (68.4)	0.07
Parenteral corticosteroid courses in the last year	7 (7.69)	3 (15.8)	0.37
Comorbidities			
Rhinitis	56 (72.7)	15 (78.9)	0.77
Gastroesophageal reflux	46 (59.7)	12 (73.2)	> 0.99
Depression	19 (24.6)	5 (26.3)	> 0.99
Dementia	1 (1.3)	0 (0)	0.36

ACQ-5: 5-item Asthma Control Questionnaire. [a]Data expressed as median [IQR] or n (%). [b]Spirometry data unavailable for 10 (10.41%) of the patients.

disorders that have been reported in older asthma patients.[29] This might explain the high prevalence of gastroesophageal reflux in our study population. In a recent study conducted in Japan, a positive association was found between lifetime cumulative corticosteroid exposure and a higher prevalence of muscle frailty and weakness.[30] In our study, no significant difference in muscle strength was found between the two groups of patients regarding their cumulative corticosteroid exposure. However, our study was not designed for this purpose and could have been underpowered to detect this relationship.

Mounting evidence indicates that frailty is a critical prognostic factor in patients with chronic respiratory disease.[31] Frailty assessment has been recommended in older adults.[32] Unfortunately, few studies have addressed the impact of frailty on asthma and vice-versa, particularly in patients with moderate to severe disease. Our findings corroborate that frailty is prevalent in this population. Interventions targeted to factors leading to the development of the frailty phenotype can contribute to improving clinical outcomes in elderly patients with asthma.

Several screening instruments have been validated to assess the risk of frailty. Choosing the most appropriate tool depends on the peculiarities of the health care system and the characteristics of the target population.[33] Despite well-established research protocols, there are several barriers to large-scale application in clinical practice.[9,34] HGS assessment is not time-consuming and is valuable as a single marker of frailty in elderly asthma patients. A more straightforward diagnostic tool such as the HGS test can help reduce patient discomfort and allow clinicians to close this gap in frailty screening programs.

In this study, HGS was found to be a reliable diagnostic tool for frailty risk assessment. Our results suggest that a cutoff of ≤ 19 kgf for females and a cutoff of ≤ 27 kgf for males constitute the optimal threshold for frailty in elderly asthma patients. As a screening method, HGS below 28 kgf showed a highly discriminative negative predictive value. Previous studies in the general geriatric population have reported accuracies ranging from 0.55 to 0.87.[35,36] The accuracy of the index test in asthma patients was slightly lower than the 0.91 reported in a study conducted in Canada and involving elderly individuals > 75 years of age receiving primary care.[13] Nonetheless, our findings suggest that this highly useful tool can contribute to population-based screening programs for frailty.

The frailty phenotype is a multifactorial condition related to a complex relationship of biological, environmental, and socioeconomic factors, which can differ across different populations. For example, in comparison with the participants of a study conducted in Europe,[37] our patients were more likely to be of non-White ethnicity and have lower socioeconomic status. Analyzing the social determinants of these disparities can contribute to a better understanding of the health-disease process in elderly asthma patients. Given the heterogeneous profile of disease severity, impaired peripheral muscle function, and socioeconomic characteristics in elderly patients with asthma worldwide, the HGS test requires validation on different populations.

This study has some limitations. First, 41 of the patients who met the eligibility criteria declined to participate. This might impact the external validity of our results; however, 75% of the eligible patients underwent frailty and HGS assessment. We conducted this study during the COVID-19 pandemic. Although it is possible that frail patients were most likely to decline to participate, the prevalence of frailty in our sample was higher than that reported in previous studies, including studies of elderly asthma patients.[6,28] Second, data from our sensitivity analysis should be interpreted with caution because of the reduced number of males in our sample. Several factors can contribute to a higher prevalence of asthma in elderly females, including postmenopausal hormonal changes, increased exposure to environmental triggers, and comorbidities. Hormonal changes during menopause can decrease estrogen levels, leading to airway inflammation and asthma symptoms.[38]

There is limited evidence on frailty treatment in older asthma patients. Current management strategies focus on symptom control and reducing exacerbations. However, a multidisciplinary approach addressing comorbidities and including nutritional intervention and exercise prescription might also improve frailty outcomes in patients with respiratory disease.[39,40] More research is needed to develop specific interventions for this population.

Understanding the frailty phenotype is a cornerstone in the management of asthma in the elderly. In our study, older adults with moderate to severe asthma had a higher prevalence of frailty than that reported in the general geriatric population in Brazil.[10] We demonstrated that HGS is an accurate diagnostic tool to assess the risk of frailty in patients with asthma. In a sex-stratified analysis, HGS cutoffs of ≤ 19 kgf in females and ≤ 27 kgf in males showed the best diagnostic accuracy for frailty risk assessment in older asthma patients. The development of a simple point-of-care diagnostic tool facilitates screening programs for frailty in older patients with chronic respiratory disease. Further investigation of HGS and other biomarkers of the frailty phenotype can bring promising results.

AUTHOR CONTRIBUTIONS

RGF, JB, and MP designed the study. RGF, VA, and MMFL collected the data. JB, AAC, and FH analyzed and interpreted the data and statistics. GPP and CVNS provided study material. RGF, JB, AAC, MP, and FH interpreted the results and wrote the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Impact of impaired pulmonary function on clinical outcomes in survivors of severe COVID-19 without pre-existing respiratory disease

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ABSTRACT

Objective: To investigate the impact of impaired pulmonary function on patient-centered outcomes after hospital discharge due to severe COVID-19 in patients without preexisting respiratory disease. **Methods:** This is an ongoing prospective cohort study evaluating patients (> 18 years of age) 2-6 months after hospital discharge due to severe COVID-19. Respiratory symptoms, health-related quality of life, lung function, and the six-minute walk test were assessed. A restrictive ventilatory defect was defined as TLC below the lower limit of normal, as assessed by plethysmography. Chest CT scans performed during hospitalization were scored for the presence and extent of parenchymal abnormalities. **Results:** At a mean follow-up of 17.2 ± 5.9 weeks after the diagnosis of COVID-19, 120 patients were assessed. Of those, 23 (19.2%) reported preexisting chronic respiratory diseases and presented with worse lung function and exertional dyspnea at the follow-up visit in comparison with their counterparts. When we excluded the 23 patients with preexisting respiratory disease plus another 2 patients without lung volume measurements, a restrictive ventilatory defect was observed in 42/95 patients (44%). This subgroup of patients (52.4% of whom were male; mean age, 53.9 ± 11.3 years) showed reduced resting gas exchange efficiency (DL_{CO}), increased daily-life dyspnea, increased exertional dyspnea and oxygen desaturation, and reduced health-related quality of life in comparison with those without reduced TLC (50.9% of whom were male; mean age, 58.4 ± 11.3 years). Intensive care need and higher chest CT scores were associated with a subsequent restrictive ventilatory defect. **Conclusions:** The presence of a restrictive ventilatory defect approximately 4 months after severe COVID-19 in patients without prior respiratory comorbidities implies worse clinical outcomes.

Keywords: Post-acute COVID-19 syndrome; Respiratory function tests; Exercise test; Quality of life; Follow-up studies.

(ClinicalTrials.gov identifier: NCT04410107 [http://www.clinicaltrials.gov/])

INTRODUCTION

Long-lasting respiratory symptoms and impaired pulmonary function have been increasingly recognized as post-COVID-19 sequelae.[1] Although the respiratory system is subject to major involvement during SARS, a substantial burden of health loss that spans several extrapulmonary systems has also been reported.[2] Perceived poor health status after COVID-19 was not related to respiratory sequelae (persistent chest imaging abnormalities) or disease severity in the acute phase in one study with a median follow-up of 75 days after diagnosis.[2] Conversely, impaired pulmonary function parameters have shown significant correlations with worse dyspnea, as assessed by the modified Medical Research Council (mMRC) dyspnea scale, and worse Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) physical functioning domain scores 45 days after hospital discharge.[3]

The impact of prior respiratory comorbidities on pulmonary function and its relationship with enduring respiratory complaints and health-related quality of life (HRQoL) was also less explored in previous studies. It is conceivable that patients with prior respiratory comorbidities should ideally be excluded for an

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unbiased analysis of the effects that pulmonary function sequelae of acute COVID-19 have on clinical outcomes.[4] Furthermore, the international standard recommendation to define lung function impairment (values below the lower limit of normal, i.e., the 5th percentile of a healthy population)[5] has not been consistently followed[1,6,7] or reported.[8]

We hypothesized that persistent pulmonary dysfunction after severe COVID-19 would further impair clinical outcomes in patients recovering from the disease. Therefore, our primary objective was to assess the impact of resting ventilatory impairment (i.e., values below the lower limit of normal) on general HRQoL, respiratory symptoms, and exercise performance after hospitalization for severe COVID-19 in patients without chronic respiratory disease. Secondary objectives were to compare these clinical outcomes between patients with and without chronic respiratory disease, and identify predictors during hospitalization on the subsequent presence of ventilatory impairment in the latter group of patients.

METHODS

This is an ongoing single-center prospective cohort study including adult patients hospitalized for severe COVID-19 pneumonia between March 31, 2020 and November 23, 2021. The burden of comorbidities was assessed by calculating the Charlson Comorbidity Index.[9] All procedures were performed during a single study visit, which occurred 2-6 months after laboratory confirmation of SARS-CoV-2 infection. During the visit, the study participants underwent full pulmonary function testing and a six-minute walk test (6MWT). Subsequently, they completed questionnaires to evaluate HRQoL and respiratory symptoms, as well as symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD). The main outcome measures were obtained from cross-sectional analysis of the aforementioned data. The clinical, laboratory, and chest imaging data obtained during hospitalization were collected from patient medical records. A semiquantitative scoring system[10] was used in order to assess lung involvement on the first chest CT scan performed during hospitalization. Each of the five lung lobes was visually scored on a scale of 0 to 5, with 0 indicating no involvement, 1 indicating an involvement of < 5%, 2 indicating an involvement of 5-25%, 3 indicating an involvement of 26-49%, 4 indicating an involvement of 50-75%, and 5 indicating an involvement > 75%. The total CT score was the sum of the individual lobar scores and ranged from 0 (no involvement) to 25 (maximum involvement). Two thoracic radiologists evaluated the chest CT images in a digital database system (IMPAX, version 8.1.2.SP&.1; Agfa HealthCare, Mortsel, Belgium), and final scores were determined by consensus.

The study was approved by the local research ethics committee (Protocol no. 2020-0169) and was performed in accordance with the Declaration of Helsinki. All participating patients gave written informed consent. The study protocol was registered at ClinicalTrials.gov (Identifier: NCT04410107).

Patients ≥ 18 years of age with laboratory-confirmed severe COVID-19 seen in the respiratory department just before discharge were invited to participate, constituting a convenience sample. Laboratory confirmation of SARS-CoV-2 infection was defined as a positive RT-PCR result from a nasal swab. Severe COVID-19 was defined as fever or suspected lower respiratory tract infection plus one of the following criteria: 1) respiratory rate > 30 breaths/min; 2) severe respiratory distress or SpO_2 of ≤ 93% on room air; or 3) pulmonary infiltrates > 50% on chest imaging within 24-48 h of hospital admission.[11] Patients who were clinically unstable 2 months before enrollment, those who had active respiratory tract infection, and those who had any clinical condition precluding the performance of the study procedures were excluded.

Procedures

Spirometry, body plethysmography, single-breath DL_{CO} measurement, and impulse oscillometry were performed in accordance with the American Thoracic Society/European Respiratory Society standards, with the use of an automated system (MasterScreen™ PFT; CareFusion, Yorba Linda, CA, USA). The last hemoglobin value measured during hospitalization was used for DL_{CO} correction. Spirometry, lung volumes, and DL_{CO} parameters were expressed as absolute and percent predicted values, in accordance with the Global Lung Function Initiative reference values.[12-14] Impulse oscillometry measurements were also expressed as absolute and percent predicted values.[15] Obstructive ventilatory defect (a reduction in the FEV_1/FVC ratio after bronchodilator administration), restrictive ventilatory defect (reduced TLC), and reduced DL_{CO} were characterized by measurements below the lower limit of normal (i.e., below the −1.645 z-score).[5]

The 6MWT was performed indoors in a flat, 25-m corridor, in accordance with the latest European Respiratory Society/American Thoracic Society technical standards. All 6MWTs were performed at least 30 min after the pulmonary function tests. Continuous monitoring of SpO_2 was performed with a pulse oximetry sensor (PureLight® 8000AA; Nonin Medical, Inc., Plymouth, MN, USA) connected to an oximeter. The six-minute walk distance was expressed as a percentage of the predicted value,[16] and values below the lower limit of normal defined reduced exercise capacity.

The mMRC dyspnea scale was used in order to grade dyspnea during activities of daily living, the levels of dyspnea being graded from 0 (absence of dyspnea during strenuous exercise) to 4 (too breathless to leave the house or breathless while dressing or undressing).[17] Cough and sputum production were assessed through an adapted translation of the American Thoracic Society respiratory symptoms questionnaire.[18]

General HRQoL was assessed with the SF-36. The SF-36 is a 36-item questionnaire divided into eight domains that measure social, physical, and mental health aspects. Each domain score ranges from 0 to 100, with higher scores reflecting better quality of life.[19] Reference values for the Brazilian population[20] were used for comparison with the values obtained in the present study.

Depression and anxiety symptoms were assessed by the Beck Depression Inventory (BDI) and the Beck Anxiety Inventory (BAI), respectively. The BDI and the BAI consist of 21 sets of statements about depression and anxiety symptoms in the last 7 days, rated on a 0-to-3 ordinal Likert scale.[21,22] A BDI > 14 and a BAI > 8 indicate some level of depression[23] and anxiety,[22] respectively.

PTSD was evaluated through the self-report PTSD Checklist, Civilian Version,[24] which comprises 17 items that assess three symptom groups during the previous month, on a scale of 1 to 5 (not at all to very much): reexperiences, avoidance behavior/emotional numbness, and increased arousal.[23] A score ≥ 3 (average) for any of the 17 items is considered clinically significant.[25]

Statistical analysis

Data were analyzed with the Predictive Analytics Software package, version 18.0 (SPSS Inc., Chicago, IL, USA). The level of significance was set at $p < 0.05$. Normality was assessed by the Kolmogorov-Smirnov test. Continuous data were presented as mean ± SD or median (25^{th}-75^{th}percentiles), depending on the data distribution. Categorical variables were reported as frequencies and proportions. Comparisons between groups were performed with the independent Student's t-test, Pearson's chi-square test, or Fisher's exact test. Stepwise logistic regression analysis was used in order to identify hospitalization variables related to abnormal lung function in individuals without prior respiratory comorbidities.

RESULTS

A total of 152 patients were evaluated for inclusion in the study. Of those, 120 (88.1%) were enrolled within a mean of 17.2 weeks of a positive RT-PCR test for SARS-CoV-2 infection (95% CI, 16.1-18.3; Figure 1). Twenty-three participants (19.2%) reported having chronic respiratory disease before COVID-19 (asthma, in 11; COPD, in 9; pulmonary tuberculosis, in 2; and bronchiectasis, in 1). Other comorbidities, daily-life dyspnea before COVID-19, duration of COVID-19 symptoms before admission, and hospitalization characteristics were similar between those with and without preexisting respiratory disease (data not shown). During the follow-up study visit, however, despite similar HRQoL and psychological symptoms, those with preexisting respiratory disease presented with worse lung function, exertional dyspnea, and oxygen saturation. Accordingly, the prevalences of obstructive ventilatory defect and abnormally reduced DL_{CO} were higher ($p < 0.001$ and $p = 0.10$, respectively; Table 1), as were the prevalences of clinically relevant cough (4-6 times a day, ≥ 4 days a week; 31.8% vs. 11.0%; $p = 0.01$) and phlegm from the chest (> twice a day; 23.8% vs. 8.8%; $p = 0.06$).

When we excluded patients with preexisting respiratory disease (n = 23) and those without lung volume measurements (n = 2), we observed a prevalence of 42/95 patients (44.2%) with restrictive disorder and a prevalence of 37/95 patients (38.9%) with abnormally reduced DL_{CO}. Of the 42 patients with restrictive ventilatory impairment, 14 (33.3%) did not show reduced DL_{CO}. None was found to have an obstructive ventilatory defect (with the use of the lower limit of normal or a fixed ratio below 0.7). Patients with a restrictive ventilatory defect had a shorter duration of symptoms before hospitalization and higher proportions of ICU admission and invasive mechanical ventilation, as well as longer length of hospital stay, longer duration of invasive mechanical ventilation, and higher chest CT scores. During the follow-up study visit, these patients presented with worse daily-life dyspnea and DL_{CO}, as well as higher prevalences of reduced exercise capacity, exertional dyspnea, and oxygen desaturation (Table 2). General HRQoL was worse in almost all domains, the exceptions being bodily pain, role-emotional, and mental health (Figure 2). Although the prevalence of significant dyspnea (i.e., an mMRC dyspnea scale score ≥ 2) was higher in those with a restrictive ventilatory defect, there were no differences between those with and those without a restrictive ventilatory defect in terms of clinically relevant cough and sputum production (Figure 3). Regarding psychological symptoms, only anxiety-related complaints were higher in the former group of patients (Table 2).

Stepwise multivariate logistic regression analysis including age, sex, and the Charlson Comorbidity Index revealed that intensive care need and the magnitude of pulmonary involvement (as assessed by chest CT scores) predicted the presence of a restrictive ventilatory defect at the follow-up visit (Table 3).

DISCUSSION

Persistent respiratory symptoms and impaired pulmonary function have been increasingly recognized as post-acute COVID-19 sequelae.[1] The extent to which preexisting respiratory conditions and impaired lung function after COVID-19 affect clinical outcomes is less clearly established. The present study showed that prior respiratory disease implied lower lung function and worse respiratory symptoms. By excluding these patients, we demonstrated that a restrictive ventilatory defect was a common finding (in 44%), usually associated with impaired gas exchange ($\downarrow DL_{CO}$) a few months (≈ 4 months) after hospitalization for severe COVID-19. A restrictive ventilatory defect was associated with negative effects on patient-centered outcomes, including exertional and daily-life dyspnea

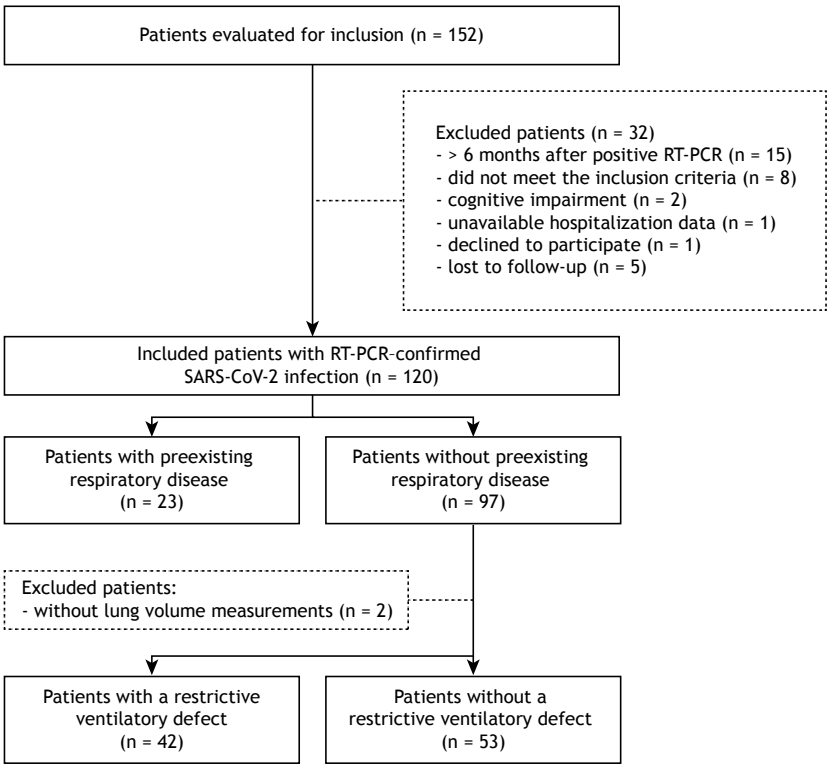

Figure 1. Flow chart of the patient inclusion process.

(an mMRC dyspnea scale score ≥ 2), as well as exercise capacity and general HRQoL.

Fatigue, dyspnea, and cough are among the most common complaints in studies examining symptoms after hospitalization or disease onset.[26] Interestingly, the aforementioned symptoms are also highly prevalent among patients not hospitalized during the acute phase. One recent study showed that persistent dyspnea after COVID-19 (13% of the sample had been hospitalized) was not associated with overt cardiopulmonary impairment or exercise intolerance.[27] Conversely, persistent dyspnea, fatigue, and exercise intolerance have been associated with peripheral oxygen delivery/utilization mismatch, respiratory limitation, or dysfunctional breathing in samples with hospital admission rates ranging from 10% to 96% during the acute phase of COVID-19.[28] In a study including only noncritically ill patients (27% of whom had no hypoxemia and were treated on an outpatient basis), those with persistent dyspnea were found to have lower FVC, lower DL_{CO}, lower six-minute walk distance, and increased exertional desaturation,[29] findings that are consistent with ours. However, the authors of the aforementioned study[29] did not quantify the severity of persistent dyspnea or measure TLC in order to diagnose a restrictive ventilatory defect. A reduced FVC and/or FEV_1 with normal FEV_1/FVC are suggestive of a restrictive pattern, and lung volume measurements are usually needed in order to confirm that. Restriction is a potential dysfunction following severe lung injury (and related medical care) caused by parenchymal abnormalities (interstitial lung disease) or extraparenchymal abnormalities (respiratory muscle wasting resulting in atrophy and weakness).[5] A low DL_{CO} in the presence of reduced TLC (and alveolar volume) may result from any one of the aforementioned mechanisms. Meanwhile, reduced DL_{CO} in patients without restriction (or obstruction) indicates impaired gas exchange efficiency, which, in the present context, indicates either interstitial lung disease (alveolar destruction, alveolar thickening, or ventilation/perfusion mismatch) without mechanical abnormalities, or it indicates pulmonary vascular disease.[30] Finally, the presence of reduced TLC with preserved DL_{CO} indicates extraparenchymal restriction.[5] The complexity of interpreting DL_{CO}, lung volume (or rather, alveolar volume), and the relationship between the two, however, makes it difficult to determine the underlying abnormality (or abnormalities) on the basis of the available data.[31] Respiratory muscle evaluation and more specific measures of the alveolar-capillary membrane (e.g., combined DL_{CO} and diffusing capacity of the lung for nitric oxide measurements or advanced chest imaging techniques) might be useful to assess the contribution of interstitial lung abnormalities, pulmonary vascular injury, and/or extraparenchymal abnormalities to reduced DL_{CO} in individual cases.[31]

The roles that acute disease severity and the extent of pneumonia on chest CT scans play in the development of impaired lung function and respiratory symptoms are also contradictory. A significant relationship between disease severity and abnormal lung function has been

Table 1. Comparison between patients with and without preexisting respiratory disease in terms of lung function, exercise performance, and health-related quality of life at the follow-up visit.[a]

Demographic/anthropometric data	Patients with preexisting respiratory disease	Patients without preexisting respiratory disease	p
	n = 23	n = 97	
Age, years	53.9 ± 17.1	56.7 ± 11.6	0.462
Weight, kg	87.4 ± 19.6	87.8 ± 17.4	0.926
Height, m	1.66 ± 0.05	1.66 ± 0.12	0.954
BMI, kg/m^2	31.6 ± 6.7	31.7 ± 5.5	0.918
mMRC dyspnea scale score	2 (0-4)	1 (0-3)	0.210
Spirometry	**n = 23**	**n = 97**	
Number of weeks after COVID-19 diagnosis	15.9 ± 8.0	17.2 ± 5.8	0.484
FVC, % predicted	78.9 ± 16.5	87.6 (72.7-98.8)	0.661
FEV_1, % predicted	76.7 ± 19.2	93.6 (83.6-106.6)	0.194
FEV_1/FVC	0.77 ± 0.11	0.87 ± 0.05*	< 0.001
FEV_1/FVC < LLN, n (%)	5 (21.7)	0*	< 0.001
Plethysmography	**n = 23**	**n = 95**	
TLC, % predicted	85.7 ± 18.4	83.8 (74.5-92.7)	0.959
TLC < LLN, n (%)	11 (47.8)	42 (44.2)	0.754
FRC, % predicted	98.8 (71.2-109.5)	81.7 (69.2-91.6)	0.255
RV, % predicted	126.4 ± 59.9	94.7 (78.7-110.2)*	0.019
Diffusing capacity of the lung	**n = 23**	**n = 95**	
DL_{CO}, % predicted	68.3 ± 22.3	83.3 (67.6-93.9)	0.149
DL_{CO} < LLN, n (%)	13 (59.1)	38 (40.0)	0.104
Impulse oscillometry	**n = 14**	**n = 62**	
Resistance at 5 Hz, % predicted	187.5 ± 60.8	127.5 (105.4-170.1)*	< 0.001
Resistance at 20 Hz, % predicted	138.8 ± 43.2	123.2 ± 34.9	0.153
R_5-R_{20}, Kpa/L/s	0.24 ± 0.14	0.08 (0.06-0.13) *	0.004
Reactance at 5 Hz, Kpa/L/s	−0.25 ± 0.15	−0.11 (−0.15 to −0.08)*	0.008
Resonance frequency, 1/s	22.4 ± 7.0	16.3 ± 4.3*	0.008
Area of resonance, Kpa/L	2.13 ± 1.52	0.53 (0.3-1.0)*	0.011
6MWT	**n = 23**	**n = 95**	
6MWD, m	377.4 ± 117.8	410.0 ± 104.0	0.201
6MWD, % predicted	69.0 ± 20.5	74.7 ± 25.1	0.329
6MWD < LLN, n (%)	14 (60.9)	37 (38.9)	0.057
Resting SpO_2, %	94.5 ± 1.9	96 (94-97)	0.568
Final SpO_2, %	91.1 ± 4.7	94 (92-96)*	0.033
Final Borg dyspnea scale score	3.0 ± 2.4	0 (0-3.2)	0.071
Final Borg leg fatigue scale score	2 (0-4)	0 (0-3)	0.698
Final Borg dyspnea score/6MWD, n/km	8.1 (0.0-12.6)	0.0 (0.0-0.9)*	0.014
SF-36	**n = 16**	**n = 70**	
Physical functioning	46.2 ± 27.6	42.5 (30-61)	0.541
Role-physical	12 (0-81)	0 (0-75)	0.637
Bodily pain	56.9 ± 25.3	51.0 (31-74)	0.689
General health	56.6 ± 22.8	62.0 (45-82)	0.411
Vitality	58.7 ± 25.0	55 (43-70)	0.542
Social functioning	53.1 ± 30.7	62 (25-87)	0.489
Role-emotional	66 (0-100)	33.3 (0-75)	0.116
Mental health	68.5 ± 24.4	58.4 ± 24.2	0.139
Psychological symptoms	**n = 16**	**n = 70**	
Beck Anxiety Inventory	18.3 ± 16.6	11.5 (4-24.2)	0.584
Beck Depression Inventory	8.5 (6.5-15.5)	9.0 (5.2-17.4)	0.934
PCL-C	25.0 (23-31)	28.0 (22.5-40)	0.328

mMRC: modified Medical Research Council; LLN: lower limit of normal (i.e., below the 5th percentile); FRC: functional residual capacity; R_5-R_{20}: resistance at 5 Hz-resistance at 20 Hz; 6MWT: six-minute walk test; 6MWD: six-minute walk distance; SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; and PCL-C: Posttraumatic Stress Disorder Checklist, Civilian Version. [a]Data presented as mean ± SD, median (IQR), or n (%). *Values of p < 0.05.

Table 2. Comparison between patients without preexisting respiratory disease presenting with a restrictive ventilatory defect at the follow-up visit and those not presenting with a restrictive ventilatory defect at the follow-up visit.[a]

Variable	RVD	No RVD	p
	n = 42	n = 53	
Age, years	53.9 ± 11.3	58.4 ± 11.3	0.061
Male sex, n (%)	22 (52.4)	27 (50.9)	0.527
Weight, kg	93.6 ± 17.9	84.0 ± 15.7*	0.007
Height, m	1.68 ± 0.1	1.64 ± 0.1	0.084
BMI, kg/m^2	33.0 ± 5.8	30.9 ± 5.0	0.067
Current or former smoker, n (%)	10 (24.4)	24 (45.3)*	0.037
Comorbidities			
Hypertension	24 (57.1)	24 (45.3)	0.251
Diabetes	13 (31)	12 (22.6)	0.361
Obesity	24 (57.1)	17 (32.1)*	0.014
Cardiovascular disease	4 (9.5)	3 (5.7)	0.371
Cerebrovascular disease	3 (7.1)	2 (3.8)	0.390
Chronic liver disease	0 (0.0)	1 (1.9)	0.558
Chronic kidney disease	2 (4.8)	1 (1.9)	0.413
Cancer	3 (7.1)	3 (5.7)	0.545
Charlson Comorbidity Index	1 (0-3)	2 (1-3)	0.784
mMRC dyspnea scale score before COVID-19	0 (0-1)	0 (0-0)	0.070
Symptoms before admission, days	6 (4-10)	8 (6-10)*	0.028
Data during hospitalization			
Length of stay, days	24 (15-45)	10 (9-15)*	< 0.001
ICU admission, n (%)	31 (73.8)	17 (32.1)*	< 0.001
NIV, n (%)	11 (26.2)	19 (35.8)	0.315
IMV, n (%)	19 (45.2)	4 (7.5)*	< 0.001
Duration of IMV, days	0 (0-20)	0 (0-0)*	0.002
Chest CT score	21 (16-24)	13 (11-18)*	< 0.001
Follow-up study visit			
Number of weeks after COVID-19 diagnosis	17.7 ± 5.9	16.8 ± 5.6	0.489
mMRC dyspnea scale score	2 (0-3)	1 (0-2)*	0.008
mMRC dyspnea scale score ≥ 2, n (%)	24 (57.1)	13 (24.5)*	0.001
Spirometry			
FVC, % predicted	72.3 ± 15.9	100.9 ± 60.0*	0.006
FEV_1, % predicted	80.0 ± 17.7	103.4 (93.2-111.5)*	0.007
FEV_1/FVC	0.87 ± 0.00	0.85 ± 0.00	0.061
FEV_1/FVC, % predicted	110.2 ± 7.2	107.5 (104-11.5)	0.569
FEV_1/FVC < LLN, n (%)	0	0	
Plethysmography			
TLC, % predicted	72.7 (61.6-77.6)	91.7 (87.8-96.1)*	< 0.001
FRC, % predicted	71.41 ± 13.10	88.7 (80.7-99.8)	0.071
RV, % predicted	84.4 ± 18.9	101.6 (92.2-119.1)*	0.009
Diffusing capacity of the lung	n = 40	n = 53	
DL_{CO}, % predicted	70.73 ± 18.40	90.6 (79.2-98.4)*	0.001
DL_{CO} < LLN, n (%)	28 (66.7)	9 (17.3)*	< 0.001
Impulse oscillometry	n = 24	n = 38	
Resistance at 5 Hz, % predicted	140.8 ± 41.7	134.9 ± 41.2	0.587
Resistance at 20 Hz, % predicted	110.5 (94.2-143.2)	125 ± 35.6	0.601
R_5-R_{20}, Kpa/L/s	0.12 ± 0.00	0.07 (0.0-0.1)*	0.027
Reactance at 5 Hz, Kpa/L/s	−0.13 ± 0.00	−0.10 (−0.10 to 0.00)	0.116
Resonance frequency, 1/s	17.4 ± 4.4	15.6 ± 4.2	0.108
Area of resonance, Kpa/L	0.67 (0.4-1.6)	0.48 (0.2-0.8)	0.124
6MWT	n = 38	n = 52	
6MWD, m	385.7 ± 94.6	430.2 ± 109.1	0.051
6MWD, % predicted	72.2 ± 15.7	77.9 ± 28.5	0.275
6MWD < LLN, n (%)	20 (52.6)	15 (28.8)*	0.020
Resting SpO_2, %	95 (2)	96 (3)*	0.030
Final SpO_2, %	93 (6)	95 (3)*	0006
Final Borg dyspnea scale score	2 (0-5)	0 (0-2)*	0.014
Final Borg leg fatigue scale score	2 (0-4)	0 (0-2)	0.164
Final Borg dyspnea score/6MWD, n/km	6.06 (0-13)	0 (0-5.3)*	0.011
Psychological symptoms	n = 29	n = 40	
Beck Anxiety Inventory	22.0 ± 17.4	8 (3-21)*	0.008
Beck Depression Inventory	11 (6-17)	8 (3-16)	0.128
PCL-C	29 (23-42)	28 (22-39)	0.952

RVD: restrictive ventilatory defect; mMRC: modified Medical Research Council; NIV: noninvasive ventilation; IMV: invasive mechanical ventilation; LLN: lower limit of normal (i.e., below the 5th percentile); FRC: functional residual capacity; R_5-R_{20}: resistance at 5 Hz-resistance at 20 Hz; 6MWT: six-minute walk test; 6MWD: six-minute walk distance; and PCL-C: Posttraumatic Stress Disorder Checklist, Civilian Version. [a]Data presented as mean ± SD, median (IQR), or n (%). *p < 0.05.

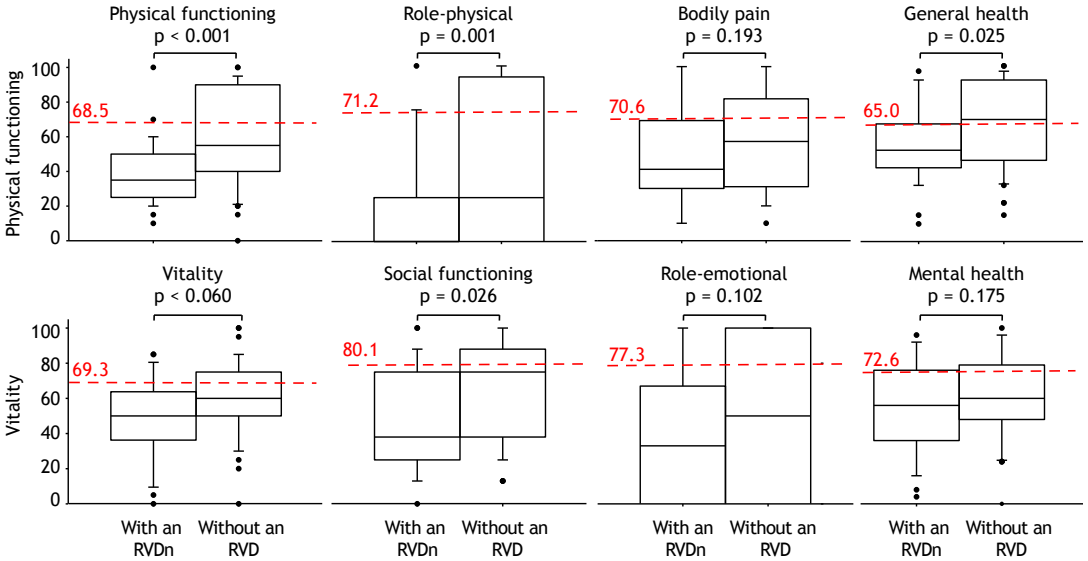

Figure 2. Comparison of general health-related quality of life (as assessed by Medical Outcomes Study 36-Item Short-Form Health Survey [SF-36] domain scores) between patients with and without a restrictive ventilatory defect (RVD) at the follow-up visit, after exclusion of those with prior respiratory comorbidities. The red dotted lines represent the mean reference values for each SF-36 domain, derived from randomly selected Brazilian men and women who were in the same age bracket as were the patients included in the present study (i.e., the 55- to 64-year age bracket).[20]

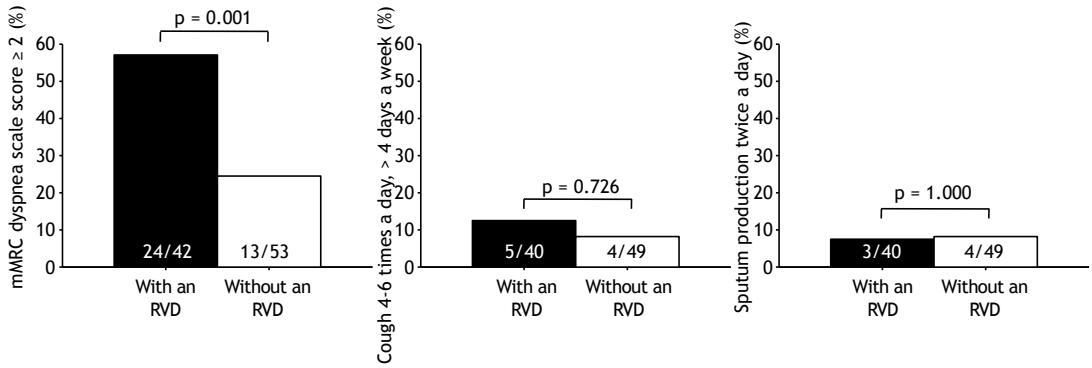

Figure 3. Comparison of respiratory symptoms between patients without prior respiratory comorbidities presenting with a restrictive ventilatory defect (RVD) at the follow-up visit and those not presenting with an RVD at the follow-up visit. mMRC: modified Medical Research Council.

Table 3. Multivariate logistic regression model to predict a restrictive ventilatory defect at the follow-up visit in patients without preexisting chronic respiratory comorbidities.[a]

	Exp (β)	95% CI		p
		Lower	Upper	
Intensive care (reference: no)	5.522	1.997	15.273	0.001
Chest CT score	1.135	1.033	1.247	0.008

[a]Other variables included in the first step of the backward stepwise logistic regression model were age, sex, and the Charlson Comorbidity Index.

reported in some studies,[6,29] but not in others.[32] In agreement with the findings of a study assessing risk factors for post-COVID-19 pulmonary fibrosis,[33] our findings show that the need for intensive care and a greater extent of acute pulmonary inflammation (i.e., a higher chest CT score) independently predicted restrictive lung disease at the follow-up visit.

Psychological stress is highly prevalent after COVID-19.[34] It is associated with breathlessness and poorer functional status in the general population.[35] In the present study, self-report questionnaires were used in order to assess the modulation of PTSD, depression, and anxiety symptoms in the relationship between impaired respiratory function and worse clinical outcomes. Mean BDI scores indicated mild to no depression. Although PTSD symptoms were clinically significant, there were no differences between patients with and without a restrictive ventilatory defect. Anxiety symptoms were significantly higher in the former group of patients, raising the question of the contribution

of anxiety symptoms to worsening clinical outcomes. Regardless of the direction of this relationship (cause or consequence), it seems valuable to assess and manage anxiety symptoms, and further research is needed in order to explore the impact of anxiety management on post-COVID-19 symptom relief.

The prevalences of asthma and COPD before COVID-19 have been reported to range from 5% to 15% and from 1% to 9%, respectively.[26] Of the patients in our sample, 19% reported baseline respiratory comorbidities and were excluded from later analyses. Significant dyspnea (an mMRC dyspnea scale score ≥ 2) was more common in patients with restrictive lung disease than in those without it (57% vs. 24%). The overall proportion of patients presenting with clinically significant cough and sputum production was not negligible for patients without preexisting respiratory conditions (i.e., 8-12%). However, this rate was not worse in the presence of a restrictive ventilatory defect. Cough and expectoration are typical symptoms of airway inflammation secondary to tracheobronchitis or pneumonia. Viral respiratory tract infections can be associated with acute bronchiolitis in adults, and constrictive bronchiolitis can be seen as a late sequela of viral lower respiratory tract infections.[36] The prevalence of an obstructive ventilatory pattern after COVID-19 was reported to be 7% in a previous systematic review.[1] However, differences across studies regarding the criteria to define obstruction and the presence of prior chronic respiratory disease justify caution in considering persistent expiratory airflow obstruction to be a late sequela of COVID-19. For example, of the studies included in the aforementioned systematic review,[1] only one[32] used the recommended lower limit of normal to define obstruction, and none of the patients in that study had an obstructive ventilatory pattern. In another study using impulse oscillometry measurements, mean values of the respiratory system resistance at an oscillation frequency of 5 Hz and of 20 Hz were reported to be normal 30 days after hospital discharge (127 ± 29% of predicted and 133 ± 31% of predicted, respectively).[37] As expected, the prevalence of obstructive lung disease was higher in our patients with preexisting respiratory disease (i.e., 21.7%), and they had worse impulse oscillometry measurements than did those without preexisting respiratory disease. Although mean values of respiratory system resistance at an oscillation frequency of 5 Hz and of 20 Hz were within the normal range in our patients without preexisting respiratory disease, the mean resonance frequency and area of resonance were altered. These findings suggest the involvement of peripheral lung parenchyma without airway disease.[38]

From a clinical perspective, we demonstrated that persistent lung function impairment implies worse dyspnea and physical functioning after COVID-19, mainly represented by a restrictive ventilatory defect associated with abnormal gas exchange. Therefore, pulmonary function testing might be useful to uncover factors contributing to such complaints; to monitor changes over time; and to guide future studies aimed at evaluating potential interventions for their relief.

One of the limitations of the present study is the lack of assessment of other potential mechanisms for respiratory symptoms and impaired HRQoL after COVID-19. Cardiac dysfunction, musculoskeletal dysfunction, immune response to SARS-CoV-2,[34] and impaired oxidative metabolism[39] have been suggested to explain dyspnea, fatigue, and exercise intolerance beyond alterations in pulmonary function. Another limitation is the relatively short-term follow-up. Although data from long-term follow-up of previous coronavirus outbreaks[40] and 12-month follow-up of the current COVID-19 pandemic[6] suggest that some patients will have long-term respiratory complications, improvement in pulmonary function is commonly observed over time.[6] Nevertheless, this is an ongoing prospective cohort study that will provide long-term (> 12-month) follow-up of pulmonary function, exercise capacity, HRQoL, and their interplay. Finally, we do not know whether our findings apply to cases of milder disease, because only patients hospitalized for severe COVID-19 pneumonia were included in the present study.

In this prospective cohort of patients followed for approximately 4 months after a confirmed diagnosis of severe COVID-19, those with preexisting chronic respiratory comorbidities showed worse lung function and respiratory symptoms. When those patients were excluded, poor resting gas exchange (reduced DL_{CO}), increased dyspnea, reduced HRQoL, and reduced exercise performance were observed in those with a restrictive ventilatory defect. Intensive care need and a greater extent of pulmonary involvement during the acute phase were associated with the presence of a restrictive ventilatory defect at the follow-up visit.

AUTHOR CONTRIBUTIONS

DCB, MBG, PTRD, and SPR: study conception/design and literature review. IGB, RMCS, GMH, GSV, and ARG: data collection. LF, VBB, and TSG: analysis and interpretation of chest CT scans. DCB, IGB, and RMCS: statistical analysis and interpretation. DCB, RMCS, GMH, and ARG: drafting of the first version of the manuscript. All authors critically reviewed and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Role of the one-minute sit-to-stand test in the diagnosis of post COVID-19 condition: a prospective cohort study

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ABSTRACT

Objective: To analyze the relationship between one-minute sit-to-stand test (1MSTST) parameters and a diagnosis of post COVID-19 condition in a cohort of patients who previously had COVID-19. **Methods:** This was a prospective cohort study of patients with post COVID-19 condition referred for body plethysmography at a tertiary university hospital. Post COVID-19 condition was defined in accordance with the current WHO criteria. **Results:** Fifty-three patients were analyzed. Of those, 25 (47.2%) met the clinical criteria for post COVID-19 condition. HR was lower in the patients with post COVID-19 condition than in those without it at 30 s after initiation of the 1MSTST (86.2 ± 14.3 bpm vs. 101.2 ± 14.7 bpm; $p < 0.001$) and at the end of the test (94.4 ± 18.2 bpm vs. 117.3 ± 15.3 bpm; $p < 0.001$). The ratio between HR at the end of the 1MSTST and age-predicted maximal HR (HR_{end}/HR_{max}) was lower in the group of patients with post COVID-19 condition ($p < 0.001$). An HR_{end}/HR_{max} of < 62.65% showed a sensitivity of 78.6% and a specificity of 82.0% for post COVID-19 condition. Mean SpO_2 at the end of the 1MSTST was lower in the patients with post COVID-19 condition than in those without it (94.9 ± 3.6% vs. 96.8 ± 2.4%; $p = 0.030$). The former group of patients did fewer repetitions on the 1MSTST than did the latter ($p = 0.020$). **Conclusions:** Lower SpO_2 and HR at the end of the 1MSTST, as well as lower HR at 30 s after initiation of the test, were associated with post COVID-19 condition. In the appropriate clinical setting, an HR_{end}/HR_{max} of < 62.65% should raise awareness for the possibility of post COVID-19 condition.

Keywords: COVID-19; Post-acute COVID-19 syndrome; Heart rate; Respiratory function tests.

INTRODUCTION

After confirmation of the potential for sequelae of COVID-19, statements were formulated recommending clinical, pulmonary function, physical capacity, and imaging evaluation of these patients.[1,2] The term "long COVID" was initially coined to describe COVID-19 patients experiencing lingering symptoms, being subsequently defined as post COVID-19 condition in the WHO ICD-11 (code RA02). The WHO also provided recommendations for the definition of post COVID-19 condition in adults: individuals with a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19, with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis; these symptoms include fatigue, shortness of breath, and cognitive dysfunction, and have an impact on activities of daily living in most cases.[3] Therefore, post COVID-19 condition is a diagnosis of exclusion, based on clinical findings. Post COVID-19 condition is a prevalent disorder; it has been estimated to affect 13.9% of individuals with a history of COVID-19, having affected 1.7% of all adults in the U.S. in 2022.[4] However, the prevalence of post COVID-19 condition decreases over time, being = 4.5% and 2.3% at 8 and 12 months after SARS-CoV-2 infection, respectively.[5]

The sit-to-stand test has been recommended as a useful and safe tool to assess physical capacity in post COVID-19 patients, provided that the test is performed under supervision (but not via telemonitoring).[2] In addition, it has been reported that the one-minute sit-to-stand test (1MSTST) can be used for evaluating exertional desaturation in COVID-19 patients because it has been validated for use in patients with chronic interstitial lung disease and in those with obstructive airway disease; however, the 1MSTST should be used only under clinical supervision because it can produce a high cardiorespiratory stress.[6] On the basis of this recommendation, the 1MSTST has been integrated into a clinical trial protocol as an assessor of improvement in exertional dyspnea/SpO_2.[7]

The current literature on the role of the 1MSTST in the assessment of COVID-19 focuses on the ability of the test to evaluate hospitalization or home discharge, or to assess the clinical status of patients after hospitalization or pulmonary rehabilitation[8]; it does not focus on the role of the 1MSTST in the diagnosis of post COVID-19 condition. In the evaluation of pulmonary rehabilitation, the thirty-second sit-to-stand test has been shown to improve leg strength, endurance, and SpO_2 in patients with post COVID-19 condition after hospital discharge.[9,10]

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Similar results have been reported for the roles of the 1MSTST and the three-minute sit-to-stand test in pulmonary rehabilitation.[11,12]

There are knowledge gaps in the diagnosis of post COVID-19 condition. The European Respiratory Society statement on long COVID follow-up suggests that longitudinal cohort studies are needed to determine effective interventions for assessing and monitoring disability in patients with post COVID-19 condition.[1] After a diagnosis of COVID-19, the understanding of what distinguishes those with from those without post COVID-19 condition allows the design of studies of lung capacity/pulmonary rehabilitation based on the expected baseline for these patients. It also allows the use of appropriate tools for an accurate diagnosis of post COVID-19 condition.

The objective of the present study was to establish a relationship between 1MSTST parameters and post COVID-19 condition as defined by the current WHO criteria.[3]

METHODS

Study setting

We prospectively enrolled adults referred for outpatient pulmonary function testing between April of 2021 and June of 2022 in the Pathophysiology Laboratory of the *Centro Hospitalar Universitário do Porto*, located in the city of Porto, Portugal. Inclusion criteria were being ≥ 18 years of age, being an outpatient followed at the *Centro Hospitalar Universitário do Porto*, and having at least one positive RT-PCR nasal/pharyngeal swab result for SARS-CoV-2 in the last 18 months. Patients performed the 1MSTST under the supervision of a cardiopulmonary technician who was blinded to whether or not they had symptoms of post COVID-19 condition.

Exclusion criteria were having a second episode of possible/confirmed SARS-CoV-2 infection before the 1MSTST, declining to participate in the study, and having any contraindication to the 1MSTST (inability to perform the test because of limited mobility or limited joint mobility/joint pain, for example; systolic blood pressure > 180 mmHg; and diastolic blood pressure > 100 mmHg). For a power of 80% and a two-sided type I error of 5%, a minimum sample size of 34 was calculated to be required to detect an effect size of at least 0.5 for HR, SpO_2, and number of repetitions over the course of the 1MSTST.

The present study was approved by the local research ethics committee, and all participating patients gave written informed consent. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Procedures and data collection

We collected data on the following: baseline demographic and anthropometric characteristics; patient medical history (including hospitalization records); tobacco exposure history; and underlying comorbidities. All patients underwent chest CT scans in the post COVID-19 period (8.9 ± 3.9 months after the diagnosis of COVID-19, at a minimum of 4 months but at no more than 14 months after diagnosis).

To determine whether patients with post COVID-19 condition had pulmonary function test results that were different from those in other post COVID-19 patients, all of the patients included in the present study underwent body plethysmography (MasterScreen™ Body/Diff v-707340; CareFusion, Hoechberg, Germany; and MasterScreen™ Body/Diff; Jaeger, Hoechberg, Germany), with the equipment being calibrated in accordance with the manufacturer recommendations. Percent predicted DL_{CO} and spirometric values were based on the Global Lung Function Initiative equations for patients ≤ 85 years of age and on the European Community for Steel and Coal equations for those > 86 years of age.[13,14] For static lung volumes, the European Community for Steel and Coal equations for adults were used.[13]

The 1MSTST was performed on a standard-height (46-cm) fixed-leg chair with no armrests and the backrest against a wall. Participants were not allowed to use their hands or arms to push against the chair seat or their body. Participants were instructed to complete as many sit-to-stand actions as possible in 1 min at a self-paced speed. Cardiorespiratory parameters, as well as systolic and diastolic blood pressure, together with shortness of breath and leg fatigue (as assessed by the modified Borg scale) were recorded before and immediately after the 1MSTST. Oxygen saturation and HR were recorded at the beginning of the test, at 30 s after initiation of the test, at the end of the test, and at 1 min after completion of the test. The evaluator had previous experience in applying the 1MSTST. In order to assess blood pressure, HR, and SpO_2, a vital signs monitor (CARESCAPE V100; GE HealthCare Technologies Inc., Chicago, IL, USA) was used.

Post COVID-19 condition was defined in accordance with the WHO criteria, i.e., adult individuals with RT-PCR–confirmed SARS-CoV-2 infection presenting with new-onset symptoms up to 3 months from the diagnosis of COVID-19 that last for at least 2 months and cannot be explained by an alternative diagnosis.

Statistical analysis

All patient data were anonymized before statistical analysis, which was performed with the IBM SPSS Statistics software package, version 26.0 (IBM Corporation, Armonk, NY, USA). The demographic and clinical characteristics of the patients were described with descriptive statistics. Data are presented as number (proportion) for categorical variables; mean ± standard deviation for continuous variables with normal distribution; and median (interquartile range) for continuous variables with non-normal distribution. The age-predicted maximal heart rate (HR_{max}) was calculated by the following equation: $HR_{max} = 220 - age$.[15,16]

Univariate analysis was performed with the chi-square test or Fisher's exact test, whereas continuous variables were compared by means of the Student's t-test or the Mann-Whitney test for nonparametric data. The multivariate model included age, sex, and variables showing $p < 0.2$ in the univariate analysis. Taking into consideration that the prevalence of post COVID-19 condition decreases over time,[5] we also adjusted our findings for the time elapsed between the diagnosis of COVID-19 and the performance of the 1MSTST. A two-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

A total of 53 patients (43.4% of whom were male, with a mean age of 49.8 ± 17.0 years) were analyzed. Of those 53 patients, 25 (47.2%) had post COVID-19 condition (Table 1). In the 25 patients with post COVID-19 condition, the most common symptoms were fatigue/insomnia (n = 12; 48%), dyspnea (n = 9; 36%), cough (n = 2; 8%), upper airway symptoms (n = 1; 4%), and headache (n = 1; 4%).

The BMI was higher in the patients with post COVID-19 condition than in those without it (28.9 ± 5.4 kg/m^2 vs. 26.7 ± 3.8 kg/m^2), although the difference was not significant (p = 0.082). Healthcare workers were mostly previously healthy patients, with 31.6% with prior lung disease. The remaining population had prior lung disease in 64.7% of the cases (p=0.021).

New-onset chest CT findings (i.e., findings that were nonexistent before COVID-19) were more common in the patients with post COVID-19 condition than in those without it (p = 0.045). In addition, the latter group of patients did not present with reticular/fibrotic opacities. The chest CT scans were performed in a similar time frame for both groups (p = 0.223), i.e., 10 ± 4.7 months after the diagnosis of COVID-19 in those with post COVID-19 condition and 7.4 ± 1.6 months in those without it.

Pulmonary function test results were overall similar between the two groups of patients (Table 2). There were no significant differences between the patients with post COVID-19 condition and new-onset respiratory symptoms (n = 12) and those with other symptoms regarding demographic characteristics, clinical characteristics, 1MSTST results, and imaging findings. However, those with new-onset respiratory symptoms had a significantly lower percent predicted carbon monoxide transfer coefficient (86.7 ± 14.2% vs. 101.6 ± 15.7%; p = 0.021).

Figure 1 shows HR at the beginning of the 1MSTST, at 30 s after initiation of the test, at the end of the test, and at 1 min after completion of the test. The groups of patients with and without post COVID-19 condition showed similar HR at rest (76.0 ± 12.8 bpm vs. 78.5 ± 12.1 bpm; p = 0.476). HR was lower in those with post COVID-19 condition at 30 s after initiation of the test (86.2 ± 14.3 bpm vs. 101.2 ± 14.7 bpm; p < 0.001) and at the end of the test (94.4 ± 18.2 bpm vs. 117.3 ± 15.3 bpm; p < 0.001), as well as at 1 min after completion of the test (81.2 ± 14.4 bpm vs. 90.5 ± 12.9 bpm; p = 0.016). Regarding mean SpO_2, there were significant differences between the groups of patients with and without post COVID-19 condition, although only at the end of the 1MSTST (94.9 ± 3.6% vs. 96.8 ± 2.4%; Figure 2).

As can be seen in Table 3, the patients with post COVID-19 condition performed fewer repetitions on the 1MSTST than did those without it (p = 0.020). The

Table 1. Characteristics of the study population.[a]

Characteristic	Total sample (N = 53)	Group		p
		Post COVID-19 condition (n = 25; 47.2%)	No post COVID-19 condition (n = 28; 52.8%)	
Age, years	49.8 ± 17.0	52.9 ± 14.8	47.0 ± 18.7	0.216
Male sex	23 (43.4)	10 (40.0)	13 (46.4)	0.637
Current/former smoker	20 (37.7)	9 (36.0)	11 (39.3)	0.805
Smoking history, pack-years[b]	31.1 ± 16.3	30.6 ± 15.5	31.5 ± 17.7	0.703
BMI, kg/m^2	27.7 ± 4.7	28.9 ± 5.4	26.7 ± 3.8	0.082
Hospitalization for COVID-19	11 (20.8)	6 (24.0)	5 (17.9)	0.582
Time elapsed between the diagnosis of COVID-19 and the 1MSTST	7.0 [5.0-9.5]	7.0 [5.0-10.5]	7.0 [5.0-9.0]	0.535
New-onset chest CT findings	25 (47.2)	16 (64.0)	8 (28.6)	0.045
Ground-glass opacities	17 (32.1)	8 (32.0)	8 (28.6)	
Reticular/fibrotic opacities	8 (15.1)	8 (32.0)	0	
Preexisting lung disease	29 (54.7)	14 (56.0)	15 (53.6)	0.662
Asthma	18 (34.0)	8 (32.0)	10 (35.7)	
COPD	5 (9.4)	1 (4.0)	4 (14.3)	
Interstitial lung disease	2 (3.8)	2 (8.0)	0 (0.0)	
OSA	4 (7.5)	3 (12.0)	1 (3.6)	

1MSTST: one-minute sit-to-stand test; and OSA: obstructive sleep apnea. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]For current/former smokers only.

Table 2. Pulmonary function test results.[a]

Parameter	Total sample (N = 53)	Group		p
		Post COVID-19 condition (n = 25; 47.2%)	No post COVID-19 condition (n = 28; 52.8%)	
FVC, L	3.45 ± 0.94	3.24 ± 0.63	3.38 ± 0.98	0.460
FVC, % predicted	94.1 ± 15.7	93.6 ± 13.3	94.0 ± 17.1	0.856
FEV_1, L	2.73 ± 0.79	2.61 ± 0.60	2.64 ± 0.78	0.561
FEV_1, % predicted	92.2 ± 18.8	92.7 ± 17.3	92.1 ± 20.7	0.975
FEV_1/FVC ratio	78.5 ± 9.0	78.8 ± 9.1	77.9 ± 8.8	0.830
Airway resistance	0.30 ± 0.18	0.31 ± 0.22	0.29 ± 0.14	0.747
Airway resistance, % predicted	101.4 ± 61.9	104.7 ± 75.3	97.8 ± 45.5	0.725
RV	2.03 ± 0.80	2.05 ± 0.97	2.02 ± 0.59	0.895
RV, % predicted	108.2 ± 31.0	108.4 ± 36.3	107.9 ± 25.3	0.963
TLC	5.45 ± 1.18	5.42 ± 1.10	5.48 ± 1.28	0.871
TLC, % predicted	102.9 ± 16.4	103.2 ± 16.3	102.6 ± 17.0	0.911
Single-breath DL_{CO}	6.68 ± 1.61	6.97 ± 1.47	6.37 ± 1.74	0.643
Single-breath DL_{CO}, % predicted	82.7 ± 17.2	86.2 ± 17.9	79.1 ± 16.1	0.496
K_{CO}	1.50 ± 0.56	1.63 ± 0.73	1.37 ± 0.25	0.599
K_{CO}, % predicted	93.2 ± 16.6	96.9 ± 17.0	89.3 ± 15.7	0.117

K_{CO}: carbon monoxide transfer coefficient. [a]Values expressed as mean ± SD.

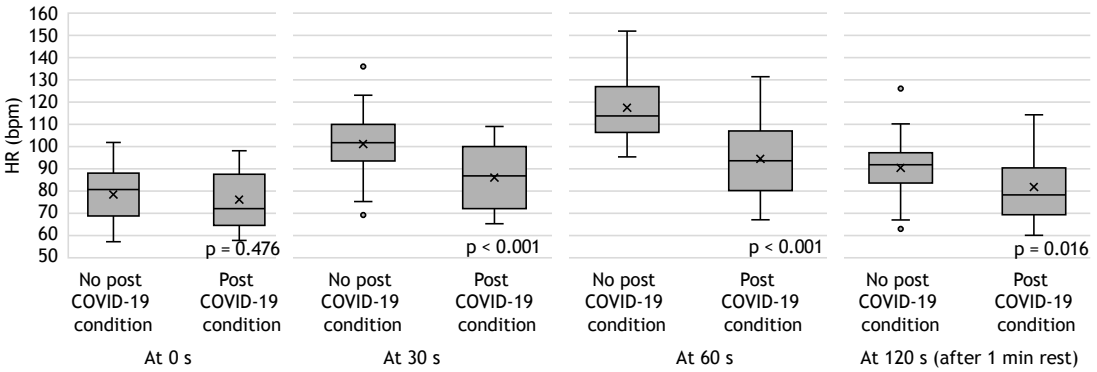

Figure 1. HR over the course of the one-minute sit-to-stand test in the groups of patients with and without post COVID-19 condition.

ratio between HR at the end of the 1MSTST and HR_{max} (HR_{end}/HR_{max}) was lower in the group of patients with post COVID-19 condition ($p < 0.001$). The HR_{end}/HR_{max} cutoff that maximized both sensitivity and specificity was 62.65% (sensitivity, 78.6%; specificity, 82.0%). In our cohort, all of the patients without post COVID-19 condition had an HR_{end}/HR_{max} above 51.48% (sensitivity, 100%; specificity, 48.0%).

Systolic blood pressure and diastolic blood pressure were similar between the two groups at the beginning of the 1MSTST ($p = 0.464$ and $p = 0.864$, respectively) and at the end of the test ($p = 0.784$ and $p = 0.475$, respectively), as well as at 1 min after completion of the test ($p = 0.261$ and $p = 0.768$, respectively).

DISCUSSION

In this study, new-onset chest CT findings were more common in the patients with post COVID-19 condition than in those without it. Although there have been reports of an increased number of CT abnormalities after the diagnosis of COVID-19 (particularly severe COVID-19), there are currently no studies comparing COVID-19 patients with and without post COVID-19 condition.[17] Regarding pulmonary function tests, the results were similar between the groups of patients with and without post COVID-19 condition in the present study. Those with post COVID-19 condition and new-onset respiratory symptoms had a significantly lower percent predicted carbon monoxide transfer coefficient (86.7 ± 14.2% vs. 101.6 ± 15.7%; $p = 0.021$). However, the results of this subgroup analysis should be interpreted with caution because of the small sample size (n = 12). The most commonly described abnormalities in COVID-19 patients are changes in DL_{CO}, a restrictive ventilatory pattern, and an obstructive ventilatory pattern.[18] However, there have been no studies comparing patients with and without post COVID-19 condition.

Regarding the 1MSTST, the patients with post COVID-19 condition in the present study had lower HR at 30 s after initiation of the test, at the end of

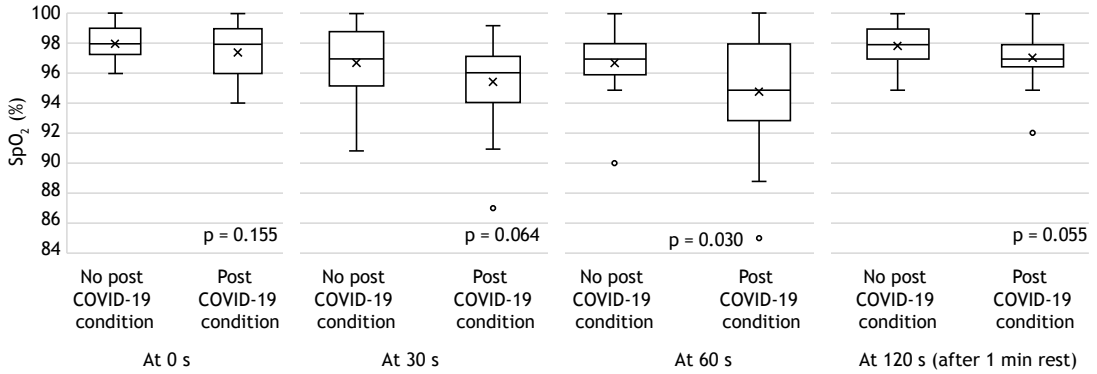

Figure 2. SpO_2 over the course of the one-minute sit-to-stand test in the groups of patients with and without post COVID-19 condition.

Table 3. HR, SpO_2, blood pressure, and number of repetitions over the course of the one-minute sit-to-stand test.[a]

	Total sample (N = 53)	Group: Post COVID-19 condition (n = 25; 47.2%)	Group: No post COVID-19 condition (n = 28; 52.8%)	p (univariate)	p* (multivariate)
HR, bpm					
At the beginning of the 1MSTST	77.3 ± 12.4	76.0 ± 12.8	78.5 ± 12.1	0.476	
At 30 s after initiation of the 1MSTST	94.1 ± 16.2	86.2 ± 14.3	101.2 ± 14.7	< 0.001	0.005
At the end of the 1MSTST	106.5 ± 20.2	94.4 ± 18.2	117.3 ± 15.3	< 0.001	< 0.001
At 1 min after completion of the 1MSTST	86.1 ± 14.3	81.2 ± 14.4	90.5 ± 12.9	0.016	0.073
HR_{end}/HR_{max}, %	62.9 ± 12.4	56.8 ± 11.7	68.4 ± 10.4	< 0.001	< 0.001
SpO_2, %					
At the beginning of the 1MSTST	97.7 ± 1.5	97.4 ± 1.8	98.0 ± 1.0	0.155	0.368
At 30 s after initiation of the 1MSTST	96.1 ± 2.6	95.3 ± 2.8	96.7 ± 2.3	0.064	0.117
At the end of the 1MSTST	95.9 ± 3.1	94.9 ± 3.6	96.8 ± 2.4	0.030	0.037
At 1 min after completion of the 1MSTST	97.6 ± 1.5	97.2 ± 1.7	97.9 ± 1.2	0.055	0.183
No. of repetitions on the 1MSTST	35.5 ± 8.6	32.6 ± 7.0	38.0 ± 9.1	0.020	0.060
Systolic BP, mmHg					
At the beginning of the 1MSTST	128.2 ± 16.0	129.7 ± 15.5	126.7 ± 16.5	0.464	
At the end of the 1MSTST	147.2 ± 22.6	146.3 ± 18.6	148.1 ± 26.2	0.784	
Diastolic BP, mmHg					
At the beginning of the 1MSTST	74.8 ± 9.6	74.5 ± 8.5	75.2 ± 10.6	0.864	
At the end of the 1MSTST	79.1 ± 10.3	80.2 ± 9.4	78.1 ± 11.1	0.475	

1MSTST: one-minute sit-to-stand test; HR_{end}/HR_{max}: ratio between HR at the end of the 1MSTST and age-predicted maximal HR; and BP: blood pressure. [a]Values expressed as mean ± SD. *The multivariate model included age, sex, time elapsed between the diagnosis of COVID-19 and the performance of the 1MSTST, and variables showing p < 0.2 in the univariate analysis of patient demographic data (i.e., BMI).

the test, and at 1 min after completion of the test, as well as lower SpO_2 at the end of the test and lower HR_{end}/HR_{max}. After adjusting for age, sex, time elapsed between the diagnosis of COVID-19 and the performance of the 1MSTST, and variables showing $p < 0.2$ in the univariate analysis, we found that all of the variables remained statistically significant, the exception being HR at 1 min after completion of the test. In an attempt to find an HR_{end} cutoff adjusted for the expected HR_{max} to support the diagnosis of post COVID-19 condition, we found that all of the patients without post COVID-19 condition in our cohort had an HR_{end}/HR_{max} above 51.48%, and the optimal threshold value (Youden index) for a diagnosis of post COVID-19

condition was 62.65% (sensitivity, 78.6%; specificity, 82.0%).

An inappropriate sinus tachycardia at rest appears to affect 20% of all patients with post COVID-19 condition; this is probably due to autonomic nervous system disorder (postinfectious dysautonomia).[19] It is not known whether patients with post COVID-19 condition are more affected by inappropriate sinus tachycardia at rest than are other COVID-19 patients. Sinus bradycardia is known to occur during sleep in patients with COVID-19.[20] Orthostatic hypotension and postural orthostatic tachycardia syndrome have also been reported to be common after SARS-CoV-2 infection,[19,21] with both conditions being interpreted as complications of dysautonomia.[21] The higher prevalence of exertional bradycardia in patients with post COVID-19 condition occurs in opposition to the high prevalence of inappropriate sinus tachycardia at rest in these patients. A major role of the autonomic nervous system in the pathophysiology of HR dysregulation is consistent with inadequate HR responses to rest and exercise in patients with post COVID-19 condition.[19,21,22]

Although we did not perform continuous HR monitoring throughout the 1MSTST, we recognize that it would be valuable to perform a cardiac stress test to understand whether post COVID-19 condition is associated with sinus bradycardia or bradyarrhythmia during exercise tests. Furthermore, the 1MSTST requires a reasonable degree of lower limb joint integrity, and this explains the limited sample size for the study period and the relatively low mean age of the study population (49.8 years). In order to validate the exercise capacity results obtained with the 1MSTST, it would have been of interest to perform the six-minute walk test. However, this study was initiated at a time when the six-minute walk test was performed only in selected patients, after having been suspended worldwide because of the COVID-19 outbreak.

In the appropriate clinical setting, an HR_{end}/HR_{max} below 62.65% (in particular, an HR_{end}/HR_{max} below 51.48%) appears to be suggestive of a diagnosis of post COVID-19 condition.

AUTHOR CONTRIBUTIONS

NF: conceptualization, data curation, formal analysis, investigation, methodology, project administration, software, visualization, drafting of the manuscript, and reviewing and editing of the manuscript. TO: conceptualization, formal analysis, methodology, validation, and reviewing and editing of the manuscript. PP and VA: conceptualization, data curation, formal analysis, methodology, project administration, software, validation, and reviewing and editing of the manuscript. RC and MJF: data curation and investigation. MS: formal analysis, project administration, and reviewing and editing of the manuscript. JG: conceptualization, formal analysis, investigation, methodology, project administration, software, supervision, validation, drafting of the manuscript, and reviewing and editing of the manuscript. All of the authors read and approved the final manuscript.

CONFLICTS OF INTEREST

None declared.

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ORIGINAL ARTICLE

Ninety-day outcomes in patients diagnosed with COVID-19 in São Paulo, Brazil: a cohort study

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ABSTRACT

Objective: COVID-19 has been associated with a significant burden to those who survive the acute phase. We aimed to describe the quality of life and symptoms of anxiety, depression, and posttraumatic stress disorder (PTSD) at 90 days after hospital discharge of COVID-19 patients. **Methods:** Patients with COVID-19 admitted to a private hospital in the city of São Paulo, Brazil, between April of 2020 and April of 2021 were interviewed by telephone at 30 and 90 days after discharge to assess the quality of life and symptoms of depression, anxiety, and PTSD. **Results:** A total of 2,138 patients were included. The mean age was 58.6 ± 15.8 years, and the median length of hospital stay was 9.0 (5.0-15.8) days. Between the two time points, depression increased from 3.1% to 7.2% ($p < 0.001$), anxiety increased from 3.2% to 6.2% ($p < 0.001$), and PTSD increased from 2.3% to 5.0% ($p < 0.001$). At least one physical symptom related to COVID-19 diagnosis persisted in 32% of patients at day 90. **Conclusions:** Persistence of physical symptoms was high even at 90 days after discharge. Although the prevalence of symptoms of anxiety, depression, and PTSD was low, these symptoms persisted for three months, with a significant increase between the time points. This finding indicates the need to identify at-risk patients so that they can be given an appropriate referral at discharge.

Keywords: COVID-19; Anxiety; Depression; Stress disorders, post-traumatic; Quality of life; Critical care outcomes.

INTRODUCTION

During the first two waves of the COVID-19 pandemic in Brazil, approximately half of patients hospitalized with the disease were admitted to an ICU. During these two waves, 44% to 55% of these critically ill patients experienced ARDS and required invasive mechanical ventilation, and mortality rates were higher than 75%.[1]

Overall, survivors of COVID-19 now amount to more than 400 million worldwide.[2] There is a high probability that at least some of these patients experience new or worsened physical, cognitive, and mental health symptoms that persist after hospital discharge, especially those who were admitted to the ICU (post-intensive care syndrome).[3,4] Severely ill patients with COVID-19 are often discharged home with some degree of functional disability.[5] These patients will most likely benefit from meticulous follow-up with rehabilitation programs aiming at physical and neuropsychological recovery.[6]

Pre-COVID-19 epidemiological studies have shown that up to 75% of patients undergoing mechanical ventilation in the ICU suffer from delirium during their stay.[7] COVID-19 patients have been proven to be especially vulnerable to delirium, with more than 54% of those developing it during the first 21 days of ICU in a multicenter cohort.[8] As a result, these patients may be at an increased risk of long-term cognitive impairment.[9]

There is now evidence of the psychiatric implications of COVID-19 both during the acute phase and after hospital discharge.[4,10] A single-center study has shown that sequelae of COVID-19 were common (in 49% of patients), and symptoms, such as anxiety or depression, were present in 26% 1 year after the diagnosis of COVID-19. Moreover, even patients who have physically recovered from symptoms are at risk of suffering from long-term mental health problems such as posttraumatic stress disorder (PTSD), anxiety, and depression, which can negatively impact their quality of life (QoL).[11,12] However, most studies have evaluated either the persistence of symptoms or the QoL after COVID-19. Therefore, we aimed to describe the QoL and symptoms of anxiety, depression, and PTSD at 90 days after hospital discharge in COVID-19 patients using validated instruments.

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METHODS

Study design and participants

This is a single-center retrospective cohort study performed at the *Hospital Sírio-Libanês*, a private tertiary health care center in São Paulo, Brazil. We included all adult patients (≥ 18 years of age) with laboratory-confirmed COVID-19 by RT-PCR who were hospitalized and discharged alive between April of 2020 and April of 2021. All eligible patients received a telephone call at 30 and 90 days after hospital discharge and were invited to answer specific questions on their health status. This telephone follow-up interview was part of an institutional initiative to evaluate outcomes for COVID-19 patients and generate benchmarking and research data. The study protocol was approved by the local research ethics committee (*Hospital Sirio-Libanês*, approval number CAAE 51460021.6.0000.5461), which waived the need for informed consent.

Data collection during hospital-stay

The following demographic and clinical data were collected during hospital stay: age, sex, symptoms at admission, level of education, comorbidities, need for ICU admission, hospital/ICU length of stay (LOS), respiratory support (oxygen therapy, high flow nasal cannula, noninvasive mechanical ventilation, invasive mechanical ventilation, and extracorporeal membrane oxygenation), hemodynamic support (vasopressors, intra-aortic balloon pump, and extracorporeal membrane oxygenation), nosocomial infections, treatments (antibiotics, corticosteroids, and others), need for tracheostomy, use of psychological support, need for physical rehabilitation, and vital status at hospital discharge.

30- and 90-day follow-up of COVID-19 survivors

A structured telephone interview questionnaire was administered twice (at 30 and 90 days after hospital discharge). The questionnaire contained questions on demographics, persistence of symptoms, need for oxygen therapy, need for dialysis, need for specific medical or rehabilitation care, return to work, among others.

Three specific validated questionnaires were also administered. To assess the quality of life, including usual activities of daily living, we used the EuroQol Group 5-Dimension 3-Level questionnaire (EQ-5D-3L),[13,14] which has five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) that are scored on a categorical scale ranging from 1 to 3, where 1 indicates no problem, 2 indicates some problems, and 3 indicates a severe problem. To screen for depression, we administered the Patient Health Questionnaire-2 (PHQ-2),[15,16] a two-item questionnaire about the frequency of depressed mood and anhedonia in the past two weeks, ranging from 0 to 6 (scores ≥ 3 indicate a high likelihood of major depression). To screen for anxiety, we administered the Generalized Anxiety Disorder-2 (GAD-2),[17] a two-item questionnaire about the frequency of anxiety and worrying symptoms in the past two weeks, ranging from 0 to 6 (scores ≥ 3 indicate a high likelihood of generalized anxiety disorder). Finally, PTSD was defined according to the Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition) criteria.[18]

Statistical analysis

Absolute and relative frequencies were used for qualitative variables and mean ± standard deviation or median (IQR), as appropriate, was used to describe quantitative characteristics. The association with the outcomes of qualitative variables was assessed using the chi-square test or exact tests (Fisher's exact test or likelihood ratio), and that of quantitative variables was assessed with the Student's t-test. The analyses were performed with R (R version 4.0.2) and R Studio version 1.3.959 (The R Foundation for Statistical Computing, Vienna, Austria). Significance was set at $p < 0.05$.

RESULTS

A total of 3,086 patients with PCR-confirmed COVID-19 were admitted to the *Hospital Sírio-Libanês* during the study period. Of these, 2,952 (95.7%) were discharged alive. The mean age of survivors was lower than that of nonsurvivors (58.6 ± 15.8 years vs. 80.8 ± 10.5 years; $p < 0.001$). Additionally, survivors had shorter hospital lengths of stay as compared with nonsurvivors—median: 9.0 (5.0-15.8) days vs. 25.0 (13.0-48.0) days; $p < 0.001$). A total of 735 (23.8%) of patients were admitted to the ICU with a median ICU length of stay of 10 (5-17) days, 396 (53.9%) of whom required invasive mechanical ventilation for a median of 10 (6-21) days. The in-hospital mortality of patients admitted to the ICU was 14.6%.

Of the 2,952 patients discharged alive, 1,122 (38.0%) completed the interview on both occasions (at 30 and 90 days after discharge), 670 (22.6%) completed only the first interview (day 30), and 346 (11.7%) completed only the second interview (day 90). A total of 2,138 (72.3%) of patients completed the interview at least once after hospital discharge (Figure 1). The characteristics of the patients included at each time point are described in Table 1. There was no statistically significant difference between the groups of patients who completed the interview at 30 days (30-day group), at 90 days (90-day group), and on both occasions (30+90-day group), except for the use of corticosteroids during hospital stay, which was lower in the 90-day group.

On day 30, 41.2% of non-ICU patients reported persistence of at least one physical symptom related to COVID-19 diagnosis. Although a significant decrease was shown on day 90, 30.3% of the patients reported persistence of symptoms ($p < 0.001$). This decrease was also evident in the patients who had been admitted to the ICU—56.9% and 37.8% reported persistence

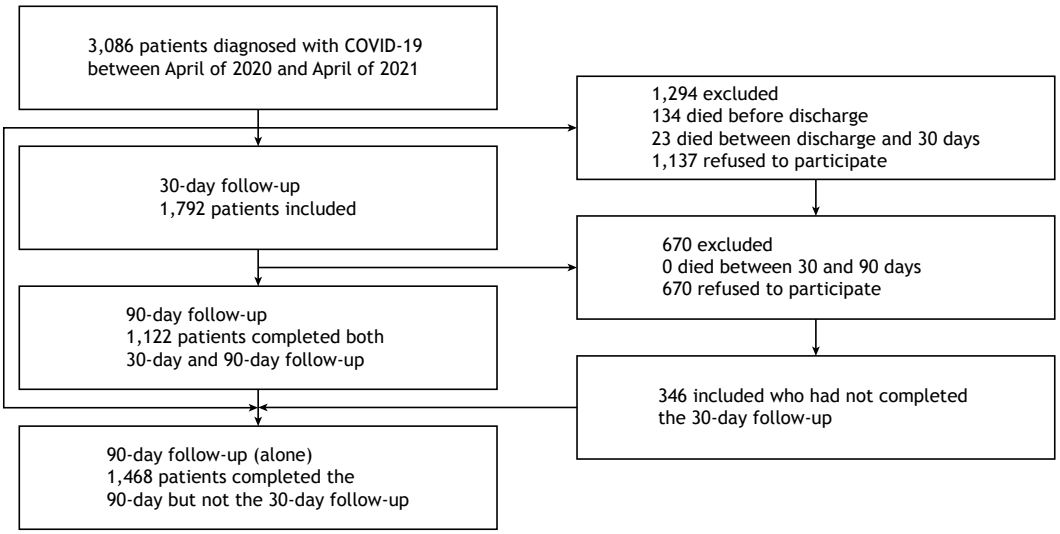

Figure 1. Flow chart of patient inclusion at 30- and 90-day follow-up interviews.

Table 1. Characteristics of the patients.[a]

Characteristic	Group			p
	30-day (n = 1,792)	90-day (n = 1,468)	30 + 90 day (n = 1,122)	
Age, years	59.3 ± 15.8	59.6 ± 15.5	59.9 ± 15.6	0.59
Sex at birth, female	626 (34.9)	491 (33.4)	374 (33.3)	0.57
Ethnicity, White	1,571 (95.6)	1,306 (96.0)	990 (96.2)	0.52
Marital status, married	1,438 (81.1)	1,184 (81.5)	923 (83.2)	0.4
Higher education	1,509 (86.2)	1,257 (87.2)	963 (87.5)	0.38
Comorbidities	1,399 (78.1)	1,148 (78.2)	879 (78.3)	0.98
Arterial hypertension	702 (39.2)	587 (40.0)	456 (40.6)	0.72
Diabetes	381 (21.3)	324(22.1)	251 (22.4)	0.74
Cardiovascular disease	325 (18.1)	285 (19.4)	222 (19.8)	0.47
Cerebrovascular disease	48 (2.7)	39 (2.7)	30 (2.7)	0.99
Corticosteroids	1,385 (77.3)	1,015 (69.1)*,†	839 (74.8)	< 0.001
High-flow nasal cannula	323 (18.0)	227 (15.5)	188 (26.8)	0.15
NIV	446 (24.9)	327 (22.3)	278 (24.8)	0.17
Invasive MV	195 (10.0)	137 (9.3)	111 (9.9)	0.28
Vasopressor use	162 (9)	130 (8.9)	107 (9.5)	0.83
Psychological support during hospitalization	213 (11.9)	157 (10.7)	125 (11.2)	0.55
Rehabilitation support during hospitalization	1,414 (79.0)	1,127 (76.8)	875 (78.1)	0.34
Need of ICU admission	391 (21.8)	326 (22.2)	252 (22.4)	0.91
ICU LOS, days	15 [10-25]	15 [9-24]	16 [10-26]	0.15
Hospital LOS, days,	8 [5-14]	8 [5-13]	8 [5-14]	0.62

NIV: noninvasive ventilation; MV: mechanical ventilation, and LOS: length of stay. [a]Values expressed as n (%), mean ± SD, or median [IQR]. [b]Only for patients admitted to the ICU. To correct for multiple comparison between two groups of study participants, we used a Bonferroni corrected p-value of 0.0167 for statistical significance. *p < 0.001 (90-day vs. 30-day). †p = 0.002 (90-day vs. 30+90-day.

of symptoms on day 30 and on day 90, respectively (p < 0.001; Table 2).

The temporal trends in the EQ-5D-3L domains, GAD-2 score, PHQ-2 score, and other symptoms in non-ICU and ICU patients are shown in Table 2. Between 30 and 90 days after hospital discharge, the proportion of ICU patients with mobility problems decreased (from 31.6% to 21.0%, p = 0.003), as did the proportion of ICU patients with problems in performing usual activities (from 21.3% to 14.5%; p = 0.047), whereas there was no difference in the self-care and pain/discomfort domains of the EQ-5D-3L. Non-ICU patients had similar mobility, self-care, and usual activities domain results, but there was a decrease in the proportion of non-ICU patients without pain or discomfort (from 92.3% to 84.1%; p < 0.001) between 30 and 90 days after hospital discharge. In both the ICU and non-ICU groups, there was a decrease in the number of patients

Table 2. Outcomes at 30 days and at 90 days after discharge.

Outcome	Total sample (n = 2,138)			Group					
				30-day (n = 1,792)			90-day (n = 1,468)		
	30-day	90-day	p	Non-ICU	ICU	p	Non-ICU	ICU	p
EQ-5D-3L									
Mobility			0.1			< 0.001			< 0.001
I have no problems in walking about	1,458/1,783 (81.8%)	1,237/1,462 (84.6%)		1,192/1,394 (85.5%)	266/389 (68.4%)		981/1,138 (86.2%)	256/324 (79%)	
I have some problems in walking about	292/1,783 (16.4%)	202/1,462 (13.8%)		184/1,394 (13.2%)	108/389 (27.8%)		146/1,138 (12.8%)	56/324 (17.3%)	
I am confined to bed	33/1,783 (1.8%)	23/1,462 (1.6%)		18/1,394 (1.3%)	15/389 (3.9%)		11/1,138 (1%)	12/324 (3.7%)	
Self-care			0.87			< 0.001			< 0.001
I have no problems with self-care	1,640/1,783 (92%)	1,347/1,463 (92.1%)		1,306/1,394 (93.7%)	334/389 (85.9%)		1,062/1,138 (93.3%)	285/325 (87.7%)	
I have some problems washing or dressing myself	104/1,783 (5.8%)	81/1,463 (5.5%)		66/1,394 (4.7%)	38/389 (9.8%)		58/1,138 (5.1%)	23/325 (7.1%)	
I am unable to wash or dress myself	39/1,783 (2.2%)	35/1,463 (2.4%)		22/1,394 (1.6%)	17/389 (4.4%)		18/1,138 (1.6%)	17/325 (5.2%)	
Usual activities			0.95			< 0.001			0.04
I have no problems with performing my usual activities	1,565/1,781 (87.9%)	1,289/1,461 (88.2%)		1,258/1,391 (90.4%)	307/389 (78.7%)		1,012/1,137 (89%)	277/324 (85.5%)	
I have some problems with performing my usual activities	178/1,781 (10%)	142/1,461 (9.7%)		111/1,391 (8%)	67/389 (17.2%)		107/1,137 (9.4%)	35/324 (10.8%)	
I am unable to perform my usual activities	38/1,781 (2.1%)	30/1,461 (2.1%)		22/1,391 (1.6%)	16/389 (4.1%)		18/1,137 (1.6%)	12/324 (3.7%)	
Pain/Discomfort			<0.001			0.03			0.95
I have no pain or discomfort	1,623/1,772 (91.69%)	1,223/1,455 (84.1%)		1,279/1,386 (92.3%)	344/386 (88.4%)		953/1,133 (84.1%)	270/322 (83.8%)	
I have moderate pain or discomfort	134/1,772 (7.6%)	198/1,455 (13.6%)		99/1,386 (7.1%)	35/386 (9%)		153/1,133 (13.5%)	45/322 (14%)	
I have extreme pain or discomfort	15/1,772 (0.8%)	34/1,455 (2.3%)		8/1,386 (0.6%)	7/386 (1.8%)		27/1,133 (2.4%)	7/322 (2.2%)	
Anxiety/Depression			< 0.001			0.82			0.4
I am not anxious or depressed	1,529/1,765 (85.7%)	1,151/1,451 (79.4%)		1,198/1,379 (86.9%)	331/386 (85.1%)		902/1,130 (79.8%)	249/321 (77.5%)	
I am moderately anxious or depressed	195/1,765 (11%)	256/1,451 (17.6%)		149/1,379 (10.8%)	46/386 (11.8%)		192/1,130 (17%)	64/321 (20%)	
I am extremely anxious or depressed	41/1,765 (2.3%)	44/1,451 (3%)		32/1,379 (2.3%)	9/386 (2.3%)		36/1,130 (3.2%)	8/321 (2.5%)	

Continue...▶

Table 2. Outcomes at 30 days and at 90 days after discharge. (Continued...)

Outcome	Total sample			Group					
				30-day (n = 1,792)			90-day (n = 1,468)		
	30-day (n = 2,138)	90-day	p	Non-ICU	ICU	p	Non-ICU	ICU	p
GAD-2 ≥ 3	48/1,478 (3.2%)	77/1,245 (6.2%)	< 0.001	36/1,190 (3%)	10/287 (3.5%)	0.68	63/987 (6.4%)	14/258 (5.4%)	0.57
PHQ-2 ≥ 3	46/1,477 (3.1%)	90/1,247 (7.2%)	< 0.001	42/1,191 (3.5%)	6/287 (2.1%)	0.21	69/989 (7%)	21/258 (8.1%)	0.52
Persistence of any physical symptoms related to the COVID-19 diagnosis	795/1,779 (44.6%)	466/1,457 (32%)	< 0.001	573/1,389 (41.2%)	222/390 (56.9%)	< 0.001	343/1132 (30.3%)	123/325 (37.8%)	0.01
Post-traumatic stress disorder									
Repetitive and disturbing thoughts, memories or images	34/1,476 (2.3%)	63/1,251 (5%)	< 0.001	22/1,188 (1.9%)	12/288 (4.2%)	0.02	38/990 (3.8%)	25/260 (9.6%)	< 0.001
Physical symptoms related to the hospitalization	45/1,476 (3%)	37/1,243 (3%)	0.89	34/1189 (2.9%)	11/287 (3.8%)	0.38	22/985 (2.2%)	15/258 (5.8%)	0.002

EQ-5D-3L: EuroQol Group 5-Dimension 3-Level questionnaire; GAD-2: Generalized Anxiety Disorder-2; and PHQ-2: Patient Health Questionnaire-2.

without anxiety or depression feelings (anxiety/depression domain of the EQ-5D-3L), from 85.1% to 77.5% (p = 0.012) and from 86.9% to 79.8% (p < 0.001), respectively.

In a sensitivity analysis, we obtained similar results when we restricted all comparisons to the 1,122 patients in the 30+90-day group (Table 3).

There was an increase in the number of patients with a PHQ-2 score ≥ 3 from day 30 to day 90 in both the non-ICU (from 3.5% to 7.0%; p < 0.001) and ICU groups (from 2.1% to 8.1%; p = 0.001; Table 2). Only in the non-ICU group was there a significant increase in the number of patients with a GAD-2 score ≥ 3 from day 30 to day 90 (from 3.0% to 6.4%; p < 0.001). The number of patients with symptoms of PTSD, that is, with disturbing thoughts referring to the recent illness, increased from day 30 to day 90 in both non-ICU (from 1.9% to 3.8%; p = 0.004) and ICU groups (from 4.2% to 9.6%; p = 0.01). Conversely, there was no significant difference in physical symptoms related to the hospitalization from day 30 to day 90 in either group.

The worsening of PTSD (p = 0.931), GAD-2 score, and PHQ-2 score showed no significant correlations with the inability of patients to return to work. However, a noticeable deterioration in mobility (p < 0.001) and an increase in pain or discomfort (p = 0.013) were significantly correlated with the inability to return to work.

DISCUSSION

In this large Brazilian cohort treated at a private hospital, we showed that the persistence of physical symptoms related to COVID-19 diagnosis decreased over time but still affected 3 in 10 patients 90 days after hospital discharge. Also, patients who had been admitted to the ICU showed improved mobility and usual activities within this period. The number of patients experiencing subjective symptoms, such as pain, discomfort, anxiety, and depression, increased over time, mostly among non-ICU patients. This increase had no association with whether patients could return to work or not.

We described the prevalence of anxiety and depression at 90 days after discharge. Some studies have evaluated psychiatric disorders after COVID-19.[4,10,19] From the clinical perspective, the essence of COVID-19 should be seen as a sepsis-induced viral infection and has the essential characteristics of sepsis induced by other pathogens.[20] We showed that COVID-19, like sepsis and septic shock,[21] leads to long-lasting neuropsychiatric consequences, with almost 1 in 10 patients still experiencing anxiety, depression, and PTSD three months after discharge. We, however, found the prevalence of these conditions to be lower than that found by others. Huang et al.[4] found that 23% of patients admitted to the hospital due to COVID-19 had anxiety or depression six months after discharge, whereas a meta-analysis showed a pooled

Table 3. Patients who completed the questionnaires at 30 and 90 days after discharge (n = 1,122).[a]

	Total			Group					
				30-day			90-day		
	(n = 1,122)			(n = 1,122)			(n = 1,122)		
	30 days	90 days	p	Non-ICU	ICU	p	Non-ICU	ICU	p
EQ-5D-3L									
Mobility			0.112			< 0.001			< 0.001
I have no problems in walking about	918 (82.2)	944 (84.5)		746 (85.9)	174 (69.3)		746 (85.9)	201 (79.8)	
I have some problems in walking about	175 (15.7)	152 (13.6)		111 (12.8)	64 (25.5)		113 (13.0)	39 (15.5)	
I am confined to bed	24 (2.1)	21 (1.9)		11 (1.3)	13 (5.2)		9 (1.0)	12 (4.8)	
Self-Care			0.584			< 0.001			< 0.001
I have no problems with self-care	1,030 (92.2)	1,025 (91.8)		817 (94.2)	215 (85.3)		807 (93.0)	221 (87.7)	
I have some problems washing or dressing myself	61 (5.5)	60 (5.4)		37 (4.3)	24 (9.5)		46 (5.3)	14 (5.6)	
I am unable to wash or dress myself	26 (2.3)	32 (2.9)		13 (1.5)	13 (5.2)		15 (1.7)	17 (6.7)	
Usual activities			0.803			< 0.001			0.011
I have no problems with performing my usual activities	975 (87.4)	985 (88.3)		784 (90.4)	194 (77.0)		774 (89.3)	214 (84.9)	
I have some problems with performing my usual activities	117 (10.5)	105 (9.4)		70 (8.1)	47 (18.7)		79 (9.1)	26 (10.3)	
I am unable to perform my usual activities	24 (2.2)	26 (2.3)		13 (1.5)	11 (4.4)		14 (1.6)	12 (4.8)	
Pain/Discomfort			< 0.001			0.057			0.800
I have no pain or discomfort	1,020 (92.3)	927 (83.9)		804 (93.2)	222 (89.2)		722 (83.4)	212 (85.1)	
I have moderate pain or discomfort	75 (6.8)	150 (13.6)		54 (6.3)	22 (8.8)		121 (14.0)	31 (12.4)	
I have extreme pain or discomfort	10 (0.9)	28 (2.5)		5 (0.6)	5 (2.0)		23 (2.7)	6 (2.4)	
Anxiety/Depression			< 0.001			0.700			0.452
I am not anxious or depressed	971 (88.2)	869 (78.9)		760 (88.4)	218 (87.2)		688 (79.8)	190 (76.3)	
I am moderately anxious or depressed	114 (10.4)	201 (18.3)		89 (10.3)	27 (10.8)		150 (17.4)	52 (20.9)	
I am extremely anxious or depressed	16 (1.5)	31 (2.8)		11 (1.3)	5 (2.0)		24 (2.8)	7 (2.8)	
GAD-2 ≥ 3	**17 (1.9)**	**50 (5.6)**	**< 0.001**	**15 (2.0)**	**4 (2.2)**	**0.777**	**42 (5.6)**	**9 (4.7)**	**0.623**
PHQ-2 ≥ 3	**25 (2.8)**	**66 (7.4)**	**< 0.001**	**19 (2.5)**	**6 (3.2)**	**0.610**	**48 (6.4)**	**18 (9.4)**	**0.144**
Persistence of any physical symptoms related to the COVID-19 diagnosis	509 (45.9)	364 (32.9)	< 0.001	367 (42.5)	143 (56.7)	< 0.001	264 (30.6)	102 (40.5)	0.003
Post-traumatic stress disorder									
Repetitive and disturbing thoughts, memories or images	19 (2.1)	52 (5.8)	< 0.001	13 (1.7)	8 (4.3)	0.049	33 (4.4)	22 (11.4)	< 0.001
Physical symptoms related to the hospitalization	26 (2.9)	22 (2.5)	0.608	20 (2.7)	6 (3.2)	0.663	13 (1.7)	12 (6.3)	0.001

EQ-5D-3L: EuroQol Group 5-Dimension 3-Level questionnaire; GAD-2: Generalized Anxiety Disorder-2; and PHQ-2: Patient Health Questionnaire-2. [a]Values expressed as n (%).

prevalence of depression and anxiety of 45-47% after COVID-19 infection.[22] Several reasons could underlie this difference. First, many studies used the EuroQol-5D to determine the prevalence of anxiety and depression, while we used the GAD-2 and PHQ-2 questionnaires. When measured by the EuroQol-5D

(20.5%), the prevalence of anxiety and depression was similar to that in the study by Huang et al.,[4] but still considerably lower than that described by Deng et al.[22] Second, we studied patients from a hospital that serves a population of high socioeconomic status, with full access to health care both before and after hospitalization. The differences in prevalence may result from differences in accessibility to health care.

Our study has several limitations. First, it was a single-center, retrospective study in a hospital which is not representative of most of Brazilian health care institutions. Thus, the generalizability of our findings is limited, at least to most people living in low- and middle-income countries. Second, we used an administrative database not originally designed for research purposes to assess 30- and 90-day outcomes. However, this database is systematically fed by dedicated personnel with previous training on administering different questionnaires over the phone. Third, we could only obtain 90-day follow-up interviews of two-thirds of the patients who participated in the telephone interview at 30 days. However, in a sensitivity analysis in which we restricted all comparisons to patients who completed the interviews on both occasions, the results were not appreciably altered. Finally, we used simplified versions of questionnaires for anxiety (GAD-2) and depression (PHQ-2), which are mainly used as screening, not diagnostic tools.

In conclusion, we found that hospital admission due to COVID-19 seems to be associated with a relatively low prevalence of anxiety and depression 90 days after hospital discharge. However, of concern is the fact that there was an increase over time in the prevalence of anxiety and depression 90 days after discharge, which points to the necessity to identify patients at risk of developing anxiety/depression so that they can be given an appropriate referral at discharge.

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AUTHOR CONTRIBUTIONS

RRLF, ELVC, and BMT: formal analysis; methodology; writing of the original draft; and review and editing of the manuscript. LVC and MMSS: data curation; project administration; and review and editing of the manuscript. CBL, TCN, LFC, LPJ, and JMVJ: conceptualization; formal analysis; methodology; project administration; and review and editing of the manuscript. CVM, LCPA, MSO, and LUT: reviewing/editing the manuscript.

All authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Geographic patterns and hotspots of pediatric tuberculosis: the role of socioeconomic determinants

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ABSTRACT

Objective: Children are an important demographic group for understanding overall tuberculosis epidemiology, and monitoring of childhood tuberculosis is essential for appropriate prevention. The present study sought to characterize the spatial distribution of childhood tuberculosis notification rates in continental Portugal; identify high-risk areas; and evaluate the association between childhood tuberculosis notification rates and socioeconomic deprivation. **Methods:** Using hierarchical Bayesian spatial models, we analyzed the geographic distribution of pediatric tuberculosis notification rates across 278 municipalities between 2016 and 2020 and determined high-risk and low-risk areas. We used the Portuguese version of the European Deprivation Index to estimate the association between childhood tuberculosis and area-level socioeconomic deprivation. **Results:** Notification rates ranged from 1.8 to 13.15 per 100,000 children under 5 years of age. We identified seven high-risk areas, the relative risk of which was significantly above the study area average. All seven high-risk areas were located in the metropolitan area of Porto or Lisbon. There was a significant relationship between socioeconomic deprivation and pediatric tuberculosis notification rates (relative risk = 1.16; Bayesian credible interval, 1.05-1.29). **Conclusions:** Identified high-risk and socioeconomically deprived areas should constitute target areas for tuberculosis control, and these data should be integrated with other risk factors to define more precise criteria for BCG vaccination.

Keywords: Child; Poverty; Vaccination; Mycobacterium bovis.

INTRODUCTION

Tuberculosis still has a significant burden worldwide: 10.6 million people fell ill with tuberculosis in 2021, 11% of whom were children.[1] The number of tuberculosis deaths in 2020 was approximately 1.5 million; of those, 140,000 occurred among children.[2] Despite advances in tuberculosis control, tuberculosis continues to play a significant role in mortality worldwide and is expected to rank second among the leading causes of death from a single infectious agent in 2020, after COVID-19.[3]

Regarding tuberculosis infection in children and adolescents, treatment is critical to avoid progression to tuberculosis disease and to prevent them from becoming the future reservoir for tuberculosis transmission.[4] It might be more complex to determine the precise extent of tuberculosis in children than in adults because of the lack of a standard case definition and because of diagnostic challenges such as the difficulty of bacteriological confirmation, the low specificity of clinical signs and symptoms, the high frequency of extrapulmonary disease, and underreporting.[3] Most children are infected by household members or other close contacts with tuberculosis disease, particularly parents or other caregivers, and represent a missed opportunity by the health care system to prevent the disease.[5] Children under five years of age represent an important demographic group for understanding the epidemiology of tuberculosis because it frequently progresses rapidly from primary or latent tuberculosis infection to tuberculosis disease, and severe disease manifestations are more common in this age group.[4] Therefore, these children serve as sentinel

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cases, indicating recent and/or ongoing transmission in the community.[5]

In Portugal, there has been a reduction in the incidence of tuberculosis in recent years; in 2014 Portugal reached the threshold value (of < 20/100,000 population) to be considered a low-incidence country.[3,6] Simultaneously, other criteria for adequate tuberculosis control recommended by the WHO were fulfilled: the existence of an effective surveillance system and an annual incidence of tuberculous meningitis in children below 1/10,000,000 population in the last five years.[6,7] Thus, in 2016, in line with what was already being done in other countries with low tuberculosis incidence, the strategy of selective vaccination of children under 6 years of age belonging to risk groups was adopted by the Directorate-General of Health of Portugal.[8]

The association between higher rates of tuberculosis and socioeconomic deprivation has been established in several countries, particularly in those with low income, high crowding, less education, and high unemployment.[9-12] One study evaluated the relationship between tuberculosis notification and socioeconomic deprivation across municipalities in Portugal.[13] Although the tuberculosis notification rate was not significantly associated with the Portuguese version of the European Deprivation Index (EDI-PT), it was significantly associated with some of the EDI-PT components, namely, the proportion of manual workers and the unemployment rate.[13] The EDI-PT has been positively and significantly associated with multidrug-resistant tuberculosis and non-multidrug-resistant tuberculosis notification rates in the metropolitan area of Lisbon, Portugal.[14] Although less is known about the influence of socioeconomic deprivation on childhood tuberculosis, children might be particularly vulnerable to the socioeconomic features of the community. Factors known to have an impact include the level of education of the adult population, because educated parents/adults are more likely to recognize symptoms and seek medical care,[15] and housing conditions such as overcrowding, because children are more likely to share spaces with other children and adults.[16,17] Therefore, it is plausible that composite area-level measures of socioeconomic deprivation, such as the EDI-PT, are significantly associated with childhood tuberculosis.

The epidemiological characterization of childhood tuberculosis contributes to a better diagnostic approach to tuberculosis in the overall population, and monitoring and follow-up of childhood tuberculosis cases are essential for appropriate prevention and treatment. Thus, we sought to characterize the spatial distribution of childhood tuberculosis notification rates in Portugal; identify high-risk areas; and determine whether there is an association between childhood tuberculosis notification rates and area-level socioeconomic deprivation. To our knowledge, this is the first study in Portugal to evaluate these aspects of childhood tuberculosis.

METHODS

Data collection and study area

In Portugal, tuberculosis notification is mandatory. The data were collected from the Portuguese National Tuberculosis Surveillance System. We evaluated the notification rates of childhood tuberculosis per municipality in continental Portugal (n = 278) between January of 2016 and December of 2020. We included all tuberculosis cases in children under six years of age. Archipelagos were excluded because only two cases were notified in a single municipality (Ribeira Grande, on the Azores Islands), and this would have yielded highly unstable notification rates.

Population data were extracted from the Statistics Portugal website (https://www.ine.pt/), and we used population estimates by municipality for the study period (age group, 0-5 years).

Socioeconomic deprivation

The EDI-PT was used in order to assess socioeconomic deprivation across municipalities in continental Portugal. The EDI-PT comprises eight census variables and was calculated on the basis of the equation presented in Chart 1.[18]

Statistical analysis

We used hierarchical Bayesian spatial models to estimate the relative risk (RR) and notification rates for each area and to determine high-risk and low-risk areas. We assumed that the response variable (tuberculosis cases in each area) followed a Poisson distribution where E_i is the expected number of cases and θ_i is the RR (equation 1). We used the tuberculosis notification rates for the entire country as a reference to compute the expected number of cases. The expected number of cases was obtained by summing the product of the notification rates for the reference population (i.e., the population in continental Portugal) by the population of each municipality (n = 278).

$$O_i \sim Poisson\ (E_i, \theta_i) \quad \text{(Equation 1)}$$

$$Log\ (\theta_i) = \alpha + S_i \quad \text{(Equation 2.1)}$$

where α is an intercept quantifying the mean number of tuberculosis cases in the 278 municipalities. The area-specific effect S_i was modeled on the basis of a Besag-York-Mollié model[19] with a parameterization suggested by Dean et al. (equation 2.2.).[20]

$$S_i = \tau\ (\sqrt{\varphi} * \upsilon_i + \sqrt{1-\varphi} * \nu_i) \quad \text{(Equation 2.2)}$$

where υ_i is the structured effect and ν_i is the unstructured effect. The effect was scaled to render the model more intuitive and interpretable,[21] so that φ expresses the proportion of the spatial effect caused by the structured part and $1/\tau$ is the marginal variance of S_i.

Additionally, we used the function excursions to determine high-risk and low-risk areas.[13,14,22] High-risk areas are those whose RR is significantly above 1 (i.e., above the study area average), whereas low-risk areas are those whose RR is significantly below 1 (i.e.,

Chart 1. Equation used in order to calculate the European Deprivation Index for Portugal.

Variables
EDI-PT = % non-owned households × 1.191 + % households without indoor flushing × 1.729 + % household with 5 rooms or less × 0.964 + % blue-collars × 0.370 + % residents with low education level × 0.511 + % non-employers × 0.620 + % unemployed looking for a job × 0.268 + % foreign residents × 1.038

EDI-PT: Portuguese version of the European Deprivation Index. Adapted from Ribeiro et al.[18]

below the study area average). This method uses the posterior joint distribution computed from the Integrated Nested Laplace Approximations (INLA). It considers the dependence structure, allowing accurate identification of areas where the RR is greater than 1. To facilitate interpretation, RR was converted into rates per 100,000 population in the 0- to 5-year age bracket.

We also used the aforementioned models to evaluate the association between pediatric tuberculosis and area-level socioeconomic deprivation. The association was expressed in RR, which represents the risk increment per unit increase in the socioeconomic deprivation score. An RR was considered significantly higher or lower if Bayesian credible intervals did not include the value 1. RRs and Bayesian credible intervals were derived from their posterior means and quintiles. Posterior distributions were obtained using the INLA, which was implemented in the R INLA library.[23] RR, high-risk areas, and low-risk areas were mapped with the free, open-source geographic information system QGIS, version 3.16.

Ethical considerations

Ethical approval and informed consent were not required, because all patient data, collected for an official Portuguese national surveillance system, were anonymized in accordance with the ethical research guidelines in Portugal.

RESULTS

Between 2016 and 2020, 152 childhood tuberculosis cases were notified in Portugal (number of cases per year: 19 in 2016, 31 in 2017, 34 in 2018, 43 in 2019, and 25 in 2020). This corresponds to a crude childhood tuberculosis notification rate of 5.48 notifications per 100,000 children in the 0- to 5-year age bracket. Notification rates of childhood tuberculosis ranged from 1.88 notifications (in Portimão, in the Algarve) to 13.15 notifications (in Loures, in the metropolitan area of Lisbon) per 100,000 children in the 0- to 5-year age bracket. In the study period, annual live births ranged from 84,530 to 87,126; in 2016, there were 9,277 children vaccinated with BCG (10.6%).[24,25] With regard to severe forms of tuberculosis (disseminated tuberculosis, meningeal tuberculosis, or a combination of the two), 4 cases were reported in 2018 (all 4 were unvaccinated children, and 3 with met the eligibility criteria for BCG vaccination), and 7 cases were reported in 2019 (5 were unvaccinated children, and 1 met the eligibility criteria for BCG vaccination).[6] In 2020, seven of the 25 notified children with tuberculosis (28.0%) had been vaccinated with BCG.[24]

The spatial distribution of the notification rates of pediatric tuberculosis is portrayed in Figure 1A, and the delimitation of high-risk and low-risk areas is shown in Figure 1B. As can be seen in Figure 1B, there are seven high-risk areas for pediatric tuberculosis in Portugal (Lisbon, Loures, Sintra, Amadora, Odivelas, Matosinhos, and Vila Nova de Gaia), all of which are located in the metropolitan area of Porto or Lisbon.

A significant positive association was found between the EDI-PT and the pediatric tuberculosis notification rates (RR = 1.16; Bayesian credible interval, 1.05-1.29). Thus, for each unit increase in the deprivation index, the notification rate of childhood tuberculosis increased by 16%.

DISCUSSION

In this study, we characterized the geographic distribution of the pediatric tuberculosis notification rates in Portugal during the five years following the transition from a universal to a selective BCG vaccination strategy.

Given that Portugal is a country with a low incidence of tuberculosis, the most appropriate prevention strategy in children, without increasing the risk to public health, is early screening of exposed children, preventive treatment, and vaccination of children in risk groups, because they are the ones who individually benefit the most from vaccination. It is therefore recommended that the risk in unvaccinated children < 6 years of age be reassessed every time there is a contact with the health services, because the individual risk situation can change.[26] However, in recent years there have been severe forms of tuberculosis in children who are unvaccinated but meet the criteria for BCG vaccination. This highlights the importance of identifying and vaccinating cases eligible for vaccination.

Considering this detailed spatial distribution at the municipality level, we identified high-risk and low-risk areas for childhood tuberculosis across Portugal. As previously reported in studies of spatial analysis of tuberculosis in general at the national level[13,27] and at the international level,[28] we also found a highly heterogeneous spatial distribution of childhood tuberculosis.

Because there was no predefined cutoff for determining the childhood tuberculosis incidence rate, we used as a criterion an RR significantly above the study area average. Seven high-risk areas were thus identified, all of which are located in the metropolitan area of Porto or Lisbon. While this concentration of tuberculosis in the metropolitan areas has been reported in other spatial analysis studies, high-risk areas for adult tuberculosis in Portugal can also be found in

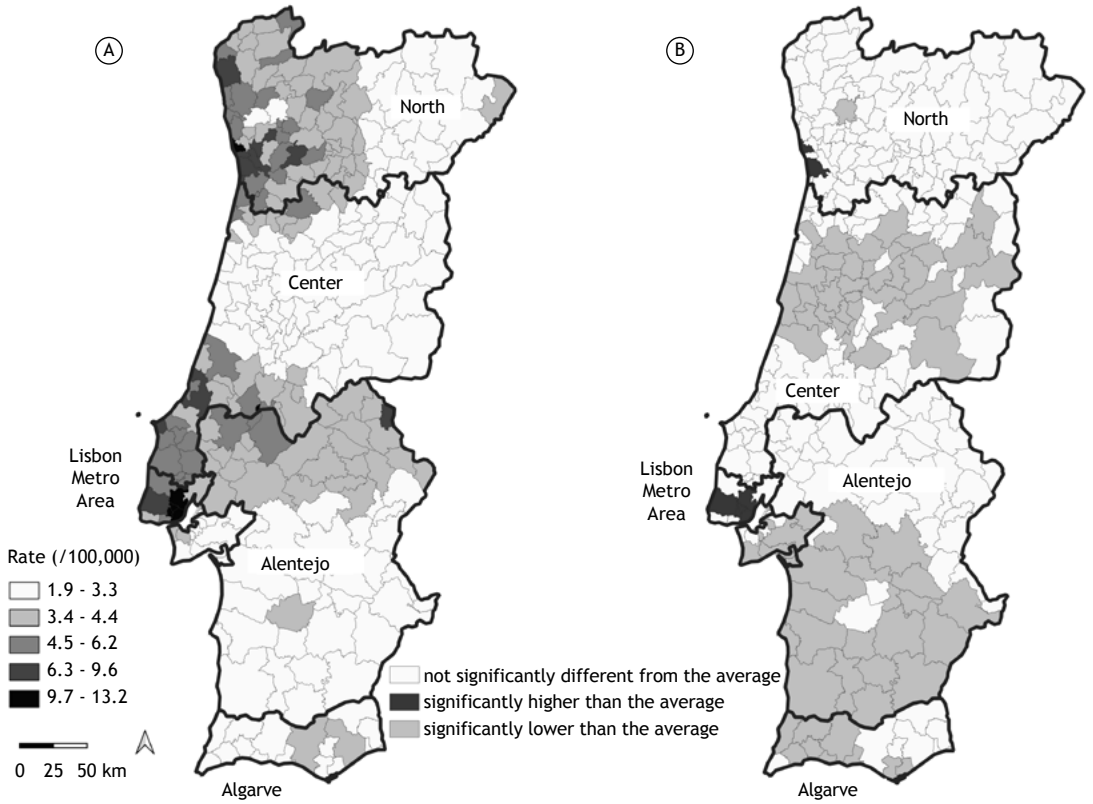

Figure 1. Spatial distribution of the notification rates of pediatric tuberculosis (in A) and corresponding delimitation of high-risk and low-risk areas (in B). High-risk areas are those whose relative risk (RR) is significantly above 1 (i.e., above the study area average), whereas low-risk areas are those whose RR is significantly below 1 (i.e., below the study area average).

peripheral and industrial regions of the metropolitan area of Porto; on the Alentejo coast; and in the Algarve.[27,29,30] To our knowledge, this type of spatial analysis of childhood tuberculosis in Portugal had never been performed. Given its unique approach, adult data should not be extrapolated to the pediatric population. Several studies have assessed the spatial distribution of tuberculosis and its association with socioeconomic deprivation; however, less is known about childhood tuberculosis. The relationship between a variety of socioeconomic factors and pediatric tuberculosis has been demonstrated in some regions: lower access to health care in the Philippines,[21] higher population density in Indonesia,[31] and higher poverty in Spain.[32] We demonstrated a significant positive association between childhood tuberculosis notification rates and socioeconomic deprivation in Portugal. For each unit increase in the EDI-PT, the notification rate of childhood tuberculosis increased by 16%, this effect being greater than that for adult tuberculosis, the percent increase for which is 5% only (unpublished results). Our results suggest that socioeconomic deprivation is a risk factor for childhood tuberculosis. These findings are not supported by a previous study conducted in Portugal, in which the composite EDI-PT was not related to the tuberculosis notification rate.[13] However, in that study,[13] a different version of the EDI-PT was used. Instead, we used an updated version. In addition, the aforementioned study[13] evaluated the overall tuberculosis notification rate, whereas, in our study, the focus was on childhood tuberculosis, reflecting epidemiological differences between tuberculosis in adults and in children. Therefore, this might be a relevant criterion when selecting candidates for BCG vaccination and the risk groups already defined by the Directorate-General of Health of Portugal for selective vaccination.[8]

One of the strengths of this study is the robust statistical methods used in order to describe the geographic distribution of childhood tuberculosis cases, which led to the identification of risk areas for childhood tuberculosis. The use of an updated socioeconomic deprivation score such as the EDI-PT, validated for use in the Portuguese population, is another strength of the present study. Some of the limitations of our study are its retrospective nature and the use of data from the Portuguese national notification system, which do not allow a more detailed characterization of the study population. As previously shown, there are numerous other recognized risk factors for childhood tuberculosis, such as malnutrition, illiteracy, overcrowded housing, immunosuppression (including HIV infection), and smoking status.[33-35] Therefore, we believe that it would be relevant to analyze other risk factors in this

population in order to gain a better understanding of the pathways behind the association between socioeconomic deprivation and adult tuberculosis.

In conclusion, we found a heterogeneous geographic distribution in childhood tuberculosis notification rates and identified high-risk areas across municipalities in Portugal. Thus, priority should be given to these areas in order to raise awareness for disease prevention in cases with known risk factors, as well as early identification and treatment of tuberculosis disease cases in adults and children. In addition, we established that socioeconomic deprivation is significantly associated with childhood tuberculosis notification rates, playing a stronger role than it does in adult tuberculosis. Furthermore, the EDI-PT was found to be a sensitive measure to capture tuberculosis-related inequalities, which might also be an important factor to consider when identifying cases eligible for vaccination. These findings should be integrated with other possible risk factors in order to define more accurate criteria for BCG vaccination and be used in order to inform public health policies related to tuberculosis disease control.

AUTHOR CONTRIBUTIONS

RD: study conception and design. SD and SC: database organization, drafting of the manuscript (both contributed equally). AIR and ETK: statistical analysis. AIR: drafting sections of the manuscript. All authors contributed to manuscript revision and approved the submitted version.

CONFLICTS OF INTEREST

None declared.

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Loss of response to calcium channel blockers after long-term follow-up treatment in patients with idiopathic pulmonary arterial hypertension

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ABSTRACT

Idiopathic pulmonary arterial hypertension (PAH) patients with a positive response to acute vasodilator challenge and a clinical response to calcium channel blockers (CCBs) for at least one year are traditionally designated true responders. Nevertheless, little is known about a sustained response to CCBs over longer periods of time. We evaluated the loss of response to CCBs after long-term treatment in a cohort of idiopathic PAH patients previously classified as being true responders. Our data suggest that idiopathic PAH patients can lose clinical response to CCBs even after one year of clinical stability, reinforcing the need for constant multidimensional reevaluation to assess the need for targeted PAH therapies and to classify these patients correctly.

Keywords: Pulmonary hypertension; Vasodilator agents; Calcium channel blockers.

Idiopathic pulmonary arterial hypertension (PAH) is a rare condition that is characterized by progressive remodeling of small pulmonary arteries in the absence of associated conditions; this remodeling leads to increased pulmonary vascular resistance and mean pulmonary artery pressure (mPAP), which in turn lead to right heart failure and death.[1-3] Vasoconstriction can play a role in the development of idiopathic PAH in patients who respond to acute vasodilator challenge, characterizing a different phenotype.[4] In a prospective study published in 1992, Rich et al. showed for the first time that idiopathic PAH patients presenting with an acute response to vasodilators could benefit from treatment with calcium channel blockers (CCBs).[5] In a retrospective study published in 2005, Sitbon et al. investigated a cohort of patients with idiopathic PAH and found that 12.6% were responders to acute vasodilator challenge; however, the clinical status of almost half of those patients did not improve with CCB treatment after one year of follow-up.[6] The authors also showed that those who remained responders to CCBs after one year had a better survival rate.[6] Nevertheless, the proportion of patients who remain responsive to CCBs after periods longer than one year remains unknown. The objective of the present study was to evaluate a sustained clinical response to CCBs in patients with idiopathic PAH.

We evaluated retrospective data obtained from the medical records of all consecutive patients diagnosed with idiopathic PAH and responding to acute vasodilator challenge between January of 2003 and December of 2018 at a referral center for PAH. Baseline data included New York Heart Association (NYHA) functional class, brain natriuretic peptide (BNP) levels, the six-minute walk distance (6MWD), and hemodynamic parameters. There are new criteria for the diagnosis of idiopathic PAH.[7] However, because of the retrospective nature of the present study, we defined idiopathic PAH as an mPAP ≥ 25 mmHg, a normal pulmonary artery wedge pressure of ≤ 15 mmHg, and a pulmonary vascular resistance > 3 Wood units in the absence of other causes of precapillary pulmonary hypertension.[8] All patients underwent right heart catheterization in accordance with standard techniques, and all vasodilator challenges were performed in accordance with the same protocol during the study period, with inhaled nitric oxide for 10 min. The test was considered positive if there was a decrease in mPAP of at least 10 mmHg to an absolute mean of < 40 mmHg without a decrease in cardiac output.[9,10]

After a positive response to vasodilator challenge, patients were started on treatment with CCBs. Short-term responders were defined as those who failed to reach or maintain NYHA functional class I or II, or those in whom BNP levels remained elevated and/or the 6MWD remained short during the first year of treatment with CCBs. True responders were defined as those who achieved or remained in NYHA functional class I or II after treatment with CCBs for at least one year,[6] with improvements in BNP levels and the 6MWD, remaining clinically stable during the follow-up period. Loss of response to CCBs after long-term treatment was defined as any worsening of NYHA functional class, the 6MWD, and/or BNP levels followed by prescription of specific PAH therapy after one year of treatment with CCBs, at the discretion of the attending physician. The one-year mortality risk

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was assessed in accordance with criteria described elsewhere,[11] being classified as low or not low at baseline, 3-6 months after initiation of treatment with CCBs, and before initiation of targeted PAH therapies. Because these were not the criteria that were classically used at the time in order to define response to CCBs, we used them exclusively to reinforce the need for multidimensional assessment.

All statistical analyses were performed with the IBM SPSS Statistics software package, version 26 (IBM Corporation, Armonk, NY, USA). Continuous variables are expressed as mean ± standard deviation, whereas categorical data are expressed as proportions. Differences between groups were analyzed by means of the Student's t-test or the chi-square test, as appropriate. A value of $p < 0.05$ was considered statistically significant.

We collected data on 26 patients presenting with a positive response to acute vasodilator challenge, those patients corresponding to 16.1% of all patients diagnosed with idiopathic PAH during the study period. All 26 patients met the criteria for an acute vasodilator response (Figure 1). Baseline clinical, demographic, and hemodynamic characteristics are presented in Table 1. Four patients (2.4%) had a positive response to acute vasodilator challenge but showed no clinical improvement after treatment with CCBs, therefore being classified as short-term responders. Twenty-two patients (13.6% of the total of patients diagnosed with idiopathic PAH during the study period) met the criteria for response to CCBs over the course of at least one year of treatment. However, only 11 (6.8% of the total of patients diagnosed with idiopathic PAH during the study period) remained stable for periods longer than one year, without the need for specific PAH therapy, and were therefore classified as true responders to treatment with CCBs. The group of 11 patients who responded to treatment with CCBs for more than one year but later showed no clinical response (6.8% of the total of patients diagnosed with idiopathic PAH during the study period) did so after a mean follow-up period of 47 months and were then prescribed specific PAH therapy. At diagnosis, there were no significant differences in clinical, hemodynamic, and functional characteristics between the group of true responders and that of those who lost response after long-term follow-up.

After initial treatment with CCBs, only 27% of the patients who later had a loss of response to CCBs did not meet the criteria for a low mortality risk in one year. Those patients were reassessed before initiation of targeted PAH therapies, and 82% were classified as not being at a low mortality risk.

We had four deaths in our cohort. Two deaths occurred in the group of patients who lost response to CCBs, and two occurred in the group of patients who were still receiving treatment with CCBs at the time of analysis. Three deaths occurred because of infections followed by right ventricular failure. One death occurred in the postoperative period after lung transplantation, in a patient in whom treatment with CCBs had failed.

We found that one year of clinical response to CCBs might be insufficient to predict a long-term clinical benefit and a favorable outcome in patients with idiopathic PAH. Approximately 50% of patients with a positive clinical response for one year showed clinical and functional worsening and required specific PAH therapy after approximately four years of follow-up.

In contrast with our findings, Sitbon et al.[6] reported that all but one idiopathic PAH patient who had at least one year of clinical benefit with CCBs after a positive response to acute vasodilator challenge had an excellent prognosis after seven years of follow-up and did not require add-on therapy for the treatment of PAH. However, our results show that this phenotype of idiopathic PAH is not absolute, and a one-year follow-up period may not be enough to identify patients who will have a favorable outcome while on treatment with CCBs exclusively. Genetic evaluation of idiopathic PAH patients, comparing vasodilator-responsive with vasodilator-nonresponsive patients, showed that multiple genetic variants are present in the same individual.[12] Therefore, it is quite possible that an acute vasodilator response and a one-year response to treatment with CCBs encompass multiple genotypic features, resulting in similar, although not identical, phenotypic patterns.

The concept of risk stratification is recent[11,13,14] and has not been used in order to determine response to CCBs. According to Sitbon et al., long-term responders are those who are in NYHA functional class I or II and show a sustained hemodynamic improvement without the need for specific therapy.[6] Although these were the criteria that were used at our institution in the last decade, it is of note that evaluation by risk stratification also reflected the loss of response. Although this is apparently obvious, it had not been previously demonstrated and reinforces the need for multidimensional reassessment in patients deemed to be responders.

Our study has limitations that are inherent to its retrospective nature, such as a small sample size. Furthermore, hemodynamic variables such as cardiac index and stroke volume were not available to refine risk assessment, and neither was hemodynamic reassessment at follow-up. In addition, no specific thresholds were used in order to determine CCB response, and neither was it a multidimensional assessment. Nevertheless, our findings raise questions that merit further investigation in prospective and controlled cohorts to validate the latest changes in the classification of PAH,[15] which now includes CCB responders as a separate subgroup of PAH patients.

In conclusion, our data suggest that idiopathic PAH patients can lose clinical response to CCBs even after one year of clinical stability, reinforcing the need for constant multidimensional reevaluation to assess the need for targeted PAH therapies and to classify these patients correctly.

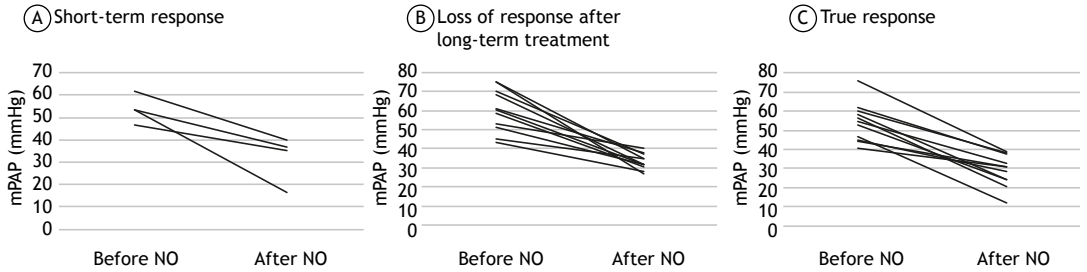

Figure 1. Mean pulmonary artery pressure (mPAP) reached during acute vasodilator testing with inhaled nitric oxide (NO) in the 4 patients who lost response to calcium channel blockers (CCBs) in less than one year (in A), in the 11 patients who lost response to CCBs after long-term treatment with CCBs (in B), and in the 11 patients who remained responders to CCBs after long-term treatment with CCBs (in C).

Table 1. Baseline characteristics of patients at diagnosis of idiopathic pulmonary arterial hypertension, by type of response to treatment with calcium channel blockers.[a]

Characteristic	Short-term response (n = 4)	Loss of response after a long-term response (n = 11)	True response (n = 11)	p*	Total (N = 26)
Female sex	4 (100)	10 (91)	9 (81)	0.53	23 (88)
Age, years	34.2 ± 12.9	33.6 ± 9.8	33.7 ± 13.9	0.98	33.8 ± 11.7
NYHA functional class	-	1 (11.1)	1 (9.1)	0.54	2 (9.1)
I	2 (100)	5 (55.6)	6 (54.5)		13 (59.1)
II	-	3 (33.3)	2 (18.2)		5 (22.7)
III	-	-	2 (18.2)		2 (9.1)
IV					
BNP, pg/dL	128.5 ± 72.8	155.7 ± 153.8	47.0 ± 45.4	0.11	98.3 ± 111.7
6MWD, m	435 ± 77	475 ± 61	458 ± 94	0.69	463.7 ± 77.0
Hemodynamic parameters					
RAP, mmHg	5.8 ± 5.7	10.0 ± 3.6	9.0 ± 4.7	0.61	8.8 ± 4.5
mPAP, mmHg	53.7 ± 6.1	60.2 ± 11.1	54.2 ± 10.1	0.19	56.6 ± 10.2
PAWP, mmHg	9.8 ± 2.9	10.2 ± 2.5	9.2 ± 3.2	0.44	9.7 ± 2.8
Cardiac output, L/min	4.0 ± 1.4	3.7 ± 0.9	4.4 ± 1.2	0.18	4.0 ± 1.1
PVR, Wood units	11.6 ± 2.2	14.0 ± 3.9	11.3 ± 5.4	0.20	12.5 ± 4.4
mPAP after NO, mmHg	32.0 ± 10.4	33.2 ± 4.1	28.9 ± 8.3	0.14	31.2 ± 7.1
Cardiac output after NO, L/min	4.6 ± 1.2	4.2 ± 1.0	4.6 ± 1.2	0.46	4.4 ± 1.1
Not at low risk	2 (50)	7 (64)	6 (55)	0.65	15 (58)
Mean follow-up period, months	77.5 ± 81.1	117.1 ± 38.8	75.0 ± 52.6		93.2 ± 54.2
Time to loss of response, months	4.9 ± 2.7	47.2 ± 37.6	-		-

NYHA: New York Heart Association; BNP: B-type natriuretic peptide; 6MWD: six-minute walk distance; RAP: right atrial pressure; mPAP: mean pulmonary artery pressure; PAWP: pulmonary artery wedge pressure; PVR: pulmonary vascular resistance; and NO: nitric oxide. [a]Values expressed as n (%) or mean ± SD. **For the comparison between true response and loss of response after a long-term response.*

AUTHOR CONTRIBUTIONS

BP, JLAJ, and RS: study design, data collection, data analysis, drafting of the manuscript, and approval of the final version of the manuscript. CJCSF and CJ: data analysis, drafting of the manuscript, and approval of the final version of the manuscript. MC: data collection, data analysis, drafting of the manuscript, and approval of the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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The influence of N95 and FFP2 masks on cardiorespiratory variables in healthy individuals during aerobic exercise: a systematic review and meta-analysis

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Study carried out at the Faculdade de Ciências Médicas e da Saúde de Juiz de Fora – SUPREMA – Juiz de Fora (MG) and at the Universidade Paulista – UNIP – Volta Redonda (RJ) Brasil.

ABSTRACT

Objective: In view of the current COVID-19 pandemic, the objective of this study was to determine, through a systematic review and meta-analysis, whether the use of N95/FFP2 masks during aerobic exercise has a significant impact on HR, RR, SpO_2, and blood pressure (BP) in healthy individuals. **Methods:** We searched the MEDLINE database for studies published in English between 2005 and 2021. To reduce bias and increase reliability, only randomized controlled trials and randomized crossover clinical trials were considered for inclusion. The selected outcomes included HR, RR, SpO_2, and BP, with perceived exertion being evaluated by means of the Borg scale. **Results:** Eight controlled trials were included in the meta-analysis. Seven evaluated HR ($p > 0.05$), five evaluated RR ($p > 0.05$), five evaluated SpO_2 and BP ($p > 0.05$ for both), and six evaluated perceived exertion, presenting controversial results such as risk ratios that were grouped for each variable. **Conclusions:** This study suggests that N95 and FFP2 masks do not have significant effects on HR, RR, SpO_2, and BP during aerobic exercise in healthy individuals.

Keywords: N95 respirators; Heart rate; Respiratory rate; Oxygen saturation; Blood.

INTRODUCTION

Protective masks are essential pieces of personal protective equipment for health professionals, especially those who deal directly with airway infections, as in the case of the current COVID-19 pandemic.[1-3] In a study that was conducted in Singapore in 2020 and in which 30 health professionals wore N95 masks when providing care to patients who tested positive for SARS-CoV-2 infection, there was no patient-to-professional disease transmission.[4]

In a study that was conducted in South Korea in 2015 and in which 97 COPD patients wearing N95 masks were investigated, there were considerable changes in RR, SpO_2, and end-tidal carbon dioxide levels before and after mask use.[5] In another study conducted in 2020, young people who had no comorbidities and who were nonsmokers performed aerobic physical exercise wearing N95 masks for an average of 75-150 min per week and showed no considerable changes in gas concentrations.[6] Kim et al. evaluated 20 healthy young people participating in low- to moderate-intensity physical activity for 1 h while wearing four different models of N95 masks and found no significant gas exchange abnormalities.[7]

According to Chandrasekaran et al.,[8] the use of N95 masks for long periods of time could lead to changes in muscle metabolism; cardiorespiratory stress; changes in the excretory and immune systems; and changes in the brain and central nervous system. This is due to the fact that N95 masks create a closed rebreathing circuit, leading to hypercapnic hypoxia.[8-11]

In a study by Fikenzer et al.,[12] 12 healthy men underwent ergospirometry and impedance cardiography before and after the use of N95 masks, which significantly reduced pulmonary function parameters and peak blood lactate response. However, there is a lack of studies analyzing the correlation between the use of N95/FFP2 masks and possible changes in SpO_2, RR, HR, respiratory resistance, and blood pressure (BP) in the context of the current COVID-19 pandemic.[13-16]

The objective of this study was to determine, through a systematic review and meta-analysis, the effects of N95/FFP2 masks on BP, HR, RR, SpO_2, and perceived effort during aerobic physical activity in healthy individuals.

METHODS

Search strategy

A systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The study protocol was registered with the International Prospective Register of Systematic Reviews (Registration no. CRD42021282318).

We searched the MEDLINE database for articles originally published in English in the last 15 years. Only randomized controlled trials or randomized crossover clinical trials were selected for the review; therefore, the sample of

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studies tended to be homogeneous and avoided biases commonly found in cross-sectional and observational studies. Two independent evaluators searched the MEDLINE database, and, in case of divergence between the two, a third evaluator was consulted. Disagreements were resolved by consensus.

The search terms "N95," "FFRs," "FFP2," "Effects," "Physiological," "Gas," and "Blood" were used in order to identify relevant studies. The MeSH list of descriptors was used in order to identify variations of the aforementioned search terms.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are shown in Chart 1.

Data extraction

Our research group previously selected the information for data collection by separately searching the included studies for the following: title, name of the first author, year in which the study was conducted, year in which the study was published, country of origin, number of participants, mean/median and standard deviation of each variable with and without masks, aerobic interventions used, and outcomes (i.e., HR, RR, SpO_2, and BP as primary outcomes; and respiratory resistance and perceived exertion—as assessed by the Borg scale—as secondary outcomes). All of the authors independently collected the data. To evaluate the articles, two evaluators who were not part of our research group established search strategies and performed critical analyses. After the reading of the articles in their entirety, studies were excluded from the review if there were methodological biases, a lack of direct correlation with the topic of interest, or failure to provide raw data.

Statistical analysis

For the meta-analysis and risk of bias calculation, we used the following programs: Review Manager, version 5.4 (RevMan 5; Cochrane Collaboration, Oxford, UK); Microsoft Excel; and MedCalc (MedCalc Software Ltd, Ostend, Belgium). Fixed and random statistical analyses were performed, with the studies being considered homogeneous. The 95% CI was calculated for each study individually and then for all of the selected studies. The mean and standard deviation of each study were identified, and the level of significance was set at $p \leq 0.05$. The I^2 statistic was calculated in order to evaluate heterogeneity among the included studies. If I^2 was greater than 50%, we chose to use a random-effects model to match the results, and if I^2 was less than 50%, we created a fixed-effects model. The risk of publication bias was evaluated by examining a funnel plot for asymmetry.

RESULTS

Study selection

We identified 879 studies involving the use of face masks; however, after the application of the inclusion and exclusion criteria (Chart 1), only 20 studies remained. Another 10 studies were excluded after they were read in their entirety, because of methodological biases, a lack of direct correlation with the topic of interest, or failure to provide raw data. Of the remaining 10 studies, only 8 had the raw data available before and after the intervention for statistical analysis and were therefore eligible for inclusion in the meta-analysis. The analyzed studies involved 306 volunteers in the 7- to 64-year age bracket, 68.95% of whom were male. Figure 1 shows a flow chart of the study selection process.

Interventions and findings

Of the 10 studies that were included in the systematic review, 8 assessed BP, 9 assessed HR, 5 assessed RR, and 5 assessed SpO_2. Most of the clinical trials showed no significant changes in the study variables after the use of N95/FFP2 masks during low- or high-intensity aerobic exercise in healthy individuals, and 2 studies that were aimed at assessing all or most of the clinical variables analyzed in this review corroborated this finding.

Chart 1. Inclusion and exclusion criteria.

Inclusion criteria
Design: randomized controlled trials or randomized crossover clinical trials
Language: English
Involving humans only
Intervention: use of N95/FFP2 masks
Exclusion criteria
Intervention: unclear, poorly described, or inadequate
Publishing form: abstract only
Main variables analyzed
HR
RR
Blood pressure
Oxygen saturation (SpO_2)
Perceived exertion (as assessed by the Borg scale)

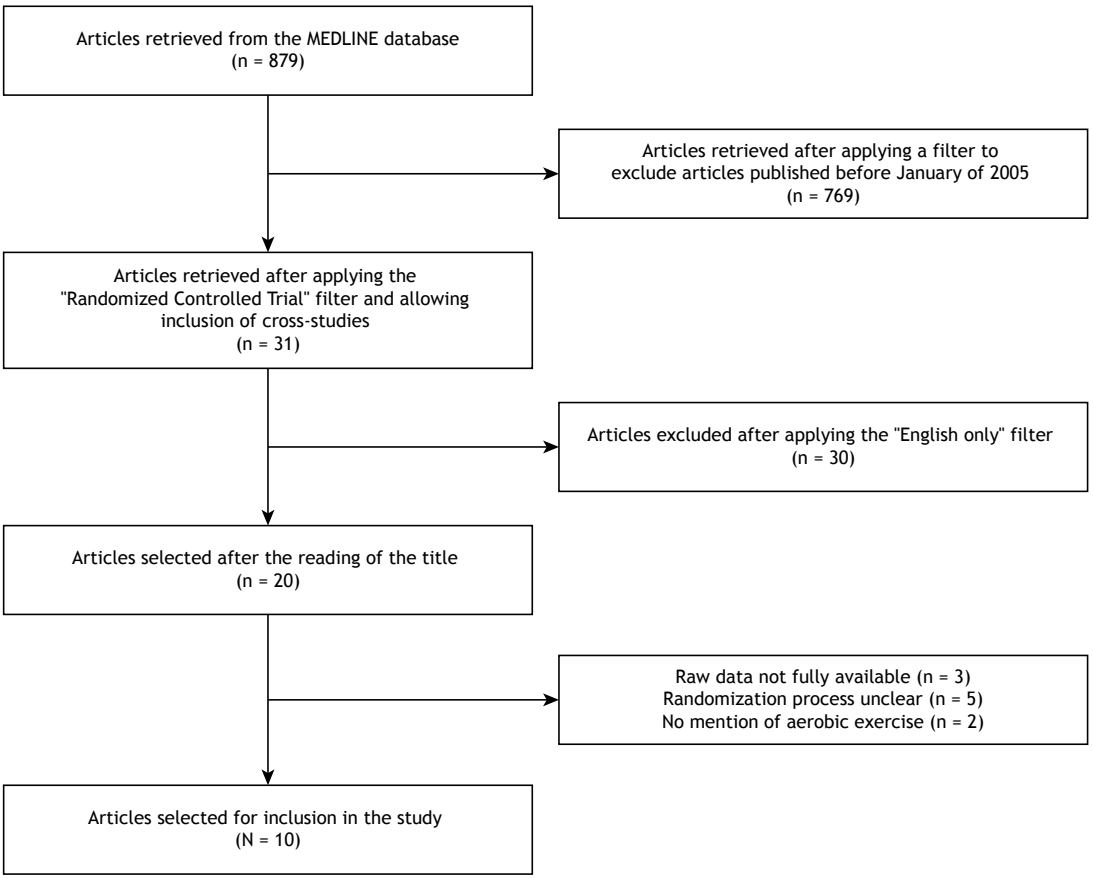

Figure 1. Flowchart of the study selection process.

In general, the interventions were of short duration, ranging from 3 min to 12 h on the same day, and participants were instructed to refrain from caffeine consumption in all studies, with the control and experimental groups being evaluated on different days.[6,16-19] Interventions varied greatly among the studies, and some used different devices and methods to measure the study variables. Interventions included walking,[5,20] treadmill walking,[18,19] medium- to high-intensity interval exercise on a cycle ergometer,[6,12,16,21] and going up and down stairs.[22]

Meta-analysis

Only 8 of the 10 studies included in this review provided sufficient data to analyze BP, HR, RR, and SpO_2 in the face of aerobic interventions with and without N95/FFP2 masks.[6,12,16,18,19,21-23] Therefore, only the aforementioned 8 were included in our meta-analysis, totaling a sample of 166 volunteers. The standardized mean difference ranged from −0.32 to 0.17 for BP, −0.27 to 0.13 for SpO_2, −0.10 to 0.27 for HR, and −0.16 to 0.28 for RR with the use of a fixed-effects model and with no statistically significant changes for any of the variables. Figures 2-5 show the analysis of the data for each of the included studies.

Figure 6 presents a synthesis of the results, a general test of heterogeneity, and differences between the subgroups. The results on the left indicate favorable values for the influence of N95/FFP2 masks on the study variables when compared with no mask use. The heterogeneity test applied in the analysis showed no significant heterogeneity among the studies; therefore, fixed-effects models were used. All of the studies investigated the effects of the use of N95/FFP2 masks on some of the variables analyzed by comparing values obtained with and without mask use.

BP

As can be seen in Figure 2, the use of N95/FFP2 masks during aerobic exercise had no significant effect on BP in any of the analyzed studies, as evidenced by the diamond crossing the vertical line of null effect, with the diamond representing the synthesis of CIs and relative risks.

SpO_2

As can be seen in Figure 3, the use of N95/FFP2 masks during aerobic exercise had no significant effect on SpO_2, as evidenced by the diamond crossing the vertical line of null effect. Although Mapelli et al.[21] showed that the use of N95/FFP2 masks had a significant

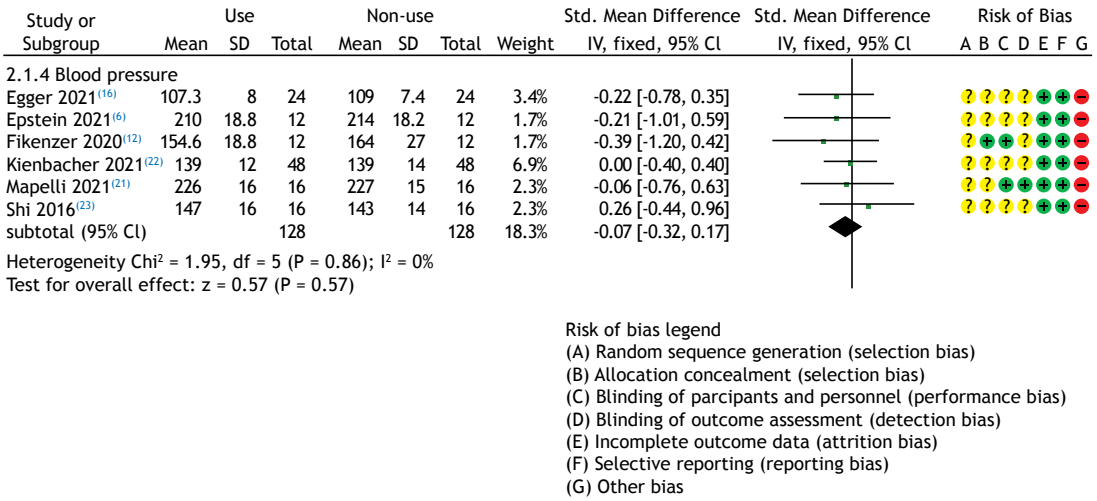

Figure 2. Forest plot of the included studies evaluating blood pressure in fixed- and random-effects models, with a standardized mean difference and a 95% confidence interval.

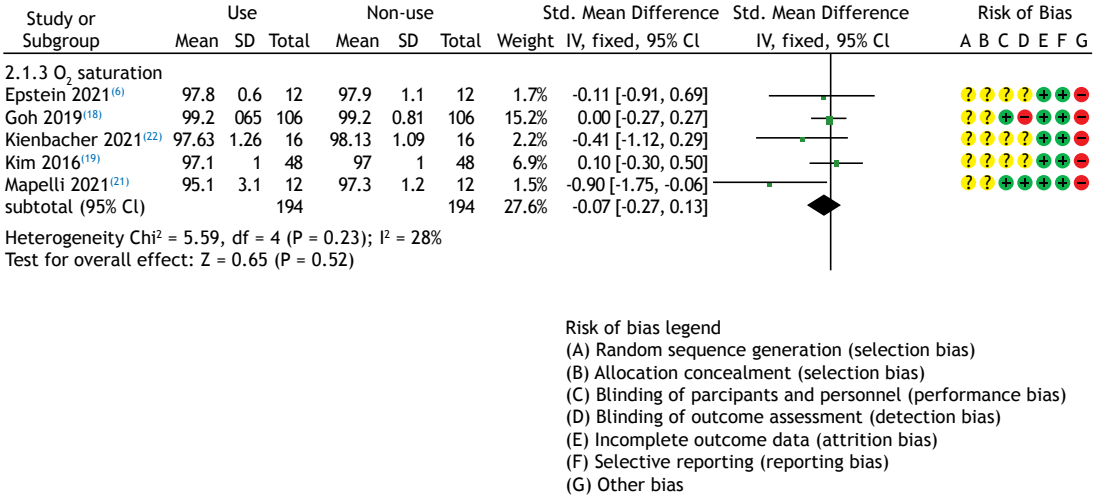

Figure 3. Forest plot of the included studies evaluating oxygen saturation in fixed- and random-effects models, with a standardized mean difference and a 95% confidence interval.

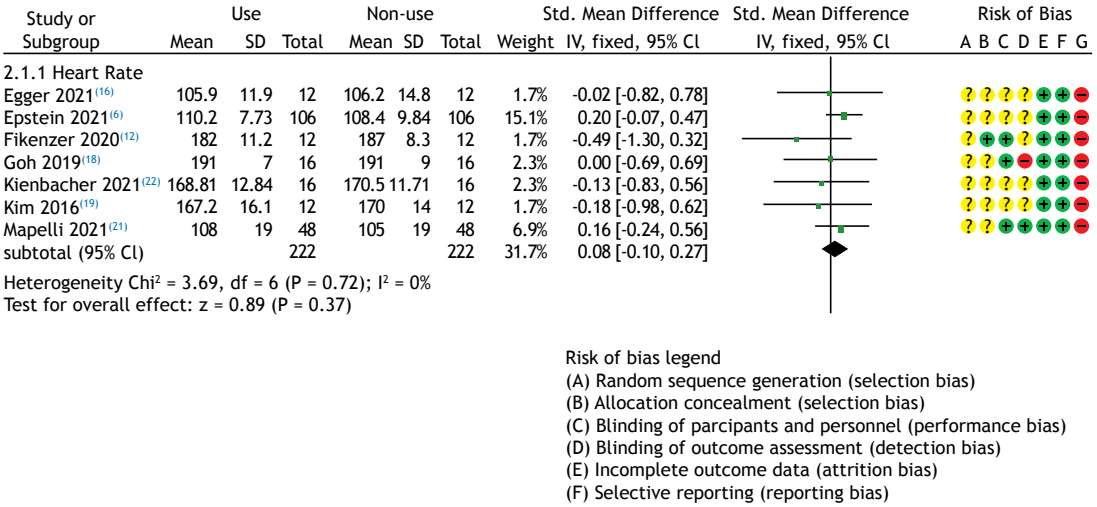

Figure 4. Forest plot of the included studies evaluating heart rate in fixed- and random-effects models, with a standardized mean difference and a 95% confidence interval.

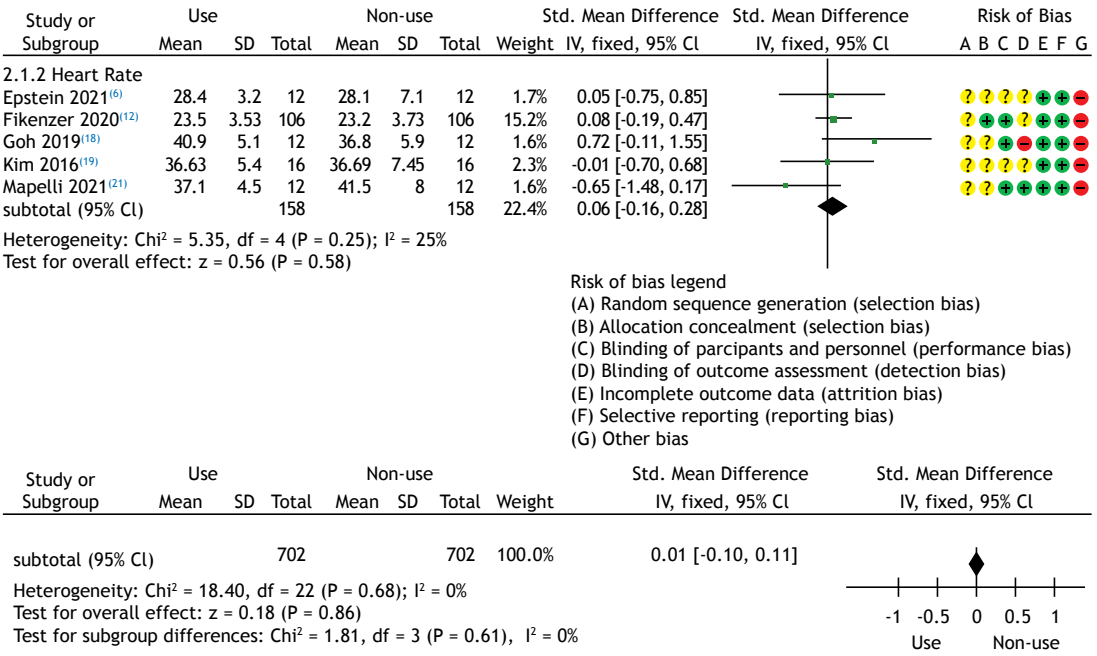

Figure 5. Forest plot of the included studies evaluating respiratory rate in fixed- and random-effects models, with a standardized mean difference and a 95% confidence interval.

effect on SpO_2, their findings did not affect the overall result, because the study sample was small.

HR

As can be seen in Figure 4, the use of N95 masks during aerobic exercise had no significant effect on HR in any of the analyzed studies, as evidenced by the diamond crossing the vertical line of null effect.

RR

As can be seen in Figure 5, the use of N95/FFP2 masks during aerobic exercise had no significant effect on RR in any of the analyzed studies, as evidenced by the diamond crossing the vertical line of null effect.

As can be seen in Figure 6, a synthesis of the values collected before and after the interventions for all of the variables in the studies selected for the present meta-analysis showed that the use of N95/FFP2 masks during aerobic exercise had no significant effect on the study variables, as evidenced by the association of CIs and relative risks with the diamond crossing the vertical line of null effect in the forest plots.

Chart 2 presents a summary of the studies selected for this systematic review, including sample size, patient age, type of analysis, interventions performed, systolic BP, HR, RR, SpO_2, and perceived effort. Values of $p < 0.05$ were considered to denote a significant change in the variables analyzed.

Publication bias

A funnel plot was used in order to assess the risk of publication bias (Figure 6). A symmetrical distribution is evident for HR, RR, and BP, whereas, in the studies that analyzed SpO_2, asymmetry is evident.

DISCUSSION

This study showed that the use of N95/FFP2 masks in healthy individuals performing aerobic exercise is safe and did not significantly change any of the variables studied. Interventions varied across studies, including aerobic exercise of different intensities, helping us assess the behavior of cardiorespiratory variables during walking and high-intensity interval training. The findings of the present study show that people can train while wearing masks and protect themselves from airway infections, without negative effects on physiological and perceptual responses to exercise.

We found that the effects of the use of N95/FFP2 masks during mild to moderate aerobic exercise presented categorical results regarding changes in BP, HR, and SpO_2 in maximum and submaximal parameters; it is possible to affirm that these variables were not significantly affected by the respective interventions.[6,12,17-22] We can affirm that BP, HR, and SpO_2 do not undergo clinically significant changes with the use of N95/FFP2 masks.

According to Harber et al.,[14] increased cardiopulmonary work is seen in individuals with COPD or asthma. This can be due to decreased circulating oxygen levels and/or blood acidosis caused by insufficient inspiration or respiratory disease. The study in question was carried out on three different days, and the groups of individuals with respiratory disease performed light- to moderate-intensity physical activities lasting an average of 8-10 min each. The study variables were tidal volume, minute ventilation, inspiratory flow rate, expiratory flow rate, inspiratory time, expiratory time, RR, mean total respiratory cycle time, and the duty cycle, which represented the proportion of the

Chart 2. Summary of the included studies and main results for systolic blood pressure, heart rate, respiratory rate, oxygen saturation (SpO_2), and perceived exertion (as assessed by the Borg scale).

Study, year	Sample	Intervention	Variables analyzed				
			BP	HR	RR	SpO_2	PE
Epstein et al., 2021[6]	16 volunteers (men only) mean age: 34 ± 4 years cross analysis	no mask use vs. surgical mask use vs. N95 mask use Participants underwent exercise testing on a cycle ergometer with a ramp protocol. initial load of 25 W at a constant speed of 55-65 rpm The initial load was increased by 25 W every 3 min until exhaustion. six tests, with a minimum rest period of 24 h between tests A 12-lead ECG was used in order to assess HR, SaO_2, and BP. RR was noninvasively assessed by means of nasal prongs.	= BP p > 0.05	= HR p > 0.05	= RR p > 0.05	= SpO_2 p > 0.05	= PE p > 0.05
Fikenzer et al., 2020[12]	12 volunteers (men only) mean age: 38.1 ± 6.2 years cross analysis	no mask use vs. surgical mask use vs. N95/FFP2 mask use Cycle ergometer with a ramp protocol at a speed of 60-70 rpm and a workload of 50 W, which was increased by 50 W every 3 min until voluntary exhaustion. An ECG and a digital spirometer were used in order to assess cardiac and pulmonary parameters, respectively.	= BP p > 0.01	= HR p > 0.01	↓ RR p < 0.05	N/A	N/A
Morishita et al., 2019[17]	50 volunteers (32 men and 18 women) mean age: 36 ± 14 years cross analysis	use of N95 masks vs. no use of N95 masks in a clinical environment and near a highway An ECG and an HR monitor were used in order to assess variations in HR. A BP monitor was used in order to analyze variations in BP every 10 min. 2 hours of observation, 5 days a week, in two different weeks	= BP p > 0.01	= HR p > 0.01	N/A	N/A	N/A
Shi et al., 2016[23]	24 volunteers (13 men and 11 women). The initial sample consisted of 30 volunteers. Six volunteers withdrew from the study. mean age: 23 years cross analysis	use of N95 masks vs. no mask use 1-h walks Variations in HR were assessed by Holter monitoring during the test. Variations in BP were analyzed with an automated BP monitor. BP was measured every 15 min during the day and every 30 min at night.	= BP p > 0.05	N/A	N/A	N/A	N/A

Continue...▶

Chart 2. Summary of the included studies and main results for systolic blood pressure, heart rate, respiratory rate, oxygen saturation (SpO_2), and perceived exertion (as assessed by the Borg scale). (Continued...)

Study, year	Sample	Intervention	Variables analyzed				
			BP	HR	RR	SpO_2	PE
Egger et al., 2021[16]	16 well-trained volunteer athletes (men only) age range: 20-34 years cross analysis	use of FFP2 masks vs. no use of FFP2 masks the Borg scale, a metabolic test system, a 12-lead ECG, and manual BP assessment initial workload of 100-150 W, increased by 50 W every 3 min on an electromagnetic cycle ergometer The test was interrupted when volunteers were unable to cycle at a minimum speed of 50 rpm for more than 10 s. an interval of at least 48 h between evaluations with and without FFP2 masks	= BP p > 0.01	= HR p > 0.01	N/A	N/A	= PE p > 0.05
Kienbacher et al., 2021[22]	48 volunteers (44 men and 4 women) mean age: 28 ± 8 years triple-test cross analysis	use of personal protective equipment (overalls, glasses, and gloves) and FFP2 masks without an exhalation valve vs. no use of FFP2 masks climb and descend stairs at a fast pace with a backpack and oxygen cylinder, followed by 12 min of chest compressions and bag-valve-mask ventilation a rest period of 30 min between tests BP, HR, and SpO_2 were assessed with a portable monitor/defibrillator.	= BP p > 0.05	= HR p > 0.05	N/A	= SpO_2 p > 0.05	↑ PE p < 0.05
Rebmann et al., 2013[20]	10 volunteer nurses (9 women and 1 man); 9 completed the study. age range: 24-48 years (mean age, 35 years)	use of N95 masks vs. use of N95 masks with a surgical mask overlay use of N95 masks for 12 h daily for 2 days Variables were analyzed every 30 min with a saturation sensor. an interval of 1 or more days between analyses	= BP p > 0.05	= HR p > 0.05	N/A	N/A	↑ PE p < 0.05
Goh et al., 2019[18]	106 volunteer children (59 boys and 47 girls) age range: 7-14 years cross analysis	no use of masks vs. use of N95 masks without a valve vs. use of N95 mask with a valve Reading in 3 5-min intervals: 1st—no mask (control); 2nd—wearing a valveless mask; and 3rd—wearing a valved mask Nasal cannulas with a multiparameter ECG monitor and a continuous monitoring system were used in order to evaluate SpO_2, HR, and RR.	N/A	= HR p > 0.05	= RR p > 0.05	= SpO_2 p > 0.05	↑ PE p < 0.05
Kim et al., 2016[19]	12 volunteers (men only) mean age: 23.5 ± 1.6 years cross analysis	use of N95 FFRs or similar vs. no mask use Individuals walked for 1 h at 5.6 km/h on a treadmill at a 0% slope. temperature, 35°C; relative humidity, 50% tests performed on two different days (first without an FFR, then with an FFR) A pulse oximeter with a transcutaneous carbon dioxide sensor connected to the ear, a monitoring chest strap, and an HR monitor were used in order to evaluate SaO_2, RR, and HR, respectively.	N/A	= HR p > 0.05	= RR p > 0.05	= SpO_2 p > 0.05	= PE p > 0.05

Continue...▶

Chart 2. Summary of the included studies and main results for systolic blood pressure, heart rate, respiratory rate, oxygen saturation (SpO_2), and perceived exertion (as assessed by the Borg scale). (Continued...)

Study, year	Sample	Intervention	Variables analyzed				
			BP	HR	RR	SpO_2	PE
Mapelli M et al., 2021[21]	12 volunteers (6 men and 6 women) mean age: 41 ± 12.4 years cross analysis	no use of FFP2 masks vs. FFP2 mask use maximal progressive exercise testing on a cycle ergometer Spirometry and a BP monitor were used in order to analyze variables.	= BP p > 0.05	= HR p > 0.05	= RR p > 0.05	↓ SpO_2 p < 0.05	

BP: blood pressure; PE: perceived exertion (as assessed by the Borg scale); ECG: electrocardiogram; FFP2: filtering facepiece 2; FFR: filtering facepiece respirator; ↑: significant increase in the variable; ↓: significant decrease in the variable; and =: no significant change in the variable. p > 0.05 or p > 0.01 indicates no significant difference between the control and intervention groups.

total respiratory cycle during which inspiratory effort was made.

A decrease in the amount of oxygen is mainly detected by the central chemoreceptors in the carotid body. These chemoreceptors induce respiratory upregulation by the effect of the vagus and glossopharyngeal nerves on the ventral respiratory group. Although this is true, it occurs in situations that significantly affect the amount of oxygen available.

Changes in the variables discussed in this review may be more commonly observed in individuals with preexisting heart and lung disease.[5,13-15] Therefore, on the basis of the studies that were aimed at investigating BP, it cannot be affirmed that N95/FFP2 masks cause significant changes.[6,12,16,17,20-,23] This is also true for the studies that evaluated SpO_2 and HR.[6,12,16-22]

Of the 5 studies that evaluated changes in RR,[6,12,18,19,21] only 1 found a significant decrease in RR.[12] Respiratory resistance was analyzed as a secondary variable, and the 2 studies that analyzed it presented conflicting results; 1 found significant changes, and the other did not.[6,16] These results can be explained by reduced VO_2max, decreased inspiratory ventilation, and the formation of a negative pressure rebreathing nucleus in some cases.[8,12,24,25] Despite not being included in this review (because they did not meet the inclusion criteria), several clinical studies analyzing respiratory resistance showed significant changes.[1,23,24] However, well-structured clinical trials involving larger samples and a variety of interventions are required in order to confirm this.

Although some of the studies evaluating RR and respiratory resistance showed significant changes in both, these findings are not enough to confirm that the use of N95/FFP2 masks causes significant changes in these variables. Respiratory resistance, which was measured noninvasively by means of nasal prongs and metabolic tests, was increased in one of the two studies evaluating it.[12,16] With different interventions and small samples, respiratory resistance is a variable for which there is no consensus regarding changes caused by N95/FFP2 mask use.

Some studies have shown that respiratory resistance increases with the use of N95 masks during mild- to moderate-intensity aerobic exercise.[1,12,24] Despite an increase in the number of studies, there is a lack of well-designed experimental and longitudinal studies evaluating the physiological changes caused by mask use. The studies evaluating respiratory resistance included in this review confirm that the use of N95/FFP2 masks during mild to intense aerobic exercise significantly influences this variable.[6,16] Respiratory resistance has been the target of large studies, especially because of the COVID-19 pandemic; therefore, reduced VO_2max, decreased inspiratory ventilation, and the formation of a negative pressure rebreathing nucleus remain under investigation.[8,12,24-26]

Conflicting results were also found in the six studies that evaluated ratings of perceived exertion on the

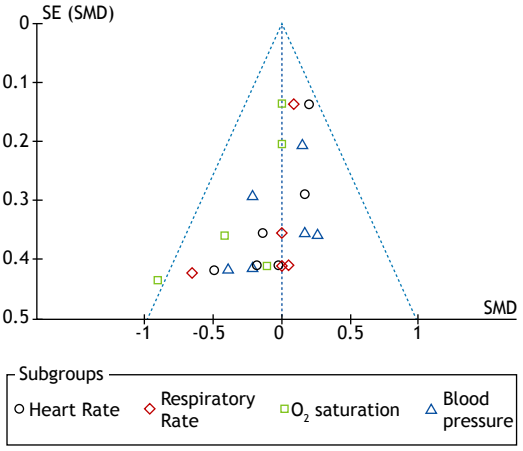

Figure 6. Funnel plot of the included studies with all of the study variables, showing asymmetry in the distribution of studies examining oxygen saturation. SE: standard error; and SMD: standardized mean difference.

Borg scale.[6,16,19-22] Three studies showed increasingly significant changes,[21-23] whereas the remaining three showed no significant changes.[6,16,19] Further clinical studies are needed in order to fill this gap because it was impossible to analyze the correlation between changes in ratings of perceived exertion and the study samples given the differing interventions, patient characteristics, and exercise intensities across studies.

The evidence developed in the 1990s suggests that the restrictive gas stimulus to oxygen chemoreceptors caused by the respiratory nucleus of face masks results in a decrease in available oxygen, triggering sympathetic stimulus and increasing HR and RR by activation of the ventral respiratory group through the activity of the vagus and glossopharyngeal nerves in the upregulation of these chemoreceptors.[27,28] However, the hypothesis that face masks are capable of causing changes in the cardiorespiratory system has been questioned, especially because of their widespread use during the current COVID-19 pandemic, which has demonstrated that this hypothesis is inconsistent with the results of related studies.

Of the 5 studies evaluating RR, only 1 found a significant change contributing to a decrease in RR, a finding that can be attributed to the small sample size (N = 12). The variation between intensity of cardiorespiratory stimulus and burst cannot be confirmed, and nor can the changes related to the use of masks. Clinical trials involving different interventions and larger samples are needed in order to reach a definitive conclusion.[1,2,6,12-14,16,17,26-28] Rebmann et al.[20] also evaluated these variables; however, the evaluations were performed with participants wearing either an N95 mask alone or an N95 mask and a surgical mask, showing no considerable changes. In contrast, Fikenzer et al.[12] observed a decrease in RR. In that study,[12] which is one of the five studies analyzing the variability of RR, the intervention consisted of incremental exercise performed on a cycle ergometer at a speed of 60-70 rpm, the workload being increased by 50 W (as a ramp) every 3 min until voluntary exhaustion. This reinforces the assumption that the variability and intensity of aerobic exercise play a highly relevant role in clinical changes. In recent studies,[5,13,14] individuals presenting with COPD of varying severity and wearing face masks were investigated; mask use was found to cause significant changes in some of the aforementioned physiological parameters, especially respiratory parameters, with a higher degree of disease severity translating to more significant changes. Therefore, clinical conditions and aerobic exercise intensity have strong clinical relevance.

There were no significant changes in HR, BP, and SpO_2 in individuals in the 7- to 64-year age bracket wearing N95/FFP2 masks in comparison with those not wearing them.[6,7,12,16-18,21,22] Of the 10 studies included in this review, 8 had BP as one of the study variables, and none of the interventions resulted in significant changes in BP.[6,12,17,18-23] Thus, it cannot be inferred that BP changes significantly during and after mask use because the interventions ranged from mild to moderate aerobic exercise in samples of 12-50 participants in the studies showing no significant changes in BP; although these studies together analyzed a total of 188 individuals (i.e., a considerable sample size), studies examining larger samples are needed.

In the 5 studies analyzing SpO_2, no significant changes were observed during submaximal exercise (mild- to moderate-intensity aerobic exercise); one study found a significant change in SpO_2 during maximal exercise.[6,18,19,21,22] The sample size (a total of 198 volunteers) and the differing interventions across studies suggest that N95 and FFP2 masks can cause no changes in SpO_2 during mild- to moderate-intensity aerobic exercise. These results may be conflicting because of the differing exercise intensities across studies.

Nine studies evaluated HR with and without mask use during the interventions, which ranged from mild- to moderate-intensity aerobic exercise,[6,12,15-19,21,24] showing no significant changes in HR. A total of 282 individuals underwent HR analysis. Given that the findings regarding HR were the same in all 9 studies, the changes observed in the individuals who wore N95/FFP2 masks during aerobic exercise appear to be nonsignificant. However, it is of note that some of the studies that did not meet the criteria for inclusion in this review showed significant changes in HR. These changes may be due to the sample size, a lack of randomization and control (leading to heterogeneity and increased bias), the type of mask used, and the rest period between peak activities, which was considered high.

One of the limitations of the present study is the use of only one database for article retrieval. Another limitation is the fact that we did not assess the quality of the evidence using the Grading of Recommendations Assessment, Development and Evaluation method, which is based on analysis of the risk of bias of the selected studies. It is also important to point out the

limitations of the studies included in this review: (1) limitations related to the study design (i.e., the difficulty in evaluating physiological parameters in individuals wearing N95/FFP2 masks); (2) differing methods across studies, including differences in exposure time, type of aerobic exercise, and exercise intensity; (3) small sample sizes; (4) differing mask brands and seals across studies; (5) use or lack of use of an exhalation valve; (6) unblinded analyses or inadequate randomization; and (7) inadequate rest period and use of the same sample subjected to different interventions, introducing systematic bias.

FINAL CONSIDERATIONS

This study suggests that wearing N95/FFP2 masks during aerobic exercise does not have significant effects on the variables analyzed, their use therefore being safe for human health. Respiratory resistance and perceived exertion (as assessed by the Borg scale) during aerobic exercise showed results that are conflicting and inconclusive. Therefore, further clinical trials are required, involving larger samples and different interventions. Finally, we can affirm that, in cases of preexisting diseases of the cardiorespiratory system, changes in HR, RR, and SpO_2 tend to be more significant.

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AUTHOR CONTRIBUTIONS

GLSL, TCR, GPLSJ, and MTM: study conception and design; statistical analysis; and writing of the manuscript. GLSL, TCR, and GPLSJ: data analysis and interpretation. MTM: critical revision of the manuscript for important intellectual content.

CONFLICTS OF INTEREST

None declared.

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Telehealth and telemedicine in the management of adult patients after hospitalization for COPD exacerbation: a scoping review

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ABSTRACT

Objective: A substantial number of people with COPD suffer from exacerbations, which are defined as an acute worsening of respiratory symptoms. To minimize exacerbations, telehealth has emerged as an alternative to improve clinical management, access to health care, and support for self-management. Our objective was to map the evidence of telehealth/telemedicine for the monitoring of adult COPD patients after hospitalization due to an exacerbation. **Methods:** Bibliographic search was carried in PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus, *Biblioteca Virtual de Saúde*/LILACS and Cochrane Library databases to identify articles describing telehealth and telemonitoring strategies in Portuguese, English, or Spanish published by December of 2021. **Results:** Thirty-nine articles, using the following concepts (number of articles), were included in this review: telehealth (21); telemonitoring (20); telemedicine (17); teleconsultation (5); teleassistance (4); telehomecare and telerehabilitation (3 each); telecommunication and mobile health (2 each); and e-health management, e-coach, telehome, telehealth care and televideo consultation (1 each). All these concepts describe strategies which use telephone and/or video calls for coaching, data monitoring, and health education leading to self-management or self-care, focusing on providing remote integrated home care with or without telemetry devices. **Conclusions:** This review demonstrated that telehealth/telemedicine in combination with telemonitoring can be an interesting strategy to benefit COPD patients after discharge from hospitalization for an exacerbation, by improving their quality of life and reducing re-hospitalizations, admissions to emergency services, hospital length of stay, and health care costs.

Keywords: Pulmonary disease, chronic obstructive; Symptom flare up; Telemedicine; Patient discharge.

INTRODUCTION

COPD is one of the major causes of morbidity and mortality worldwide, causing substantial economic and social burden. People with COPD suffer from this disease for years and die prematurely from the disease or its complications.[1] The WHO has predicted that COPD will be the third leading cause of death worldwide, being responsible for approximately 6% of total deaths.[2]

A substantial number of people with COPD suffer from exacerbations, which are defined as an acute worsening of respiratory symptoms that require a change in treatment. Exacerbations are an important health problem and are related to worse survival.[3]

As a result of the high prevalence of COPD in adults and the advances in the treatment of COPD, the demand for health services has increased.[4] To alleviate the burden, telehealth has emerged as an alternative for improving clinical management in chronic respiratory diseases.[5]

According to the WHO, telemedicine and telehealth can be used as synonyms to encompass a wide definition of remote care. Telemedicine is defined as the delivery of health care services by health care professionals, where distance is a critical factor, using communication technologies for the exchange of valid information for diagnosis, treatment, and prevention of disease and injuries, as well as for research, evaluation, and continuing education of health care providers, aiming at the interests of individuals and communities. Some authors distinguish telemedicine from telehealth by considering the former to be restricted to physicians and the latter to comprise health professionals in general.[6]

Telehealth/telemedicine can be delivered by different technologies such as terrestrial and wireless

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communication, wearable devices, videoconferencing, internet platforms, mobile applications, among others.[7] These technologies can operate synchronously (e.g., real-time video conferencing or telephone call) or asynchronously (e.g., remote consultation using e-mail, smartphone messages, notifications, and recording and communicating symptoms to health care providers).[4]

In people with COPD, telehealth/telemedicine has a wide range of applicability, such as to increase accessibility to health care for patients living in remote areas, to decrease the demand on hospital and health care services, to promote health education, to deliver and to manage treatment, to measure treatment adherence, and to identify disease worsening rapidly.[8]

The COVID-19 pandemic drew attention to the necessity of incorporating telehealth/telemedicine into the usual clinical management in chronic respiratory diseases. Special attention should be given to exacerbations in chronic respiratory diseases, which are responsible for the increased demand for health care services and are related to worse outcomes. Therefore, it is important to know which strategies have been used in telehealth/telemedicine, how they have been used, and what effects they have had on the management of a COPD exacerbation.

The objective of this scoping review was to map the evidence of telehealth/telemedicine for the monitoring of adult COPD patients after hospitalization due to an exacerbation.

METHODS

Search strategy and selection of telehealth/telemedicine applications

This scoping review is registered on Open Science Framework (https://osf.io/d8gp7). It was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Scoping Review (PRISMA-ScR10) Statement[9] and was conducted according to the Joanna Briggs Institute Manual.[10] This method allows mapping the concept and clarifying definitions used in the literature.[11]

The research question was defined based on the Population, Concept and Context framework[10] as follows: population—adult patients hospitalized for COPD exacerbation; concept—telehealth/telemedicine strategies; and context—discharge after hospitalization. The guiding question was: "What is the scientific evidence on telehealth/telemedicine strategies for the management of adult patients after hospital stay for a COPD exacerbation?"

Bibliographic search was carried in PubMed, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Web of Science, Scopus, *Biblioteca Virtual de Saúde*/LILACS and Cochrane Library databases between August and September of 2020 and later, in December of 2021. The search strategy was customized for each database, and the respective keywords, descriptors, and combinations are presented in Chart 1.

Assessment criteria

The eligibility criteria were studies that have used telehealth/telemedicine, describing the strategies applied in detail. The articles should describe telehealth/telemedicine strategies delivered to adult patients after hospitalization due to a COPD exacerbation, be electronically available, and have been published in Portuguese, English, or Spanish by December of 2021. Exclusion criteria were articles not available in full, and dissertations, theses, end-of-course works, texts from the Internet, editorials, theoretical essays, and reflective texts.

Chart 1. Search strategies (keywords, descriptors, and combinations).

Database	Search strategy
Scopus Cochrane Library Web of Science PubMed-Medline CINAHL	("Pulmonary Disease, Chronic Obstructive" OR "Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "COAD" OR "COPD" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Lung Diseases") AND ("Telemonitoring" OR "Telemedicine" OR "Remote Consultation" OR "Cell Phone" OR "Mobile Applications") AND ("Patient Discharge" OR "Hospitalization")
BVS/LILACS	("Pulmonary Disease, Chronic Obstructive" OR "Enfermedad Pulmonar Obstructiva Crónica" OR "Doença Pulmonar Obstrutiva Crônica" OR "COAD" OR "COPD" OR "DPOC" OR "Doença Obstrutiva Crônica Pulmonar" OR "Doença Obstrutiva Crônica das Vias Aéreas" OR "Doença Obstrutiva Crônica do Pulmão" OR "Obstrução Crônica do Fluxo Respiratório" OR "Obstrução do Fluxo Respiratório Crônica" OR "Airflow Obstruction, Chronic" OR "Airflow Obstructions, Chronic" OR "Chronic Airflow Obstruction" OR "Chronic Airflow Obstructions" OR "Chronic Obstructive Airway Disease" OR "Chronic Obstructive Lung Disease" OR "Chronic Obstructive Pulmonary Disease" OR "Lung Diseases" OR "Enfermedades Pulmonares" OR "Pneumopatias") AND ("Telemonitoring" OR "Telemonitorización" OR "Telemonitoramento" OR "Telemedicine" OR "Telemedicina" OR "Remote Consultation" OR "Consulta Remota" OR "Cell Phone" OR "Teléfono Celular" OR "Telefone Celular" OR "Mobile Applications" OR "Aplicaciones Móviles" OR "Aplicativos Móveis") AND ("Patient Discharge" OR "Alta del Paciente" OR "Alta do Paciente" OR "Alta Hospitalar" OR "Alta do Hospital" OR "Planejamento da Alta" OR "Hospitalization" OR "Hospitalización" OR "Hospitalização")

CINAHL: Cumulative Index to Nursing and Allied Health Literature; and BVS: *Biblioteca Virtual de Saúde*.

Selection and data extraction

Initially, the studies were compiled in the EndNote software, and two independent reviewers read the titles and abstracts. Full-text articles were reviewed using the selection criteria. The reviewers compared their selections, and disagreements were discussed and resolved by consensus.

Data from the included studies were extracted independently by the reviewers using a structured data extraction form. The data recorded were country of origin, study design, professionals responsible to deliver telehealth/telemedicine, study aims, and outcomes.

RESULTS

A total of 1,250 articles were selected, and 39 articles were included in this review. Reasons for exclusion were nature of publication, different populations from that investigated in this study, and lack of description of the telehealth/telemedicine intervention delivered (Figure 1).

Characteristics of included studies

The studies included comprised 21 clinical trials, 14 observational studies, 2 qualitative studies, and 2 feasibility studies. The concepts used were telehealth, in 21 studies; telemonitoring, in 20; telemedicine, in 17; telecare, in 4; teleconsultation, in 5; teleassistance, in 4; tele homecare, in 3; telerehabilitation, in 3; telecommunication, in 2; mobile health in 2; e-health-management, in 1; e-coach, in 1; tele home, in 1; telehealth care, in 1; and tele-video-consultation, in 1. The objectives and outcomes of each study are summarized in Chart 2.[8,12-49]

Variation among terms used to deliver remote care

The most commonly used terms to describe the delivery of remote health care were "telehealth"[13,17,19,21,22,23,29,31,32,33,34,36,37,38,39,40,42,43,44,46,48] and "telemonitoring."[15,16,18,21,22,24,25,29,30,32,33,34,35,37,38,40,41,42,43,48] The terms "telemedicine",[8,12,13,14,16,17,18,20,23,24,26,28,30,37,38,47,48] "telecare," "teleassistance," "tele homecare," "teleconsultation," or "telecommunication" were used as interchangeable terms. All of these concepts were used in order to describe strategies that use telephone and/or video calls for coaching, data monitoring, and health education leading to self-management or self-care. "Telemonitoring" was used with the terms "home monitoring", "monitoring intervention," and "monitoring system" to refer to the monitoring of signs and symptoms for prevention of exacerbations. The term "telerehabilitation" was specifically used for pulmonary rehabilitation.[19,28] The term "mobile health" (mHealth) referred to medical or health care interventions delivered through mobile technology (e.g., smartphones) in the studies.[45,49]

Remote care interventions

The most common interventions were health education to support self-management improvement, rehabilitation, and monitoring of signs/symptoms by treatment management, counseling, motivation, and prevention of exacerbations. The main key concepts related to remote consultations of COPD patients after discharge focused on providing remote integrated home care with or without the use of telemetry devices (Figure 2).

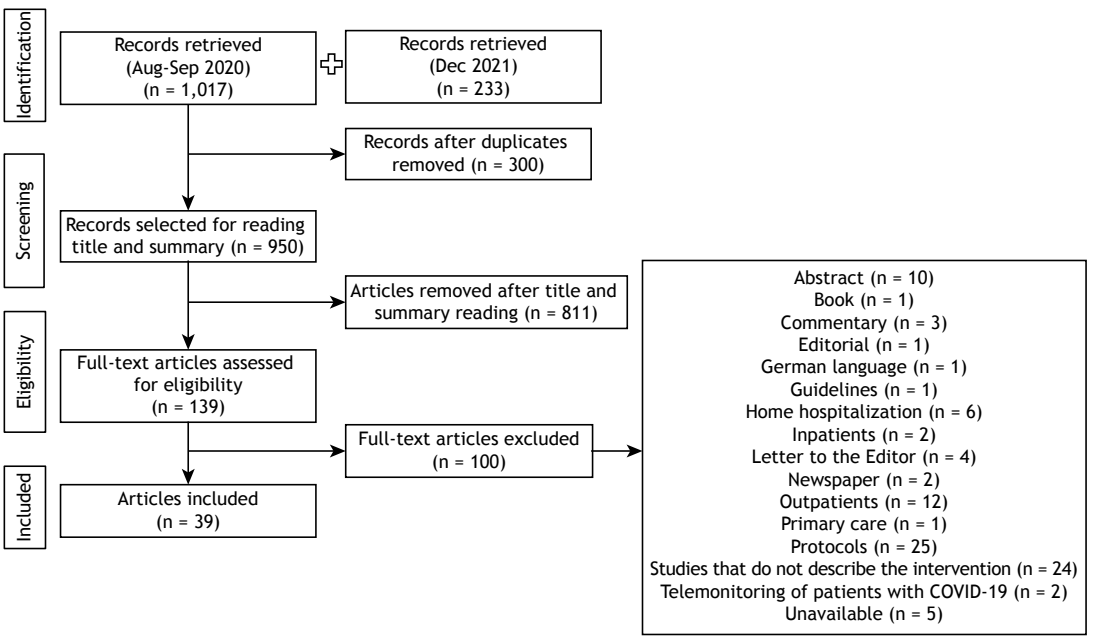

Figure 1. Flow chart of study selection process for inclusion in the systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.

Chart 2. Overview of selected studies. Scoping review, 2022.

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Vitacca; et al, Italy, 2018[8]	Observational study	Nurse, physician.	To test the feasibility of and patient satisfaction with an advanced care plan for severe COPD patients followed by teleassistance at home for six months, focusing on monitoring patient's palliative topics by means of a dedicated checklist	N = 10	Telemedicine Teleassistance	Phone call	High level of satisfaction of the service
Ratner et al., USA, 2001[12]	Clinical trial	Nurse, doctor	To describe the Wealth from Health program, which utilizes current and future technologies to help the health care system become a leader in health care delivery and to assist many communities at an affordable cost	N = 78 Intervention vs. control groups[a]	Telemedicine Telecommunication	Phone call	Reduction in re-hospitalizations and medical costs Improvement in quality of life
Vontetsianos et al., Greece, 2005[13]	Clinical trial	Nurse, doctor, physiotherapist, social worker, clinical psychologist, dietician, and pharmacist	To evaluate the clinical utility of an advanced system of e-health services in home-based integrated care for patients suffering mainly from COPD	N = 18 Intervention vs. control groups[a]	Telehealth Telemedicine	Video call	Reduction in hospitalizations, emergency department visits, and use of health services Improvement in disease knowledge, self-management, and perception of the quality of life Total costs were lower after study period
Finkelstein et al, USA, 2006[14]	Clinical trial	Nurse	To identify and document the benefits of a telemedicine application compared with standard care for homebound patients receiving home health services after an acute hospitalization for a long-term condition	N = 53 Intervention (n = 35) vs. control (n = 18) groups	Telemedicine Telehomecare Telecommunication	Telemetry/ Data sending Video call	Reduction in costs to deliver home healthcare
Vitacca et al., Italy, 2006[15]	Observational study	Nurse, doctor	To test the feasibility of telemedicine out of hospital use	N = 45	Telemonitoring Teleassistance Teleconsultation	Telemetry/ Data sending	Feasibility of home monitoring

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Trappenburg et al., Netherlands, 2008[16]	Clinical trial	Respiratory nurse, general practitioner, pulmonary physician	To determine the effects of a home-based telemonitoring device, the Health Buddy, on health consumption and HRQoL in patients with moderate to severe COPD	N = 115 Intervention (n = 59) vs. control (n = 56) groups	Telemedicine Telemonitoring	Phone call Message	Reduction in the number of exacerbations and hospitalizations
Cardozo & Steinberg, USA, 2010[17]	Observational study	Nurse, physiotherapist, occupational therapist, social work, and dietician	To evaluate whether case-managed telemedicine as a care delivery system is practical and accepted by elderly patients and could lead to a reduction of costs to the health system, lower emergency care and readmission rates, and provide improved clinical outcomes	N = 851	Telehealth Telemedicine	Telemetry/ Data sending	Reduction in re-hospitalizations and emergency visits improvement in disease, knowledge, and quality of life
Sorknaes et al., Denmark, 2011[18]	Clinical trial	Respiratory nurse	To investigate the effect of telemedicine/ video consultations between respiratory nurses at the hospital and patients with exacerbated COPD after hospital discharge on early readmissions	N = 100 Intervention (n = 50) vs. control (n = 50) groups	Telecare Telehome Telemedicine Telemonitoring Teleconsultations	Video call Phone call Telemetry/ Data sending	Reduction in hospitalizations and median length of stay
Dinesen et al., Denmark, 2012[19]	Clinical trial	Nurse and general practitioner	To test whether preventive home monitoring of COPD patients would reduce hospital admission rates and hospitalization costs	N = 105 Intervention (n = 57) vs. control (n = 48) groups	Telehealth Telerehabilitation	Telemetry/ Data sending Video call	Reduction in admissions during the 10-month follow-up period
Sorknaes et al., Denmark, 2013[20]	Clinical trial	Nurse	To investigate the effect of daily real-time teleconsultations	N = 100 Intervention (n = 50) vs. control (n = 50) groups	Telemedicine Teleconsultation	Telemetry/ Data sending Video call	No significant difference in re-hospitalizations and mortality rate
Bentley et al., England, 2014[21]	Clinical trial	Specialist nurse, specialist physiotherapist, and community matron.	To report the results of a pilot randomized controlled trial of telehealth-supported care within a community-based COPD supported-discharge service	N = 63 Intervention (n = 32) vs. control (n = 31) groups	Telehealth Telemonitoring	Telemetry/ Data sending	Reduction in the proportion of hospitalizations and improvement in quality of life

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Segrelles Calvo et al., Span, 2014[22]	Clinical trial	Nurse, pulmonary physician	To assess the efficacy and effectiveness of a home telehealth program for COPD patients with severe airflow obstruction by measuring the number of emergency room visits, number of hospitalizations, length of hospital stay, and mortality	N = 60 Intervention (n = 30) vs. control (n = 30) groups	Telehealth Telemonitoring	Phone call Telemetry/ Data sending	Reduction in the number of emergency room visits, number of hospitalizations, length of hospital stays, need for noninvasive ventilation, and number of days to first exacerbation requiring hospitalization
Gottlieb et al., Denmark, 2014[23]	Observational study	Nurse, pulmonary physician	To assess the feasibility of a telehealth care solution when offered in connection with discharge from a pulmonary ward at a university hospital	N = 72	Telecare Telehealth Telemedicine Telehealth care	Video call	No significant difference in re-hospitalizations
Saleh et al., Norway, 2014[24]	Observational study	Specialist respiratory nurse	To assess the impact of telemedicine video consultations on the length of re-admission stays within 6 and 12 months of follow up after telemedicine video-consultations	N = 99	Telemedicine Telemonitoring Tele-video-consultation	Video call	Reduction in the number of patients readmitted due to COPD exacerbations
Davis et al, USA, 2015[25]	Observational study	Nurse	To determine the feasibility of a transitional care program that integrated mobile health technology and home visits for underserved COPD and chronic heart failure patients and to evaluate preliminary program outcomes related to acute care utilization	N = 149	Telemonitoring	Phone call Interactive voice Telemetry/ Data sending	Reduction in re-hospitalizations
Dyrvig et al., Denmark, 2015[26]	Observational study	Nurse	To investigate the effectiveness of a telemedicine intervention in COPD patients during, before, and after an RCT while adjusting for age and gender	N = 11,303	Telemedicine	Video call	Increased risk of re-hospitalizations Reduction in the risk of death
Mierdel & Owen, Canada, 2015[27]	Observational study	N/R	To evaluate pre- and post-enrollment and post-discharge data captured by the William Osler Health System's telehomecare host	N = 466	Telehomecare	Phone call Telemetry/ Data sending	Reduction in emergency department use, hospitalizations, and mean length of stay

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Rosenbek Minet et al., Denmark, 2015[28]	Clinical trial	Nurse, physiotherapist	To assess the feasibility of an individualized home-based training and counseling program via videoconference to patients with severe COPD after hospitalization, including assessment of safety, clinical outcomes, patients' perceptions, organizational aspects, and economic aspects	N = 50 Intervention vs. control groups[a]	Telemedicine Telerehabilitation	Video call	Improvement in the continuity of the rehabilitation program
Chatwin et al., England, 2016[29]	Clinical trial	Study team	To assess the impact of home telemonitoring on health service use and quality of life in patients with severe chronic lung disease	N = 175 Intervention (n = 114) vs. control (n = 61) groups	Telecare Telehealth Telemonitoring Teleassistance	Phone call Telemetry/ Data sending	No difference in the median number of days to the first admission Increased hospital admission rate, and home visits Improvement in depression rate No improvement in quality of life
Cordova et al., USA, 2016[30]	Clinical trial	Nurse, pulmonologists	To investigate whether telemedicine-based daily symptom reporting plus optimal medical therapy decreases hospitalizations and COPD-related mortality, as well as the frequency and severity of acute COPD exacerbation symptoms, in high-risk patients	N = 67 Intervention (n = 34) vs. control (n = 33) groups	Telemedicine Telehomecare Teleassistance Telemonitoring	Phone call	Improvement in daily peak flow and dyspnea scores No differences in hospitalization and mortality rates
Fitzsimmons et al., Canada/UK 2016[31]	Qualitative study	Nurse, physician	To explore qualitatively the experiences of patients with COPD who had received either a telehealth-supported or a specialist nursing intervention following hospital discharge after an admission for a COPD exacerbation	N = 29	Telehealth	Phone call Telemetry/ Data sending	Reduction in home visits by clinicians

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Ho et al., Taiwan, 2016[32]	Clinical trial	Nurse, pulmonologists	To investigate the effectiveness of telemonitoring in improving COPD patient outcomes	N = 106 Intervention (n = 53) vs. control (n = 53) groups	Telehealth Telemonitoring	Phone call Telemetry/ Data sending	Increase in the time to first re-hospitalization for COPD exacerbation Reduction in the number of all-cause readmissions and emergency room visits
Ritchie et al., USA, 2016[33]	Clinical trial	Nurse	To evaluate the impact of a technology-supported care transition support program on hospitalizations, days out of the community, and mortality	N = 478 Intervention vs. control groups[a]	e-coach Telehealth Telemonitoring	Phone call Interactive voice response Telemetry/ Data sending	No difference in re-hospitalizations Reduction in length of hospital stay
Vianello et al., Italy, 2016[34]	Clinical trial	Nurse, pulmonologist, and general practitioner	To investigate the benefits of a telemonitoring system in managing acute exacerbations in advanced-stage COPD patients to improve their HRQoL and to reduce utilization of healthcare services	N = 334 Intervention (n = 230) vs. control (n = 104) groups	Telehealth Telemonitoring	Phone call Telemetry/ Data sending	No significant difference in hospitalizations Reduction in readmission rate for acute exacerbations of COPD or for any cause No significant differences in anxiety and depression No significant difference in HRQoL
Crooks et al., UK, 2017[35]	Observational study	Study team	To describe a novel monitoring system used to record cough continuously for up to 45 days during acutely exacerbated COPD convalescence	N = 16	Telemonitoring	Telemetry/ Data sending	Improvement in early identification of exacerbations

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Kargiannakis et al., UK, 2017[36]	Clinical trial	Nurse, doctor	To undertake the first analysis of system data to determine whether telehealth monitoring can identify a COPD exacerbation, giving clinicians an opportunity to intervene with timely treatment and prevent hospital readmission	N = 23	Telehealth	Phone call Telemetry/ Data sending	No significant reduction in the re-hospitalizations
Scalvini et al., Italy, 2018[37]	Observational study	Nurse- and physician-directed	To describe a personal experience at the Centre for Telehealth and Telecare in providing continuity of care for patients with a chronic illness	N = 1,635	Telecare Telehealth Telemedicine Telemonitoring e-health management	Video call Phone call Telemetry/ Data sending	Reduction in re-hospitalization rate and costs Improvement in quality of life and patient satisfaction with the service
Barken et al., Norway, 2018[38]	Qualitative study	Nurse	To describe the lived experiences of quality of life among a group of patients living with COPD who had been included in a telemedical intervention after hospitalization for disease exacerbation	N = 10	Telehealth Telemedicine Telemonitoring	Video call Phone call Telemetry/ Data sending	Increased accessibility to health care services and improvement in quality of life
Fors et al., Sweden, 2018[39]	Clinical trial	Nurse	To evaluate the effects of person-centered support via telephone in two chronically ill patient groups: COPD and/or heart failure	N = 221 Intervention (n = 103) vs. control (n = 118) groups	Telehealth	Phone call	No significant difference in the composite score consisted of general self-efficacy, re-hospitalization, and death
Soriano et al., Spain, 2018[40]	Clinical trial	Nurse	To clarify the impact of telehealth on outcomes and costs over a 12-month time frame, and in a large sample of COPD patients	N = 169 Intervention (n = 87) vs. control (n = 82) groups	Telehealth Telemonitoring	Phone call Telemetry/ Data sending	No significant difference in COPD-related emergency room visits or hospitalizations
Walker et al., Spain, UK, Slovenia, Estonia, and Sweden, 2018[41]	Clinical trial	Nurse	To evaluate the efficacy of home monitoring of lung mechanics by the forced oscillation technique and cardiac parameters in older patients with COPD and comorbidities	N = 312 Intervention vs. control groups[a]	Telemonitoring	Phone call Telemetry/ Data sending	No significant difference in quality of life and hospitalization rate Fewer re-hospitalizations

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Bohingamu Mudiyanselage et al., Australia, 2018[42]	Clinical trial	Nurse, doctor	To assess the impact of home-based telehealth monitoring on health outcomes, quality of life, and costs over 12 months in patients with diabetes and/or COPD who were identified as being at high risk of hospital readmission	N = 171 Intervention (n = 86) vs. control (n = 85) groups	Telehealth Telemonitoring	Message Video call Phone call	No significant difference in the number of re-hospitalizations Reduction in length of hospital stay Improvement in anxiety, depression, and health literacy Improvement in quality of life at no additional costs
Lyth et al., Sweden, 2019[43]	Observational study	Nurse, doctor	To investigate the effects of the intervention on healthcare costs, number of hospitalizations, and other care required in patients with COPD and heart failure	N = 94 COPD patients (n = 36) and heart failure patients (n = 58)	Telehealth Telemonitoring	Message Telemetry/ Data sending	Reduction in hospitalization costs, but total health care costs was not significantly different from the expected costs
Arcilla et al., USA, 2019[44]	Clinical trial	Nurse	To prove that the implementation of transitional care interventions in high-risk patients with COPD, heart failure, or diabetes mellitus after hospital discharge can reduce the number of readmissions	N = 102 Intervention vs. control groups[a]	Telehealth	Phone call Interactive voice Telemetry/ Data sending	Reduction in the number of hospitalizations and 30-day re-hospitalization rates
Bentley et al., UK, 2020[45]	Randomized feasibility study	Physiotherapist	To determine the feasibility and acceptability of the SMART-COPD intervention for the self-management of physical activity and to explore the feasibility of conducting a future RCT to investigate its effectiveness	N = 63 Intervention (n = 31) vs. control (n = 31) groups	mHealth	Telemetry/ Data sending	Feasibility of home monitoring (mHealth shows promise in helping people with COPD self-manage their physical activity levels)

Continue...▶

Chart 2. Overview of selected studies. Scoping review, 2022. (Continued...)

Author, country, year	Study design	Professionals responsible for delivering telehealth	Objective of the study	Sample size	Concept	Strategy	Outcomes
Wang et al., China, 2020[46]	Clinical trial	Nurse	To investigate the effects of a mobile health smartphone application to support self-management programs on quality of life, self-management behavior, exercising, and smoking cessation behavior in patients with COPD	N = 78 Intervention (n = 39) vs. control (n = 39) groups	Telehealth	Telemetry (Application smartphone)	Improvement in the quality of life and self-management behavior
Leonard et al, USA, 2020[47]	Observational study	Respiratory therapist, pulmonary physician	To investigate the effect of home non-invasive ventilation plus the implementation of a call center following hospitalization for acute exacerbations	N = 20	Telemedicine	Phone call	No significant reduction in the re-hospitalizations Statistically significant difference to adherence to noninvasive ventilation
Marcos et al., Spain, 2020[48]	Observational study	Pulmonologist, nurse	To demonstrate if a telemonitoring system after hospital admission for a COPD exacerbation could have a favorable effect in 1-year readmissions and mortality in a real-world setting	N = 843 Intervention (n = 351) vs. control (n = 495) groups	Telehealth Telemedicine Telemonitoring Teleconsultation	Video call Telemetry/ Data sending	Reduced mortality and readmission after 12 months
Kooij et al., Netherlands, 2021[49]	Feasibility study	Pulmonary nurse, pulmonologist	To evaluate the effects of a mobile health and self-management application in clinical practice for recently discharged patients with COPD	N = 39	mHealth	Video call Telemetry/ Data sending	Knowledge and coping increased significantly over time No significant changes in recognition and management of symptoms, or adherence to treatment Readmission rate showed that 13% (5/39) of patients were readmitted within 30 days

N/R: not reported; RCT: randomized controlled trial; SMART-COPD: Self-Management supported by Assistive, Rehabilitative, and Telehealth technologies-COPD; HRQoL: health-related quality of life; and mHealth: mobile health. [a]Numbers not mentioned by the authors.

Professionals responsible to deliver remote care

The professionals majorly involved in telehealth delivery were nurses (in 35 studies) alone or together with multidisciplinary teams (Chart 2).

Remote applications and frequency of delivery of remote care

Most studies that described the remote monitoring of COPD patients after discharge from hospitalization for a COPD exacerbation used multiple strategies, different frequencies, and different applications. These strategies were organized into four groups: telephone calls, video calls, telemetry (alone or in combination with interactive voice response), and text messages (Figure 2). In the study by Wang et al.,[46] the patient, whenever necessary, used an application installed in the smartphone (Chart 2).

Effectiveness of remote care

The outcome investigated in 27 articles was hospital readmissions. Of these, 18 showed a reduction in the number of re-hospitalizations,[12,13,16,17,18,19,21,22,24,25,27,32,34,37,43,44,48,49] although no significant differences in the number of re-hospitalizations were found in 13 studies using telehealth/telemedicine strategies.[20,23,24,29,30,33,34,36,39,40,41,42,47] Quality of life was an outcome investigated in 13 studies, 9 of which showing favorable results with the use of telehealth/telemedicine.[12,13,17,21,37,38,39,42,46] In addition, factors associated with health literacy were pointed out as positively affecting the health of COPD patients.[13,17,42] Feasibility of home monitoring for self-management was reported in 2 studies (Chart 2).[15,45]

DISCUSSION

The main findings of this scoping review were as follows: i) the great majority of strategies demonstrated a positive effect on improving health care and quality of life in patients after hospitalization for COPD; ii) remote care involved an extensive variety of health service practices for different purposes, such as exchange of information, treatment, and exacerbation prevention; iii) most studies used two or more strategies, and phone calls and devices with or without telemetry were the most common ones; and iv) a substantial number of terms described the use of remote care, and the most common terms were telehealth, telemonitoring, and telemedicine.

It was observed that telehealth/telemedicine was effective for early detection and proactive intervention in patients at home after an acute exacerbation of COPD. It seems likely that adopting telehealth/telemedicine in everyday clinical practice could substantially improve the care of chronically ill patients.[13] Telehealth/telemedicine is a type of remote intervention that involves the delivery of care through various communication modalities, aiming at connecting patients to a health care professional and exchanging information to support self-management programs, which has shown to be effective in improving health-related quality of life and self-management behavior in patients with COPD.[46] For COPD patients, the use of telehealth/telemedicine may offer an opportunity to improve disease management and access to pulmonary rehabilitation programs.[2,8,12,17,26,45]

In order to improve telemonitoring effectiveness in COPD, parameters need to be well defined, easily available, and associated with COPD symptomatology.[40] Therefore, it is essential to identify the target populations among which telehealth is accepted and identify feasible interventions.[50] Defining parameters, as well as identifying and knowing the target population, leads to patient and physician satisfaction and, consequently, to the effectiveness of the proposed telemonitoring strategies.[8,40]

It is important to highlight that telemonitoring can be carried out and analyzed with or without telemetry. A telemetry system allows monitoring of physiological parameters with the use of smart wearable device systems to monitor health. A smart wearable device system may include a wide range of wearable or implantable devices, such as sensors, actuators, smart fabrics, power supplies, and wireless communication networks.[51]

Data transmitted by the devices were, in general, physiological measures (vital signs, SpO_2, lung function parameters, temperature, and weight) and reported symptoms, such as shortness of breath; aspect, quantity, and color of sputum; wheezing; and cough. In this regard, telemedicine has the potential to enhance the detection of true deterioration in clinical state.[44]

Among the terms identified to refer to remote care, telehealth was used for electronic technologies that transmit or receive data.[52] Telemedicine can be effective for detecting the worsening of clinical status and reducing morbidity, mortality, and health costs due to exacerbations.[53-55]

Telehealth is a term used interchangeably with telemedicine. Telemedicine uses e-health networks to provide health services and health education at a distance.[56] The term e-health refers to a self-management web platform designed to support patients to improve self-management of exacerbations at an early stage.[47] Tele-education utilizes web-based platforms to deliver information and services that pertain to the management of patient conditions.[52] Education intervention through telehealth/telemedicine is characterized by interventions to achieve a healthy lifestyle through the practice of physical activities, correct use of medications, smoking cessation, and emotional control, as well as to enhance patient self-management.[6,14,25,26,28,34] Telehealth/telemedicine showed positive effects on COPD patients after a hospitalization for an exacerbation, playing a central

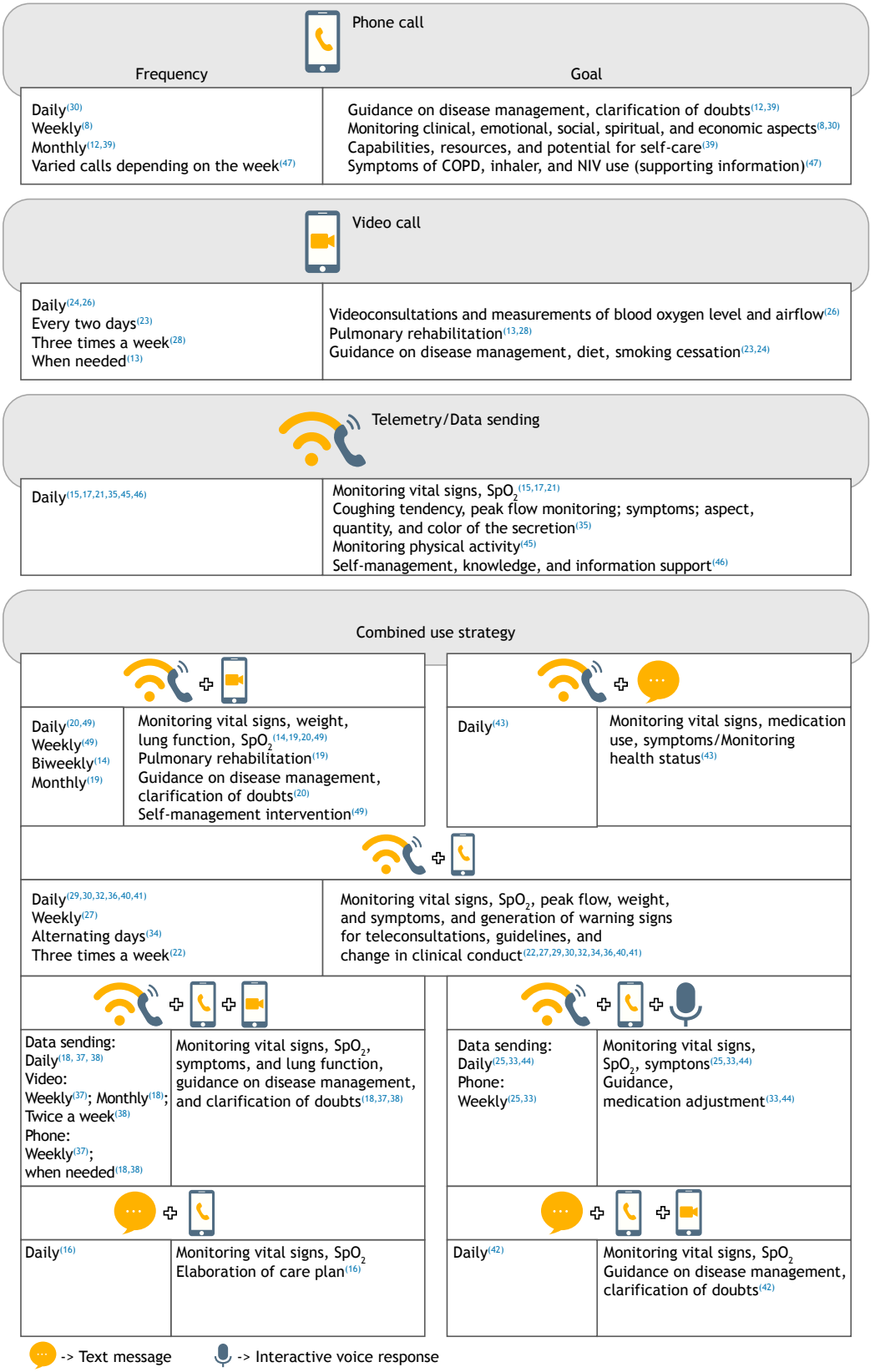

Figure 2. Telemonitoring strategies identified in the studies included, according to technologies used, frequency, and intervention goals. NIV: noninvasive ventilation.

role in self-management. The intangible benefits of the program include improvement in quality of life and in hospitalization rates.[44] These positive results support the importance of guidance and use of educational materials and methods to back a telephone call intervention. Teleconsultation might be used to change or adjust the pharmacological therapy, refer the patient to an emergency department, or even identify the need of a face-to-face home consultation.[50]

Teleconsultation, in which care is provided by videoconference and webcams connecting the healthcare practitioner with the patient, makes it possible to assess, diagnose, or treat patients remotely in addition to monitoring exercises and functional capacity in pulmonary rehabilitation.[52] Telemedicine consultations are agreed upon between the patient and the telemedicine nurse day to day. The nurse could advise the patient to consult with a general practitioner or contact a home care nurse.[18] Nurse telemedicine consultation seems to prevent early readmission and is associated with high patient and nurse satisfaction.[18]

Telerehabilitation by teleconsultation has a great potential for reducing the use of health care services, combining physical training at home, remote monitoring, health education, and promotion of self-management.[51] Telerehabilitation programs seem to be as effective as face-to-face sessions, which stimulates their use since they might solve the need for increasing access to health care.[53] The study by Rosenbek Minet et al.[28] showed that home-based supervised training and counseling via videoconference is safe and feasible and that telemedicine can help ensure more equitable access to supervised training in patients with severe COPD.

This review also highlights programs for the transition of care with the use of mobile health technologies to ensure safe coordination and continuity of care for patients with different health needs.[22,34] Transition of care is one of the pillars for integration of health systems, reducing hospitalizations, readmissions, and costs of health services, and it improves the quality of life of patients and their families.[57] Also, interventions capable of detecting and intervening on exacerbation signs at an early stage can minimize the need for emergency hospitalizations.[52] The combination of several strategies has better results. In addition, the integration of interactive telephone calls may result in higher rates of adherence to health care plans among patients with an exacerbation.[54] Telehealth/telemedicine interventions should consider individual factors that affect the usability, acceptability, and efficacy of the intervention.[45]

The limitations of the present review are related to the languages in which the studies were published, since we limited the research to those published in English, Portuguese, or Spanish. In addition, the fact that all of the studies included were carried out in developed countries might not reflect the reality in less developed countries.

FINAL CONSIDERATIONS

Telehealth/telemedicine strategies seek to accompany and encourage COPD patients to self-manage their disease by identifying signs and symptoms that can lead to an exacerbation.

This review demonstrated that there is a growing body of evidence showing that telehealth/telemedicine and telemonitoring can be an interesting strategy to benefit COPD patients after discharge from hospitalization for

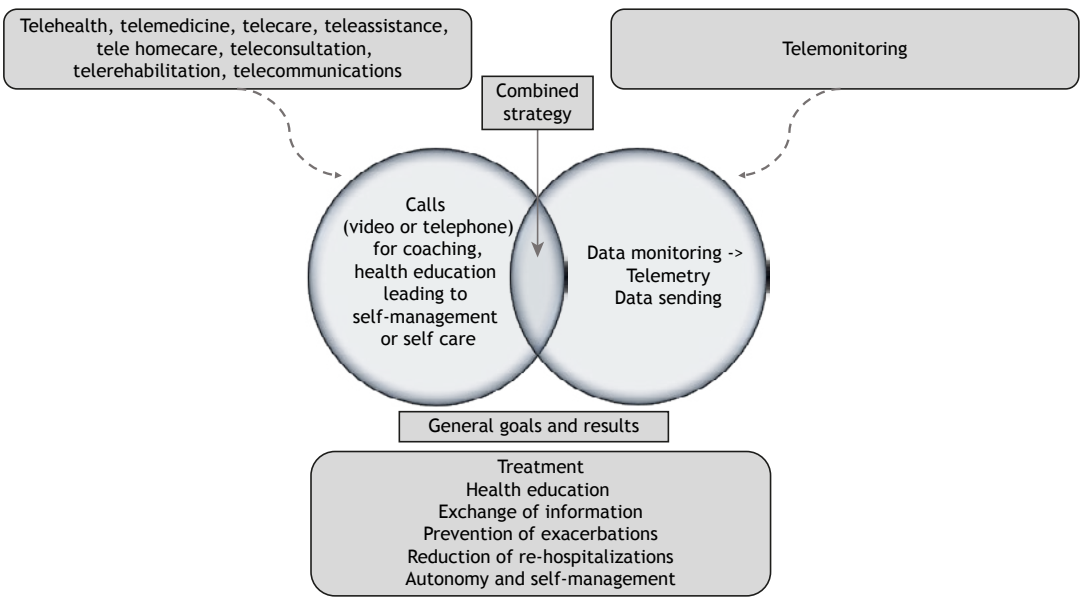

Figure 3. Telehealth mapping.

an exacerbation after being discharged by improving their quality of life and reducing re-hospitalizations, admissions to emergency services, hospital length of stay, and health care costs.

The terms to describe telehealth/telemedicine were varied and sometimes specific for different situations. The goals, the frequency of use, and the strategies adopted were also varied. Notwithstanding the differences, the great majority of studies showed that telehealth/telemedicine was beneficial regarding readmissions, quality of life, health literacy, and costs. The scope of this study is summarized in Figure 3.

AUTHOR CONTRIBUTIONS

LCR, EGR, LCP, RAG, GMR, AFC, TBC, LPSM, VMA, and KLS: study conception, protocol design, and reference management. LCR, EGR, LCP, LPSM, VMA, and KLS: drafting of the manuscript. TBF, LPSM, VMA, and KLS: critical review of intellectual content of the manuscript. All of the authors approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Trends in tuberculosis mortality among children and adolescents in Brazil, 1996-2020: a joinpoint analysis

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TO THE EDITOR:

Tuberculosis remains one of the deadliest infectious diseases worldwide. In 2020, an estimated 1.5 million people worldwide died from tuberculosis; of those, 16% were children or adolescents (< 15 years of age).[1] Childhood tuberculosis has been neglected by researchers and policy makers for decades, despite the fact that children are at high risk of acquiring tuberculosis infection and dying from tuberculosis disease. This neglect can be explained by the difficulty in diagnosing tuberculosis in children; by the fact that the risk of childhood tuberculosis transmission is low; by misplaced faith in the BCG vaccine; and by the old dictum that the best way to prevent childhood tuberculosis is to treat tuberculosis in adults.[2] To achieve the WHO End TB Strategy target of a 95% reduction in tuberculosis mortality by 2035, more priority should be given to children and adolescents, especially those in the 30 countries with the highest tuberculosis burden (among which is Brazil). Although there are numerous reports of national and global tuberculosis mortality in the general population,[3-5] there are limited data on tuberculosis mortality in the pediatric population.[6] We therefore conducted a joinpoint analysis to identify time trends of tuberculosis mortality among children and adolescents in Brazil in the 1996-2020 period.

We used an open-access database (the Brazilian Unified Health Care System Information Technology Department database) to collect data on the number of deaths from tuberculosis, as well as data on population estimates of children and adolescents in the 0- to 19-year age bracket between January of 1996 and December of 2020. Tuberculosis was classified by the following ICD-10 codes: A15—respiratory tuberculosis, bacteriologically or histologically confirmed; A16—respiratory tuberculosis, not confirmed bacteriologically or histologically; A17—tuberculosis of nervous system; A18—tuberculosis of other organs; and A19—miliary tuberculosis. We calculated the tuberculosis mortality rate per 100,000 population. We used joinpoint regression analysis (Joinpoint Software, version 4.9.0.0; National Cancer Institute, Information Management Services, Inc., Calverton, MD, USA) to estimate the annual percent change (APC) in mortality rates between trend-change points, the average APC (AAPC) during the entire study period, and 95% CIs. When there are no joinpoints (i.e., no changes in trend), the APC is constant and equals to the AAPC; otherwise, the entire period is segmented by the points with trend changes (an increasing trend, a decreasing trend, or no changes in trend). In this case, the AAPC is estimated as a weighted average of the estimated APC in each segment by using the segment lengths as weights.[7]

During the study period, 3,072 children and adolescents died from tuberculosis. Of those, 2,047 (66.6%) had respiratory tuberculosis (A15, n = 228; A16, n = 1,819), 517 (16.8%) had tuberculosis of nervous system, 129 (4.2%) had tuberculosis of other organs, and 379 (12.4%) had miliary tuberculosis. Approximately 47% of the 3,072 children and adolescents who died during the study period were female, and 76% were non-White. In addition, 892 (29%) were in the 0- to 4-year age bracket, 276 (9%) were in the 5- to 9-year age bracket, and 1,904 (62%) were in the 10- to 19-year age bracket. The overall tuberculosis mortality rate (per 100,000 population) decreased from 0.32 in 1996 to 0.17 in 2020, and the absolute number of deaths decreased from 212 to 101 in the same period. The tuberculosis mortality rates (per 100,000 population) in 1996/2020 were 0.48/0.16, 0.15/0.05, and 0.33/0.22 for children/adolescents in the 0- to 4-year age bracket, in the 5- to 9-year age bracket, and in the 10- to 19-year age bracket, respectively.

The AAPC (95% CI) in the tuberculosis mortality rate throughout the study period was −2.8% (−4.6 to −1.0), −4.2% (−7.3 to −0.9), −3.3 % (−5.3 to −1.3), and −1.4% (−3.3 to 0.5) for the sample as a whole, for those in the 0- to 4-year age bracket, for those in the 5- to 9-year age bracket, and for those in the 10- to 19-year age bracket, respectively (Table 1). The joinpoint analysis identified three trends in tuberculosis mortality in the sample as a whole: the 1996-2005 period, with a larger decreasing trend (APC, −7.9%; 95% CI, −10.0 to −5.7), the 2005-2017 period, with a smaller decreasing trend (APC, −2.3%; 95% CI, −4.0 to −0.6), and the 2017-2020 period, with a nonsignificant increasing trend (APC, 11.8%; 95% CI, −1.5 to 26.9). In the 0- to 4-year age group, the joinpoint analysis identified a decreasing trend in the 1996-2015 period (APC, −8.5%; 95% CI, −10.3 to −6.7) and a nonsignificant increasing trend in the 2015-2020 period (APC, 14.4%; 95% CI, −1.7 to 33.1). In the 10- to 19-year age group, the joinpoint analysis identified a slight decreasing trend in the 1996-2016

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Table 1. Trends in tuberculosis mortality (per 100,000 population) among children and adolescents in Brazil, 1996-2020.

Age group	AAPC (95% CI)	p	Joinpoint section	APC (95% CI)	p
Sample as a whole	−2.8% (−4.6 to −1.0)	0.003	1996-2005	−7.9% (−10.0 to −5.7)	< 0.001
			2005-2017	−2.3% (−4.0 to −0.6)	0.01
			2017-2020	11.8% (−1.5 to 26.9)	0.08
0- to 4-year age bracket	−4.2% (−7.3 to −0.9)	0.01	1996-2015	−8.5% (−10.3 to −6.7)	< 0.001
			2015-2020	14.4% (−1.7 to 33.1)	0.07
5- to 9-year age bracket	−3.3% (−5.3 to −1.3)	0.002	N/A	-	
10- to 19-year age bracket	−1.4% (−3.3 to 0.5)	0.14	1996-2016	−3.4% (−4.4 to −2.5)	< 0.001
			2016-2020	9.3% (−2.2 to 22.0)	0.11

AAPC: average annual percent change; and APC: annual percent change.

period (APC, −3.4%; 95% CI, −4.4 to −2.5) and a nonsignificant increasing trend in the 2016-2020 period (APC, 9.3%; 95% CI, −2.2 to 22.0).

Overall, the tuberculosis mortality rate in Brazilian children and adolescents in Brazil has decreased in the last two decades, with an AAPC of −2.8%. The overall tuberculosis mortality rate and the absolute number of deaths in these age groups are relatively low. However, at least three findings of this study merit attention. First, a nonsignificant increasing trend in tuberculosis mortality with an APC of 11.8% in the 2017-2022 period highlights the need to confirm this trend by continuous nationwide surveillance of tuberculosis deaths among children and adolescents in Brazil. Second, 76% of all tuberculosis deaths occurred among non-White individuals, a rate that is much higher than 56%, which is the proportion of non-White individuals in the population of children and adolescents in the 0- to 19-year age bracket. A disproportionately high tuberculosis mortality rate among non-White children and adolescents might reflect the socioeconomic inequalities in Brazil that give rise to differences in exposure and vulnerability to infection and disease, as well as in access to prompt diagnosis and treatment. Third, children/adolescents in the 10- to 19-year age bracket accounted for 62% of all tuberculosis deaths, a rate that is higher than the proportion of children/adolescents in this age group in the pediatric population (i.e., 52%). Moreover, the tuberculosis mortality rate in this age group did not decrease significantly throughout the study period, showing a nonsignificant increasing trend with an APC of 9.3% in the 2015-2020 period. The period between adolescence and early adulthood is increasingly recognized as a key period for tuberculosis disease and adverse outcomes.[8] The higher tuberculosis mortality rate among adolescents might be related to poor treatment adherence, high loss to follow-up rates, and increased comorbidities such as tuberculosis/HIV coinfection, diabetes, and risky substance use.[9] Tuberculosis has been reported as the underlying cause in less than 1% of deaths from tuberculosis/HIV coinfection,[10] and this can lead to an underestimation of tuberculosis deaths.

Despite remarkable progress in reducing tuberculosis cases and deaths in the last few decades, Brazil remains among the 30 countries in the world with the highest tuberculosis burden. This study highlights the need for establishing a specific and effective national strategy to control childhood tuberculosis in Brazil, prioritizing racial equity in health care and paying special attention to adolescent patients.

AUTHOR CONTRIBUTIONS

TGP: study conception and design; data collection, analysis, and interpretation; and drafting of the manuscript. YMC: study conception and design; data collection and interpretation; and critical revision of the manuscript for important intellectual content. MLC: data interpretation; and critical revision of the manuscript for important intellectual content. LRE: data analysis and interpretation; and critical revision of the manuscript for important intellectual content. LZ: research project coordination; study conception and design; data interpretation; and critical revision of the manuscript for important intellectual content. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

None declared.

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

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TO THE EDITOR:

This is an update of a living systematic review and meta-analysis by Batista et al.[1] We performed a search for articles published in the period between January of 2020 and December of 2022. We retrieved 431 articles, but only 14 remained. Of those 14 studies, nine had previously been evaluated.[1] Therefore, a total of five studies were included in the present update. Of those, two included hospitalized adult patients (one being an open-label randomized clinical trial—RCT—including 186 hospitalized patients with moderate COVID-19 and one being an open-label RCT including 159 patients admitted to the ICU) and three were RCTs including COVID-19 outpatients (one being a double-blind RCT and two being open-label RCTs) Because of the heterogeneity of intervention designs, three RCTs of COVID-19 outpatients were not included in the present update. Ramacciotti et al.[2] investigated extended post-discharge anticoagulation for COVID-19 patients. For the analysis of hospitalized COVID-19 patients, eight RCTs[3-10] were included in the present update, with 2,695 patients in the therapeutic-dose group (full anticoagulation) and 2,553 patients in the standard-of-care (SOC) group. There was no significant reduction in the 30-day mortality rate in patients with moderate to severe COVID-19 (risk difference [RD], −0.00; 95% CI, −0.03 to 0.02; p = 0.77; I^2 = 60%), the quality of evidence being very low. When patients with moderate COVID-19[3,4,6,7,9] or severe COVID-19[5,10] were analyzed separately, no significant difference was found between full anticoagulation and SOC in those with moderate COVID-19 (RD, −0.01; 95% CI, −0.05 to 0.03; p =0.77; I^2 = 76%), the quality of evidence being very low. Two studies assessed patients with severe COVID-19,[5,10] showing no significant difference in the mortality rate between the two groups (RD, 0.01; 95% CI, −0.04 to 0.06; p = 0.66; I^2 = 0%); the quality of evidence was very low.

Thrombotic events were assessed in seven studies,[3,5-10] with a total of 2,621 patients in the therapeutic-dose group and 2,511 patients in the SOC group. There was a significant (3%) reduction in thrombotic events at 30 days in the therapeutic-dose group in comparison with the SOC group (RD, −0.03; 95% CI, −0.05 to −0.01; p = 0.009; I^2 = 73%), the number needed to treat (NNT) being = 33 and the quality of evidence being low. This result remained significant when the severity of COVID-19 was evaluated. For patients with moderate COVID-19, three studies[6,7,9] demonstrated a 2% reduction in RD (95% CI, −0.04 to −0.00; p = 0.06; I^2 = 55%), the NNT being = 50 and the quality of evidence being low. For patients with severe COVID-19, two studies[5,10] demonstrated a significant (3%) reduction in thrombotic events after 30 days (95% CI, −0.06 to −0.01; p = 0.02; I^2 = 33%), the NNT being = 33 and the quality of evidence being moderate.

Major bleeding within 30 days was reported in seven studies,[3,5-10] with a total sample of 5,132 patients. There was no significant difference in major bleeding between patients receiving full coagulation and those receiving SOC (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.2; I^2 = 61%), the quality of evidence being very low. When patients with moderate COVID-19 were analyzed, no significant difference was found between the two groups (RD, 0.01; 95% CI, −0.01 to 0.03; p = 0.45; I^2 = 71%), the quality of evidence being very low. For patients with severe COVID-19, three RCTs[5,8,10] showed no significant differences in major bleeding between the two groups (RD, 0.01; 95% CI, −0.02 to 0.05; p = 0.46; I^2 = 51%), the quality of evidence being very low.

A total of 1,023 outpatients with COVID-19 were analyzed in three RCTs,[11-13] with 506 outpatients in the prophylactic-dose group and 517 outpatients in the SOC group. As can be seen in Figure 1A, no significant difference was found between the groups regarding the 30-day mortality rate (RD, 0.00; 95% CI, −0.01 to 0.01; p = 0.61; I^2 = 0%), the quality of evidence being very low. As can be seen in Figure 1B, there was no significant difference between the groups regarding thrombotic events (RD, 0.00; 95% CI, −0.01 to 0.01; p = 0.51; I^2 = 0%), the quality of evidence being moderate. As can be seen in Figure 1C, there was no significant difference between the groups regarding all-cause hospitalization (RD, 0.00; 95% CI, −0.02 to 0.03; p = 0.86; I^2 = 0%), the quality of evidence being very low. Major bleeding was assessed in two studies,[11,12] with a total of 401 patients in the prophylactic-dose group and 403 patients in the SOC group. As can be seen in Figure 1D, there was no significant difference between the groups regarding

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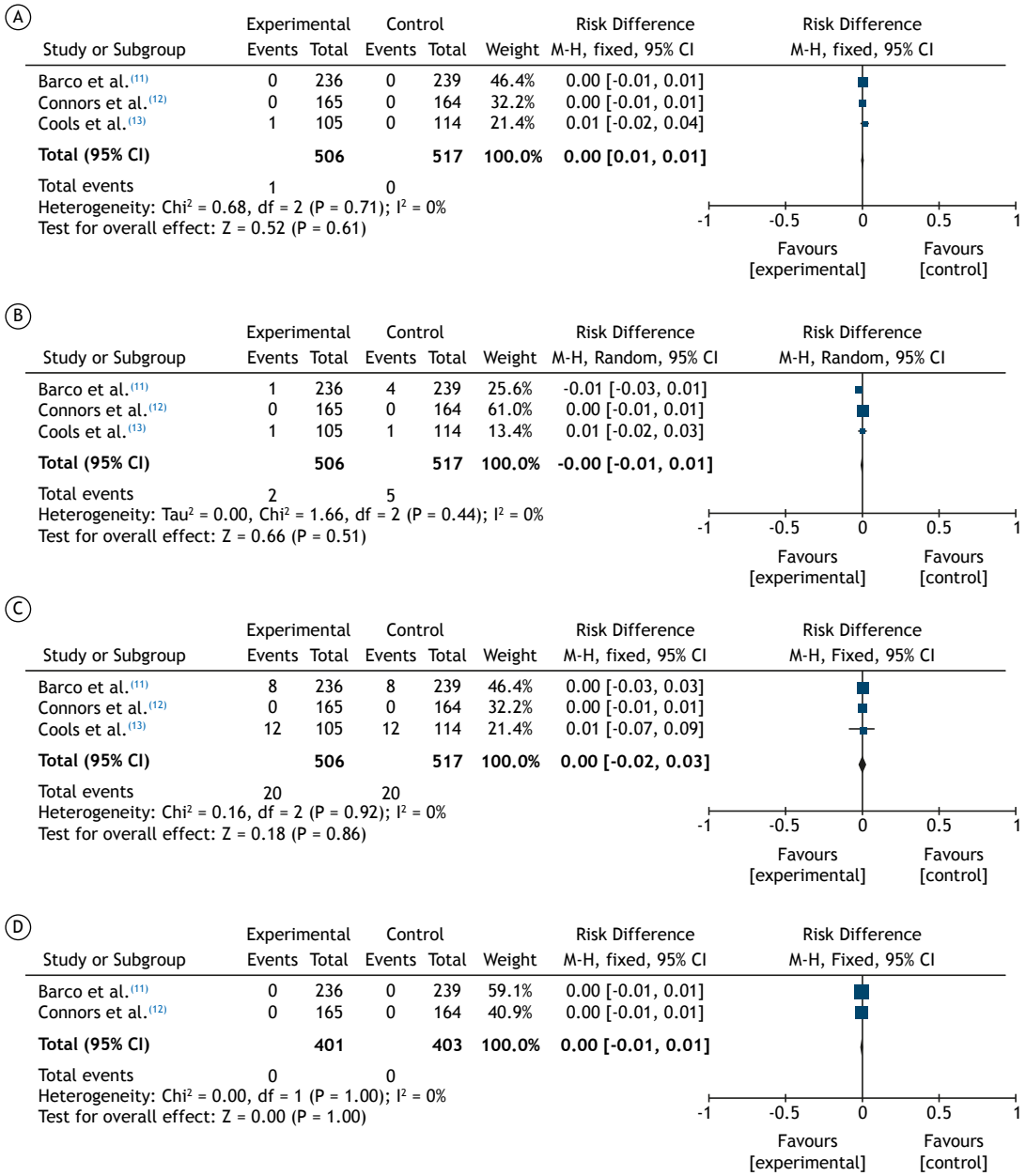

Figure 1. Forest plot of comparison: Prophylactic anticoagulation vs. standard of care/placebo—randomized clinical trials, outcome: A: mortality at 30 days, B: venous thromboembolism at 30 days, C: all-cause hospitalization, D: major bleeding at 30 days. M-H: Mantel-Haenszel (method); and df: degrees of freedom.

major bleeding (RD, 0.00; 95% CI, −0.01 to 0.01; p = 1.0; I^2 = 0%), the quality of evidence being low.

In conclusion, new evidence from RCTs of hospitalized COVID-19 patients shows that full anticoagulation can reduce the risk of thrombotic events with low risk of major bleeding. However, this evidence is highly heterogeneous and of low or very low quality and therefore should not be used for all hospitalized COVID-19 patients. For COVID-19 outpatients, our current findings are consistent with our previous results showing that there is no evidence to support the use of prophylactic anticoagulation in this population.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Small samples, big problems: lipoid pneumonia mimicking lung adenocarcinoma

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TO THE EDITOR:

Lepidic adenocarcinoma of the lung is a distinct form of lung cancer, characterized by proliferation of neoplastic cells along the alveolar lining without changes in the structure of the alveoli. It is a variant of pulmonary adenocarcinoma, the most common type of lung cancer, and generally has a better prognosis than do other forms of lung cancer, because of its slow growth and more limited pattern of spread.[1]

Sampling of small fragments of lung tissue (e.g., transbronchial biopsy) remains a commonly used diagnostic tool for lung cancer. The main limitations are as follows: 1) samples might not be representative of the entire lesion; and 2) crush artifacts that might not provide enough tissue for a comprehensive histopathological examination, including immunohistochemistry and molecular testing. This can lead to erroneous diagnostic conclusions and unnecessary treatments.[2,3]

A 62-year-old woman who had recently been diagnosed with lung adenocarcinoma—presumably confirmed through a transthoracic biopsy of the right upper lobe, performed at another facility—presented for an oncologic visit for systemic treatment initiation. The patient had no respiratory symptoms. Her medical history included chronic pain secondary to a vertebral fracture in 2015 and constipation secondary to opioids; she used mineral oil laxatives for her constipation. She had never smoked and had no family history of lung cancer.

On physical examination, her RR was = 18 breaths/min, her HR was 80 bpm and her SpO_2 was 93% on room air. Pulmonary auscultation revealed crackles, predominantly in the right hemithorax. Routine blood tests were normal. The patient underwent a PET/CT scan, which showed ground-glass opacities with septal thickening, forming a crazy-paving pattern in the right lung. These opacities were mild in the middle and lower lobes, predominating and coalescing in the upper lobe (Figure 1A). Her previous CT scan was not available. The opacities showed a slightly increased 18F-FDG uptake (maximum standardized uptake value, 3.0), and there were two normal-sized hypermetabolic lymph nodes (right hilar and right upper paratracheal lymph nodes; maximum standardized uptake value, 3.9; Figure 1B).

Before initiation of oncologic treatment, we reviewed the transthoracic biopsy specimens and found no neoplastic cells. In light of this finding, a decision was made to perform a CT-guided transthoracic biopsy of the right upper lobe. The biopsy findings were suggestive of lipoid pneumonia, with no findings suggestive of neoplasia or infection (Figure 1C).

After diagnostic confirmation, treatment with mineral oil was discontinued and nonopioid pain management options were optimized. The patient remained without respiratory symptoms during the follow-up period. The ground-glass opacities remained, showing a slight reduction after 9 months. A follow-up CT scan performed 16 months after the PET/CT scan showed yet another reduction in ground-glass opacities (Figure 1D).

Lipoid pneumonia is a rare lung condition characterized by accumulation of lipid material within the lung parenchyma, resulting from either exogenous (aspiration of oil-based products) or endogenous (disruption of lipid metabolism) sources. Clinical manifestations can vary, ranging from asymptomatic cases to those presenting with cough, dyspnea, chest pain, or fever.[4,5]

Lipoid pneumonia can present as ground-glass opacities, consolidations, or a crazy-paving pattern on chest CT scans. The differential diagnosis includes lung cancer, pulmonary alveolar proteinosis, acute interstitial pneumonia, nonspecific interstitial pneumonia, organizing pneumonia, *Pneumocystis jirovecii* pneumonia, and pulmonary hemorrhage.[6] In the case reported here, an interesting imaging finding was the presence of opacities exclusively in the right lung, predominantly in the upper lobe, an atypical finding for exogenous lipoid pneumonia. The patient later revealed that she had undergone lumbar surgery and slept exclusively on her right side ever since, thus explaining the preferential mechanism by which aspiration of lipid material had occurred. Another interesting imaging finding was an unusually long persistence of parenchymal abnormalities in the context of a lung adenocarcinoma.

In patients presenting with chest CT findings mimicking various pulmonary diseases, including lung cancer, lung biopsy plays a key role in establishing a diagnosis, and the type of biopsy should be carefully selected. The limitations of diagnosing lung cancer from small tissue samples include the risk of sampling errors, which might not capture the full heterogeneity of the tumor, and the possibility of crush artifacts obscuring important histological features. Additionally, small tissue samples might not be enough for comprehensive histopathological examination, immunohistochemistry, and molecular testing, thus limiting the identification of specific tumor subtypes or molecular characteristics crucial for personalized treatment planning.[3,7,8]

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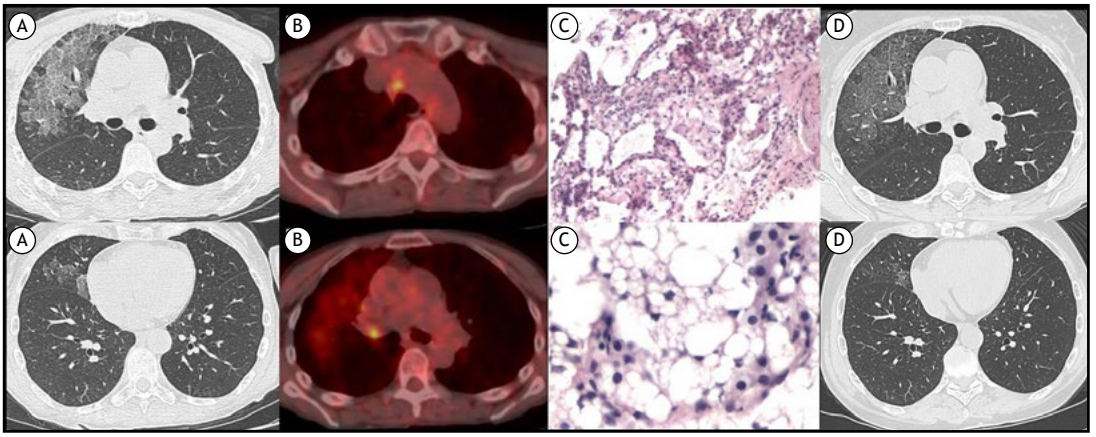

Figure 1. In A, axial CT scans of the chest showing a crazy-paving pattern in the right lung, predominantly in the upper lobe. In B, PET/CT fusion images showing 18-FDG uptake in the lung opacities and in lymph nodes. In C, histopathological images of the pulmonary parenchyma, with the upper image (H&E; magnification, ×10) showing alveolar filling and septal thickening caused by macrophage accumulation and the lower image (H&E; magnification, ×20) showing vacuoles of various sizes in the cytoplasm. In D, follow-up axial CT scans of the chest showing a reduction in ground-glass opacities.

Regarding histopathological findings, lipoid pneumonia and lepidic adenocarcinoma of the lung share some similarities, including lipid-laden macrophages within the alveolar spaces. However, there are key differences between the two. In patients with lepidic adenocarcinoma, malignant glandular epithelial cells line the alveolar walls, but the alveolar architecture is maintained, whereas, in patients with lipoid pneumonia, an alveolar-filling process is accompanied by accumulation of lipid material and a chronic inflammatory response. Immunohistochemically, lepidic adenocarcinoma typically expresses markers of glandular differentiation, such as cytokeratin 7, cytokeratin 20, thyroid transcription factor-1, and napsin A, which are absent in lipoid pneumonia.[4,9]

An alternative to avoid small transbronchial lung biopsy samples, cryobiopsy is a promising method that has proven useful in diagnosing endobronchial and peripheral lung tumors, with increased diagnostic yield and quality of collected samples for histopathological and molecular diagnosis of lung cancer. When used alone or in conjunction with fluoroscopy or radial endobronchial ultrasound, cryobiopsy can improve lung tissue sampling,[10] being similar to transthoracic biopsy or even surgical biopsy (open surgical biopsy or video-assisted thoracoscopic surgery).

Larger biopsy specimens can provide a broader and more detailed view of lung tissue, allowing a more accurate differential diagnosis, especially in cases in which a diagnosis of lung cancer does not seem to match the clinical context or in which other diagnoses are more likely.

AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Fulminant organizing pneumonia in a patient with ulcerative colitis on mesalamine and infliximab: striving to identify the cause!

Lídia Gomes[1], Maria Alcide Marques[1], Pedro Gonçalo Ferreira[1]

TO THE EDITOR:

Pulmonary involvement in inflammatory bowel disease is uncommon and often occurs secondarily to drug-induced toxicity or as an extraintestinal manifestation (EIM) of the underlying disease.[1]

We describe the case of a patient with ulcerative colitis (UC) on immunosuppressive therapy that developed fulminant interstitial lung disease (ILD) with severe hypoxemic respiratory failure. Written informed consent for publication of clinical details and images was obtained from the patient. In addition, we discuss the etiological investigation carried out.

This report relates to a 38-year-old Caucasian male who had been diagnosed with UC 2 years earlier and had been on treatment with mesalamine and infliximab for 17 and 5 months, respectively. He was a former smoker (20 pack-years), with no other relevant exposures or previous chronic respiratory disease, and was admitted with a 3-week history of worsening dyspnea, fever, and pleuritic chest pain.

On physical examination, he was polypneic, with an Spo_2 of 90% on room air and decreased breath sounds over the lung bases. Blood gas analysis showed hypoxemic respiratory failure (Po_2/Fio_2 = 232) with normal lactates. He tested negative for SARS-CoV-2. A blood panel revealed C-reactive protein of 12.9 mg/dL (normal range, < 0.5) with procalcitonin and white cell count (including eosinophils) within the normal range. A chest x-ray showed bilateral alveolar opacities (Figure 1A). Given an initial clinical suspicion of opportunistic pneumonia with ARDS, the patient was placed on broad-spectrum antibiotics with piperacillin-tazobactam and linezolid. Despite a good initial response to conventional oxygen therapy (Fio_2 = 0.35; Po_2/Fio_2 = 195), there was overall clinical worsening with persistent high fever and increasing Fio_2 demand (Fio_2 = 0.60; Po_2/Fio_2 = 148), even with CPAP. Chest CT angiography excluded pulmonary embolism and showed multifocal consolidations with a peribronchial component suggesting rapidly progressive organizing pneumonia (OP; Figure 1B). The patient underwent bronchoscopy with a comprehensive microbiological workup for viruses, bacteria, mycobacteria, and fungi, the results of which were negative. Given the progressive clinical worsening and the possibility of drug-induced acute lung injury, systemic corticosteroid therapy was initiated (methylprednisolone 125 mg/day for 3 days and then methylprednisolone 60 mg/day for 8 days, with further progressive tapering) and resulted in partial clinical and radiographic improvement. Colonoscopy excluded active UC.

Lung function testing revealed an FVC of 57% predicted and a single-breath D_{LCO} of 41% predicted. A significant oxyhemoglobin desaturation (nadir Spo_2 of 78%) was evident during the six-minute walk test, which was interrupted after four minutes (six-minute walk distance = 150 m). Reassessment with chest HRCT showed improvement of consolidations, with persistent areas of mosaic and ground-glass pattern (Figure 1C). The patient was referred for video-assisted thoracoscopic surgical lung biopsy. Histological analysis showed key features of OP, accompanied by a giant-cell reaction and chronic bronchiolitis. Given the absence of active UC, both infliximab and mesalamine were permanently discontinued, and, regarding ILD treatment, the patient was discharged on prednisolone (30 mg/day with a progressive weaning protocol) and was started on mycophenolate mofetil (target dose of 3 mg/day) and ambulatory oxygen.

After a multidisciplinary discussion of all complementary test results available and a thorough literature review, a provisional high-confidence diagnosis of mesalamine-induced lung disease (rapidly progressive OP with giant-cell reaction) was made. The case had a score of 5 on the Naranjo Adverse Drug Reaction Probability Scale and a score of 6 on the Karch-Lasagna modified algorithm ("probable adverse drug reaction").[2]

At 2-month follow-up, the patient had improved remarkably, with a normal chest X-ray, an FVC of 84% predicted, a D_{LCO} of 71% predicted, and no desaturation during the six-minute walk test (six-minute walk distance = 475 m, 75% predicted). The 6-month HRCT revealed complete resolution of the previous consolidation and patchy areas of ground-glass opacity (Figure 1D).

In our case, the final diagnosis was based on clinical presentation, imaging abnormalities, elusive lung histological features, and the exclusion of possible etiologies, including opportunistic infection. The timing of respiratory symptom onset is variable, and no clear-cut temporal association between mesalamine initiation and subsequent lung disease has been found.[3] On the other hand, most cases of infliximab-induced lung toxicity occur early after treatment initiation.[4] Pulmonary EIM was excluded based on endoscopic remission of UC and the patient's level of immunosuppression, as well as on the absence of other organ involvement. Above all, histological findings were strikingly consistent with a drug-related hypersensitivity reaction.[2] Although rare cases of OP secondary to infliximab have also been reported, there are in the literature cases of mesalamine-induced lung disease showing histological patterns of OP with focal areas of granulomatous/giant-cell reaction and

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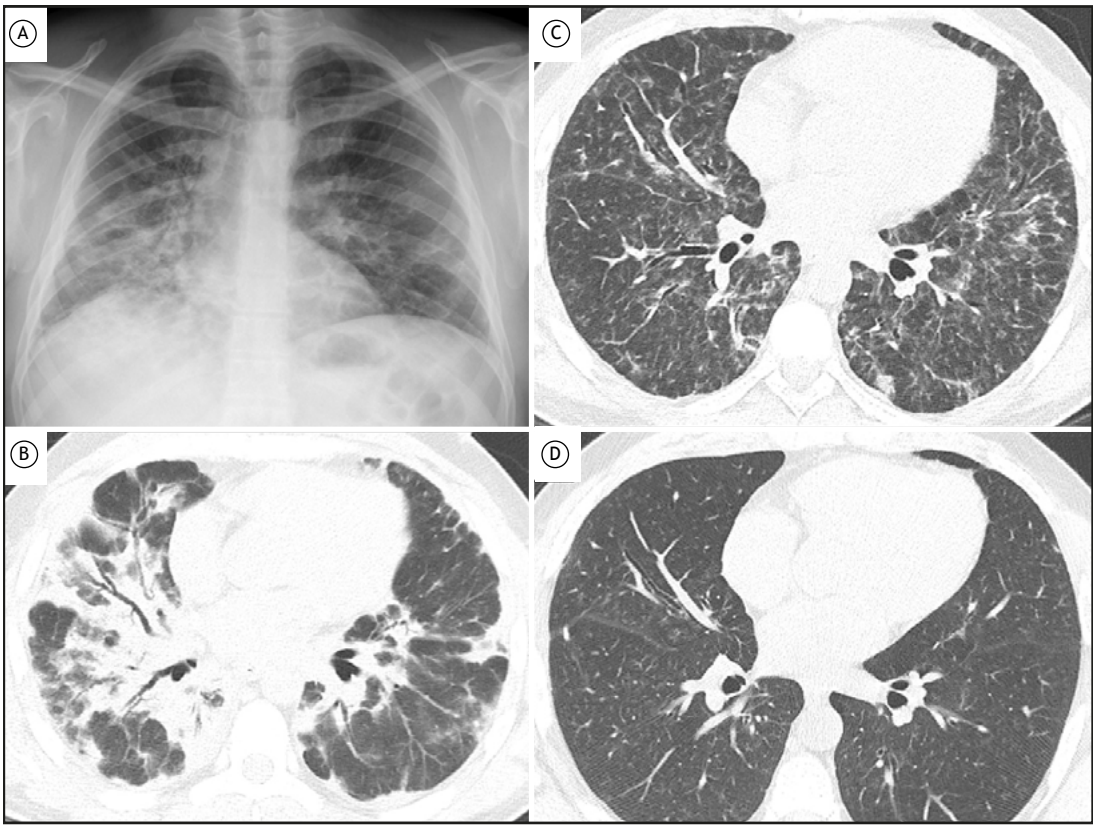

Figure 1. In A, chest X-ray showing bilateral alveolar opacities. In B, chest CT angiographic image showing multifocal consolidations with a peribronchial component. In C, chest HRCT scan showing improvement of consolidations, with persistent areas of mosaic and ground-glass pattern. In D, 6-month HRCT scan showing complete resolution of the previous consolidation and patchy areas of ground-glass opacity.

chronic bronchiolitis, which is perfectly in line with our findings.[2,3,5] Sequential drug rechallenge was not performed due to high risk.

The treatment for mesalamine-induced lung disease includes prompt discontinuation of the drug and, in severe forms, adjuvant anti-inflammatory therapy.[3] There are less than 20 case reports of histologically proven mesalamine-related OP in the literature, few of which were severe enough to require noninvasive positive airway pressure support.[3,5-7]

Overall, our case highlights the challenge of diagnosing rapidly progressive ILD in patients with UC on specific immunomodulatory maintenance therapy. Early suspicion of drug-induced lung disease in these patients, with timely exclusion of other etiologies, is crucial. Infection should be excluded at the highest possible priority (particularly if the patient is on anti-TNF agents). Differentiating a pulmonary EIM of UC from drug toxicity remains challenging; however, the absence of other EIMs, as well as remission of UC as evidenced by upper gastrointestinal endoscopy findings and patient-reported clinical information, can almost exclude pulmonary EIMs.[6] Lung biopsy can be useful in selected patients, and a thorough multidisciplinary discussion is mandatory to establish a confident diagnosis, enable early treatment, and thus avoid complications.[2]

AUTHOR CONTRIBUTIONS

LG: drafting of the manuscript.

MAM and PGF: critical review of the paper.

CONFLICTS OF INTEREST

None declared.

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Fat embolism syndrome causing a crazy-paving pattern on CT

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

A 38-year-old man was admitted 2 h after a motocross accident for treatment of a left diaphyseal femoral fracture (Figure 1A). A chest X-ray was normal. The femoral fracture was treated with intramedullary nail fixation. Two days after the accident, the patient developed fever, shortness of breath, chest pain, and neurological symptoms, including mental confusion and seizures. Physical examination revealed petechiae involving the conjunctivae (Figure 1B). Pulse oximetry revealed a decrease in oxygen saturation to 70% on room air. Chest CT showed bilateral ground-glass opacities with interlobular septal thickening causing a crazy-paving pattern (Figures 1C and 1D). A diagnosis of pulmonary fat embolism syndrome (FES) was established. The patient was treated conservatively with supplemental oxygen, and his respiratory status improved gradually.

Fat embolism is defined as the release of fat, usually derived from bone marrow, into the systemic or pulmonary circulation. FES is a potentially fatal complication of trauma (particularly long bone fractures) or orthopedic surgery. The clinical diagnosis of FES is based on a triad of hypoxia, mental confusion, and petechial rash.[1-3] FES usually presents on CT as bilateral patchy or diffuse ground-glass opacities.[1-3] In conclusion, the diagnosis of FES should be considered in patients who have a 1- to 3-day history of trauma before symptom onset in combination with the classic clinical and imaging findings of this syndrome.

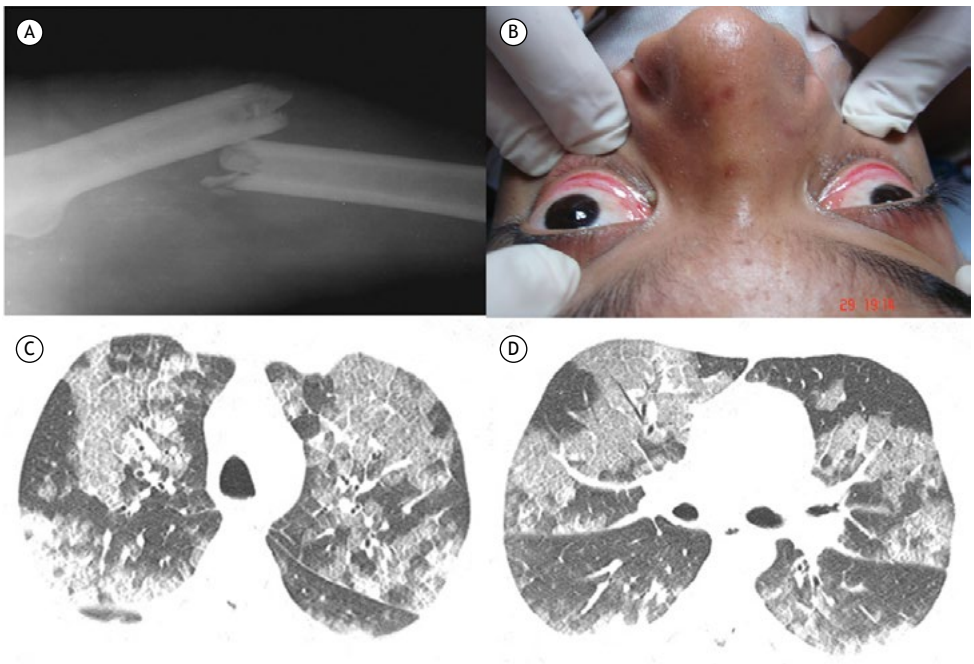

Figure 1. In A, an X-ray showing a complete diaphyseal fracture of the left femur. In B, petechiae involving the conjunctivae. In C and D, axial chest CT images obtained at the level of the upper lobes and subcarinal region demonstrate bilateral scattered ground-glass opacities with interlobular septal thickening causing a crazy-paving pattern.

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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.

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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.

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

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