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HIGHLIGHT

Prone positioning on patients with COVID-19 and ARDS

Post-tuberculosis lung disease: an international study

Donation after circulatory death and lung transplantation

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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Effects of COVID-19 on tuberculosis control: past, present, and future

Denise Rossato Silva[1], Fernanda Carvalho de Queiroz Mello[2], Giovanni Battista Migliori[3,4]

As we celebrate the World Tuberculosis Day on the 24th of March, the biggest challenge faced in tuberculosis control is the COVID-19 pandemic.[1] According to the latest report by the WHO, the number of newly diagnosed tuberculosis cases fell from 7.1 million in 2019 to 5.8 million in 2020; the number of drug-resistant tuberculosis (DR-TB) cases also decreased from 177,100 to 150,359, respectively, and the number of patients on tuberculosis preventive treatment reduced from 3.6 million to 2.8 million.[2] In fact, the Global Tuberculosis Network coordinated a multicentric study[3] and demonstrated that the COVID-19 pandemic has substantially affected tuberculosis services in many countries around the globe. In 2020, as compared with in 2019, there was an overall decrease in the total number of diagnosed and treated active tuberculosis cases, fewer DR-TB cases were managed, fewer latent tuberculosis cases were treated, and there was an increase in telehealth/internet-based visits.[3]

In this issue of the *Jornal Brasileiro de Pneumologia*, another Global Tuberculosis Network study[4] evaluated country-specific lockdown measures during the first year of the COVID-19 pandemic. Although in the pre-COVID-19 vaccination period (i.e., during the first three waves of the pandemic) lockdown measures were important in reducing transmission, limiting the pressure on hospital departments and ICUs, public health measures taken to contain the spread of COVID-19 clearly had an impact on tuberculosis control.[2,5]

In fact, in a letter to the editor,[6] the authors showed a reduction of confirmed tuberculosis cases reported in Brazil in 2020, as compared with the period from 2017 to 2019. The reduction in diagnosis compromises the WHO goals for tuberculosis elimination. At the present time and over the next few years, raising awareness about tuberculosis will be critical to diagnosing as many tuberculosis cases as possible. In this sense, new diagnostic tools might facilitate prompt tuberculosis diagnosis. Santos et al.[7] described a decision tree classifier model for the diagnosis of pleural tuberculosis, including clinical characteristics and cellular/biochemical pleural fluid testing. Considering that pleural tuberculosis is the most frequent extrapulmonary form of tuberculosis and that its diagnosis is generally difficult due to its paucibacillary nature, a predictive model with only three variables and high sensitivity and specificity that can be easily used in basic health care units is very advantageous.

The diagnosis of latent tuberculosis infection (LTBI) was also negatively impacted by the COVID-19 pandemic.[2] In order to reach the End TB Strategy target of reducing tuberculosis incidence by 90% through preventive tuberculosis treatment,[1] it will be critical to intensify efforts to diagnose and treat LTBI cases. For this reason, some individuals should be given high priority for LTBI testing and treatment. In this issue of the Journal, a prospective study[8] evaluated the prevalence of LTBI in patients with interstitial lung diseases requiring immunosuppression. The authors found a prevalence of LTBI of 9.1%, highlighting the importance of screening for LTBI in this group of patients.

Delayed tuberculosis diagnosis and treatment due to the COVID-19 pandemic can contribute to increasing the burden of tuberculosis, including that of multidrug-resistant tuberculosis (MDR-TB), in the years to come. The treatment success rate of MDR-TB is low (approximately 50%), and, therefore, the development of new drugs and shorter regimens could significantly improve tuberculosis treatment outcomes.[9] Bedaquiline is a new drug that has been used in regimens recommended by the WHO for the treatment of MDR-TB. Hatami et al.[10] conducted a systematic review and meta-analysis on the use of bedaquiline in MDR-TB treatment. They found that culture conversion and treatment success rates were high in bedaquiline-containing regimens, even in extensively drug-resistant tuberculosis cases.

As we see a great number of undiagnosed and untreated tuberculosis cases due to the COVID-19 pandemic, it is possible that these patients will more frequently experience pulmonary sequelae due to delayed diagnosis and treatment and/or the development of DR-TB. Thus, we can expect an increased number of patients with post-tuberculosis lung disease (PTLD) in the future. According to clinical standards for the assessment, management, and rehabilitation of PTLD,[11] these patients should be evaluated as soon as possible at the end of tuberculosis treatment. Furthermore, it is important to know the prevalence and severity of PTLD in different populations. A comparison of three cohorts (from Brazil, Italy, and Mexico) was published in the Journal this month.[12] It was demonstrated that the three cohorts had variable pulmonary function test results and that patients with DR-TB had more severe disease. In addition, in the Brazilian cohort, pulmonary function test results decreased over time, reinforcing the importance of pulmonary rehabilitation in those patients.

In summary, for the past two years we have been living with the COVID-19 pandemic, witnessing successive waves and its effects on global health. Currently, we are

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still facing the rise of new variants and dealing with the post-COVID-19 syndrome. At the same time, we can see COVID-19 disrupting tuberculosis control, reducing the number of tuberculosis diagnoses and patients on tuberculosis preventive treatments. At the moment and during the next few years, we will have to be prepared to diagnose more cases of tuberculosis and LTBI, and to be aware of the possible increase in MDR-TB and PTLD cases.

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AUTHOR CONTRIBUTIONS

All of the authors equally contributed to the writing and reviewing of the manuscript.

CONFLICT OF INTEREST

None declared.

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Prone positioning in COVID-19 ARDS: more pros than cons

Denise Battaglini[1], Paolo Pelosi[1,2], Patricia R M Rocco[3]

Patients with severe COVID-19 may develop acute respiratory failure requiring mechanical ventilation.[1] Prone positioning is a rescue therapy for ARDS patients with hypoxemia refractory to protective mechanical ventilation with high F_{IO_2}.[2]

In non-COVID-19 ARDS, prone positioning has been shown to improve oxygenation and is associated with improved outcomes. The improvement in oxygenation and the reduction in the risk of ventilation-induced lung injury have been explained by a more homogeneous distribution of transpulmonary pressures, which opens the dorsal atelectatic areas, thus reducing regional lung stress.[3]

In COVID-19 ARDS, different phenotypes have been proposed.[1] In phenotype 1, lung weight and lung compliance may be relatively normal, alveolar recruitment is minimal, and hypoxemia is mainly due to increased lung regions with low ventilation/perfusion ratios.[4] On the other hand, in phenotype 2, lung weight is increased, lung compliance is markedly reduced, alveolar recruitment is variable, and hypoxemia is mainly due to increased true shunting. Both phenotypes are characterized by increased wasted ventilation (high dead space ventilation and lung regions with high ventilation/perfusion ratios).[5] Therefore, the effects of prone positioning in COVID-19 ARDS may differ from those seen in non-COVID-19 ARDS. To date, few randomized controlled trials have reported benefits of prone positioning in COVID-19 ARDS.

In a study published in this issue of *Jornal Brasileiro de Pneumologia,* Cunha et al.[6] aimed to identify factors that lead to a positive oxygenation response and predictors of mortality after prone positioning in mechanically ventilated patients with COVID-19. A multicenter cohort study was performed across seven hospitals in Brazil, including patients with a suspected or confirmed diagnosis of COVID-19 who were on invasive mechanical ventilation, had a PaO_2/F_{IO_2} < 150 mmHg, and were prone positioned. An improvement in the PaO_2/F_{IO_2} ratio of at least 20 mmHg after the first prone positioning session was defined as a positive response. Of the 574 patients studied, 412 (72%) responded positively to the first prone positioning session. Multiple logistic regression showed that "responders" had lower Simplified Acute Physiology Score III and SOFA scores, lower D-dimer levels, and lower baseline PaO_2/F_{IO_2} ratios. Age, time to the first prone positioning session, number of sessions, pulmonary impairment, and immunosuppression were associated with increased mortality. Overall, although prone positioning led to an improvement in oxygenation, this improvement was not associated with better survival.

The definition of "responders" in COVID-19 patients is heterogeneous across studies,[7-9] including the use of different thresholds for response in oxygenation (e.g., a PaO_2/F_{IO_2} increase ≥ 20 mmHg; a PaO_2/F_{IO_2} increase ≥ the median percent change in PaO_2/F_{IO_2}; a PaO_2/F_{IO_2} ≥ 150 mmHg after returning to the supine position) and the use of ventilatory ratio.

The impact of improvement in oxygenation during prone positioning on ultimate outcomes is controversial. A beneficial effect of early prone positioning on survival has been reported in patients with a Pa_{O_2}/F_{IO_2} ≤ 150 mmHg or a Pa_{O_2}/F_{IO_2} ≤ 100 mmHg.[7] Other authors[8,9] found higher mortality in nonresponders (Table 1). In the study by Cunha et al.,[6] prone positioning increased oxygenation and respiratory rate, but it was not associated with improvement in respiratory system mechanics (compliance, driving pressure, or plateau pressure).

In responders, prone positioning promotes alveolar recruitment with higher regional perfusion of dorsal areas. In nonresponders, prone positioning does not redistribute lung densities, and perfusion is mainly redistributed toward dependent lung regions. In COVID-19 phenotype 2, oxygenation may improve due to the redistribution of pulmonary blood flow from dorsal to ventral lung regions but not due to effective alveolar recruitment.[10]

Data suggest that early use of prone positioning, as well as the number of prone positioning sessions, may be associated with better outcomes.[11,12] In the study by Cunha et al.,[6] the time to prone positioning was not fixed nor was it defined *a priori*, which may account for the nonresponders whose first prone positioning session occurred late in the course of COVID-19, even though the number of sessions did not differ between nonresponders and responders. This can be explained by the fact that clinicians play a crucial role in decision making, individualizing the timing and number of sessions. In most previous studies, the decision to prone patients was at the discretion of the attending physician rather than being standardized across centers (Table 1).

Data on timing of intubation have not been reported. Yet, optimal timing of intubation has become a cornerstone in COVID-19 management and is known to be associated with outcomes. Patients with COVID-19 phenotype 1 can initially benefit from noninvasive respiratory support, since they respond better to the higher oxygen fraction and moderate PEEP levels delivered by noninvasive CPAP.[13]

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Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.*

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Dell'Anna et al.[14]	9	Case series, single center	NR	NR	NR	Prone positioning increased PaO_2/FIO_2 compared with supine positioning	Prone positioning decreased pulmonary shunt fraction compared with supine positioning	NR
Concha et al.[15]	17	Case series, single center	Day 1	46 ± 18 h	3 ± 1	NR	No clear differences were found between supine and prone positioning	17.65%
Lucchini et al.[16]	96	Retrospective single center	8 (4-45) h	18 (16-32) h (standard < 24 h; extended > 24 h)	1 cycle in 31%, 2 cycles in 22%, 3 in 17%, > 3 in 30%	Significant changes in PaO_2/FIO_2 were detected before and after proning	NR	18%
Rossi et al.[10]	25	Case series, single center	NR	NR	NR	PaO_2/FIO_2 did not change significantly between supine and prone positioning	Ventilatory ratio, V_E, V_T, Ppeak, Pplat, ΔP, C_{rs} changed between supine and prone positioning	32%
Binda et al.[17]	34	Prospective, single center	NR	72 (60-83) h	NR	NR	NR	NR
Stilma et al.[18]	438	Observational prospective, multicenter	0 (0-1)	16 (11-23) h in patients with an indication for prone positioning 14 (10-19) h in patients without an indication for prone positioning	NR	$PaO_2/FIO_2 \leq 150$ mmHg was found in 90 (38.8) of the patients in the no-indication+no-prone group and in 104 (47.9) of those in the no-indication+prone group, as well as in 56 (87.5) of those in the indication+no-prone group and in 189 (85.5) of those in the indication+prone group	Significant changes in Ppeak were found between patients in the no-indication+no-prone group vs. those in the no-indication+prone group Differences in ΔP, C_{rs}, and RR were found between those in the indication+no-prone group vs. those in the indication+prone group	28.6% in the no-indication+prone group vs. 31.3% in the no-indication+no-prone group 41.3% in the indication+no-prone group vs. 34.1% in the indication+prone group

Continue...▶

Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Oujidi et al.[19]	23 patients on ECMO	Retrospective, single center	NR	16 h	NR	PaO_2/FIO_2 improved significantly after prone positioning during ECMO	V_T, Pplat, and FIO_2 were significantly higher before than after prone positioning	NR
Longino et al.[20]	27 of 49	Retrospective, multicenter	NR	NR	NR	PaO_2/FIO_2 in the prone group was lower than that in the non-prone group.	C_{rs} in the prone group was lower over days 1-10 but higher over days 1-35	NR
Park et al.[21]	23 COVID-19 ARDS patients vs. 45 non-COVID-19 ARDS patients	Retrospective, single center	9 (4-12) days in the COVID-19 group	18 (17-19) h in the COVID-19 group vs. 18 (16-19) h in the non-COVID-19 group	4 (3-9) in the COVID-19 group vs. 2 (1-4) in the non-COVID-19 group	PaO_2/FIO_2 was 107 (92-132) mmHg in the COVID-19 group vs. 96 (74-120) mmHg in the non-COVID-19 group	ΔP, RR, and V_E were higher in the non-COVID-19 group; static C_{rs} was higher in the COVID-19 group	21.7% in the COVID-19 group vs. 73.8% in the non-COVID-19 group
Rezoagli et al.[22]	23, standard prone (16 h) vs. 15, prolonged prone (40 h)	Retrospective, single center	NR	Overall, 76 ± 45 h, standard vs. 118 ± 79 h, prolonged Each cycle, 17 ± 3 h, standard vs. 39 ± 6 h, prolonged	4 (2-5), standard vs. 2 (2-4), prolonged	Oxygenation improved during prone positioning and after resupination compared with baseline	No significant differences were found in mechanics	22%, standard vs. 33% prolonged
Cour et al.[23]	18 (9 low recruiters vs. 9 high recruiters)	Case series, single center	NR	NR	1 (0-2)	In high responders, PaO_2/FIO_2 improved between supine and re-supine positioning after prone positioning; this did not happen in low responders	An increase in C_{rs} and a reduction in ventilatory ratio with improved oxygenation were found in responders during prone positioning	NR
Scaramuzzo et al.[9]	191 (96 responders vs. 95 nonresponders)	Observational prospective, multicenter	NR	16.0 (16.0-16.7) h in responders vs. 16 (16-17) h in nonresponders	NR	PaO_2/FIO_2 improved after prone positioning: 100% (67-155 mmHg) in responders vs. 19% (3-31 mmHg) in nonresponders	Nonresponders had lower C_{rs} supine and higher Pplat	33.3% in responders vs. 53.7% in nonresponders

Continue...▶

Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Liu et al.[24]	29 (13, early prone vs. 16, control prone)	Observational retrospective, single center	Within 24 h in the early group vs. after day 3 in the control group	NR	NR	PaO_2/FIO_2 improved more in the early group, but improvement was seen in both groups after prone positioning	RR improved in the early group	0% in both groups
Langer et al.[8]	648 proned patients vs. 409 non-proned patients	Observational retrospective, multicenter	NR	18.6 (16-22) h in a subgroup of 78 patients	NR	PaO_2/FIO_2 improved after prone positioning and decreased after resupination in the subgroup of 78 patients (61 responders vs. 17 nonresponders)	Pplat was higher in the prone group. In the subgroup of 78 patients, C_{rs} and ventilatory ratio did not change with prone positioning, RR increased between supine and prone positioning ΔP and Pplat were higher in nonresponders; C_{rs} was higher in responders	In-hospital mortality: 45% in the prone group vs. 33% in the non-prone group ICU mortality: 41% in the prone group vs. 28% in the non-prone group Mortality was higher among nonresponders (65%) than among responders (38%)
Vollenberg et al.[25]	13	Observational retrospective, multicenter	NR	NR	1-6	In responders, PaO_2/FIO_2 improved by 38.4%	No significant reduction was found in C_{rs} in the prone position	53.85%
Mathews et al.[7]	702 proned patients vs. 1,636 non-proned patients	Observational prospective, multicenter	Within the first 2 days of ICU admission	NR	NR	PaO_2/FIO_2 improved significantly with prone positioning	NR	46.6% in the prone group vs. 47.3% in the non-prone group

Continue...▶

Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Sang et al.[26]	20	Observational retrospective, single center	NR	NR	NR	PaO_2 improved with prone positioning	Static C_{rs} improved with prone positioning	NR
Clarke et al.[27]	20	Observational prospective, single center	1.00 (1.00-1.75) days	16.2 (15.6-17.4) h	NR	PaO_2/FIO_2 improved significantly before and after prone positioning	No differences were found in C_{rs} before vs. after prone positioning	15%
Douglas et al.[28]	61 (42 survivors vs. 19 nonsurvivors)	Observational retrospective, single center	0.28 (0.11-0.80) days	4.44 (1.97-6.24) days in survivors vs. 3.99 (3.00-9.48) days in nonsurvivors	1 session in 31 survivors (50.8) and in 15 nonsurvivors (24.6); 2 sessions in 7 survivors (11.5) and in 4 nonsurvivors (6.6); 3 sessions in 3 survivors (4.9) and in 1 nonsurvivor (1.6)	PaO_2/FIO_2 was higher in survivors vs. nonsurvivors PaO_2/FIO_2 significantly worsened between prone positioning and resupination	NR	68.85%
Shelhamer et al.[29]	62 proned patients vs. 199 non-proned patients	NR	NR	NR	NR	PaO_2/FIO_2 improved after prone positioning	NR	77.4% in the prone group vs. 83.9% in the non-prone group
Gleissman et al.[30]	44	Observational retrospective, single center	NR	14 (12-17) h	NR	PaO_2/FIO_2 improved after prone positioning	No significant changes were reported	NR

Continue...▶

Table 1. Case reports and clinical studies of prone positioning in patients with COVID-19 ARDS.* (Continued...)

Study	Number of proned patients	Study design	Initiation of prone positioning	Duration of prone positioning	Number of prone positioning sessions	Oxygenation	Pulmonary mechanics	Mortality
Weiss et al.[31]	42 (26 responders vs. 16 nonresponders)	Observational retrospective, single center	NR	16 (16-17) h	3 (2-6)	PaO_2/FIO_2 improved after prone positioning and remained improved after resupination	No differences were found between responders and nonresponders Ventilatory ratio changed between supine and prone positioning	26%
Abou-Arab et al.[32]	25	Observational single center	NR	NR	NR	PaO_2/FIO_2 improved after prone positioning	C_{rs}, Pplat, and ventilatory ratio remained unchanged before and after prone positioning	16%
Berrill[33]	34	Observational retrospective, single center	23.0 ± 62.7 h	63.5 ± 38.2 h; each patient, 16.5 ± 2.7 h	4.0 ± 2.4	PaO_2/FIO_2 improved after prone positioning	No changes from baseline were reported	NR
Zang et al.[34]	23 proned patients vs. 37 non-proned patients	Observational prospective, single center	NR	NR	NR	SpO_2 and the ROX index increased between supine and prone positioning	Not evaluated	43.5% in the prone group vs. 75.7% in the non-proned group
Garcia et al.[35]	14 patients on ECMO (11 patients on ECMO alone)	Observational retrospective, single center	NR	NR	NR	PaO_2/FIO_2 improved after prone positioning	V_T, Pplat, C_{rs}, and ΔP remained unchanged between supine and prone positioning Changes were found in RR	78.6% in the prone+ECMO group vs. 27.3% in the ECMO-only group
Carsetti et al.[36]	6	Case series, single center	NR	16 h, standard; 36 h, prolonged	NR	PaO_2/FIO_2 improved after prone positioning and after resupination	C_{rs} did not change	NR

NR: not reported; Ppeak: peak pressure; Pplat: plateau pressure; ΔP: driving pressure; C_{rs}: respiratory system compliance; ECMO: extracorporeal membrane oxygenation; and ROX index: SpO_2/FIO_2 ratio divided by RR. *Values expressed as n, n (%), mean ± SD, or median (IQR).

On the other hand, worsening of oxygenation during noninvasive respiratory support or the presence of COVID-19 phenotype 2 requires prompt and early intubation and invasive mechanical ventilation.

Cunha et al.[6] listed some limitations of their study, including its retrospective design (not all data could be found in the electronic medical records, and they were unable to control for the prescription and timing of prone positioning), the absence of an *a priori* power analysis or preplanned protocol, the small sample size, the lack of control groups, and the lack of description of other rescue therapies (e.g., inhaled nitric oxide, recruitment maneuvers, and extracorporeal membrane oxygenation), which may affect patient outcomes.

Overall mortality in the study by Cunha et al.[6] was 69.3%, which suggests that those patients with severe COVID-19 are at high risk of death. This mortality rate is high compared with those reported in other studies involving COVID-19 patients who underwent prone positioning (Table 1). Prone positioning is just one part of a therapeutic concept including a sophisticated ventilation strategy, strict fluid balance control, and dedicated hemodynamic management, all of which may affect outcomes.[3]

In conclusion, the study by Cunha et al.[6] improves our knowledge about the use of prone positioning in COVID-19 patients with severe hypoxemic respiratory failure, suggesting that this maneuver should be used early regardless of oxygenation response. However, their findings cannot be generalized without confirmation in larger randomized controlled trials.

AUTHOR CONTRIBUTIONS

DB: review and approval of the final manuscript. PP and PRMR: senior authorship and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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Is donation after circulatory death necessary in Brazil? If so, when?

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Donation after circulatory death (DCD), previously known as donation after cardiac death or non-heart-beating donation, refers to the retrieval of organs for the purpose of transplantation from patients whose death is diagnosed and confirmed using cardiorespiratory criteria.[1]

In this issue of the *Jornal Brasileiro de Pneumologia*, Reck dos Santos et al.[2] present a review and update article on DCD and lung transplantation. DCD has become an accepted practice in many countries and remains a focus of intense interest in the transplant community. However, it is not a new activity and has some ethical, legal, cultural, and economic aspects that make it difficult to use in some countries.

Since the first human kidney transplant, performed in 1933 by Yurii Y Voronoy, in Kherson, Ukraine,[3] until the late 1960s, almost all of the organs transplanted using deceased donors came from non-heart-beating donors, with unfavorable results, mainly due to renal damage caused by warm ischemia but also due to other factors such as unrefined surgical technique, inadequate preservation, insufficient immunosuppression, and inexperience in postoperative management.

At that time, only Guy Alexandre, a Belgian surgeon, based on the studies by Mollaret & Goulon[4] in Paris and Wertheimer et al.[5] in Lyon published in 1959—suggesting that the irreversible failure of brain functions can be considered as death—had not only adopted a neurological criteria for determining death but also applied those criteria in performing the first organ transplant from a brain-dead donor in 1963, a procedure that many of his colleagues considered ethically unacceptable.[6]

Only after the first heart transplant in the world, performed on December 3, 1967, by Christiaan Barnard in Cape Town, using the heart of a young woman with severe traumatic brain injury after a traffic accident and declared dead by neurological criteria,[7] the report of the Ad Hoc Committee of the Harvard Medical University School[8] and the Declaration of Sydney of the 22nd World Medical Assembly[9] were published, both in 1968, for the determination of death based on neurological criteria. Since then, almost all transplant centers abandoned the use of non-heart-beating donors, using organs from brain-dead donors, since warm ischemia time close to zero provided better results.

In the early 1990s, it was observed that the number of potential brain-dead donors—0.5-1.0% of deaths or 45-65 per million population (pmp)—was insufficient to meet the growing demand of patients on waiting lists for organ transplantation. In addition, for the last twenty years, there has been a decrease in the incidence of patients with brain death in many developed countries. In Spain, for example, comparing the incidence rates of brain death through audits in ICUs between 2001 and 2010 (65 pmp and 48 pmp, respectively), there was a decrease of 26%, as well as a progressive increase in the mean age, evidencing a quantitative and qualitative exhaustion of potential donors.[10] The decrease in the incidence of death diagnosed by neurological criteria and, therefore, the potential for donation after brain death (DBD), is primarily a consequence of improved road safety and improvements in neurocritical care management and in the outcomes of acute traumatic brain injury and intracranial hemorrhage.[10,11] In some countries, such as the United Kingdom, this rate has always been low (30-35 pmp), because patients with devastating brain injury are not referred to the ICU but to palliative care.

Because of the insufficient number of brain-dead donors to meet the growing demand for transplantation, studies with circulatory death donors were summarized during the First International Congress on Non-Heart-Beating Donors, held in Maastricht in 1995, and a classification system was established: I: irreversible cardiac arrest occurs before arrival at hospital; II: irreversible cardiac arrest occurs in hospital; III: programmed cardiorespiratory arrest in the ICU; and IV: cardiorespiratory arrest before, during or after brain death is confirmed.[12]

DCD is also classified as controlled or uncontrolled. Uncontrolled DCD refers to organ retrieval after cardiac arrest that is unexpected and from which the patient cannot or should not be resuscitated (Maastricht categories I, II, and IV). Controlled DCD refers to organ retrieval after an anticipated cardiac arrest that follows the planned withdrawal of life-sustaining treatments that have been considered to be of no overall benefit to a critically ill patient (Maastricht category III).[13]

As a result of better hemodynamic maintenance, in-situ cooling, rapid en bloc organ removal, pulsatile perfusion, better preservation solutions, and, more recently, the use of regional cardiopulmonary bypass, the results were similar to those obtained with DBD donors, both for the kidney and other organs, leading to a progressive increase in the number of DCD, up to the point that, in 2020, of the 35,368 donations from dead individuals reported in the global observatory on donation and transplantation, 8,061 were DCD (22.8%).[14] The contribution of DCD to overall deceased donor numbers varies internationally. Differences in medical practices, public attitudes, legislation, and resources will all influence the practice of DCD among countries.

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Figure 1 shows the rates of DCD, in accordance with the International Registry on Organ Donation and Transplantation,[15] which reported that 22 countries used DCD in 2020, the rates ranging from 0.07 pmp (in Japan) to 13.1 pmp (in Spain). In some countries (the UK, the Netherlands, and the USA), emphasis was placed on controlled DCD, while in others (Spain and France),[16] the predominant type was uncontrolled DCD.

Common sense might suggest that declaring death when the heart stops beating would be more straightforward than when the declaration of death is based on brainstem functions. However, the difficulty of introducing DCD is related to ethical and legal issues and to the technical and organizational complexity inherent to this type of donation, which makes it more complex than it might appear at first glance.

Despite the endorsement of the practice of DCD by professional and regulatory bodies in many parts of the world, concerns about ethics and lawfulness of both controlled and uncontrolled DCD persist. Such concerns are related to the lawfulness and acceptability of interventions before or after death that are necessary to facilitate DCD; timing, location, and manner of treatment withdrawal; and uncertainties regarding the time point when death can be confirmed using circulatory criteria. Organ retrieval teams have mobilized for a potential DCD "stand down" on 40% of occasions, because some potential donors do not die within the first two hours after the withdrawal of life support, causing the family distress during the wait, which is also a burden on the already hard-pressed ICU staff.[17]

DCD is becoming increasingly accepted and has been performed in some countries, importantly contributing to the number of organs available and providing acceptable post-transplantation outcomes.[18] However, DCD should be considered as an addition to and not as a substitute for DBD, which, in addition to having simpler logistics and lower costs, has a greater use of transplanted organs per donor. Another important aspect is that, despite the large investment in DCD, its rate is around 5-6 pmp in most countries that use this form of donation, and only 4 countries have exceeded 8 pmp (Figure 1).

The most important justification for the use of DCD is the insufficient and decreasing number of DBD to meet the demand. In each country, according to its particularities, the type of DCD is defined (controlled, uncontrolled, or both), as well as which organs will be used from these donors and how legal, ethical, logistical, cultural, and financial barriers will be addressed.

In Brazil, DCD is not used for organ transplantation, with the exception of a small number of kidney transplants, using a part of the Maastricht classification system (type IV),[12] that is, in those cases in which irreversible cardiac arrest occurs after brain death has been determined and family authorization has been given before the removal of the organs, while waiting for the results of laboratory tests or the arrival of the teams to remove the organs.

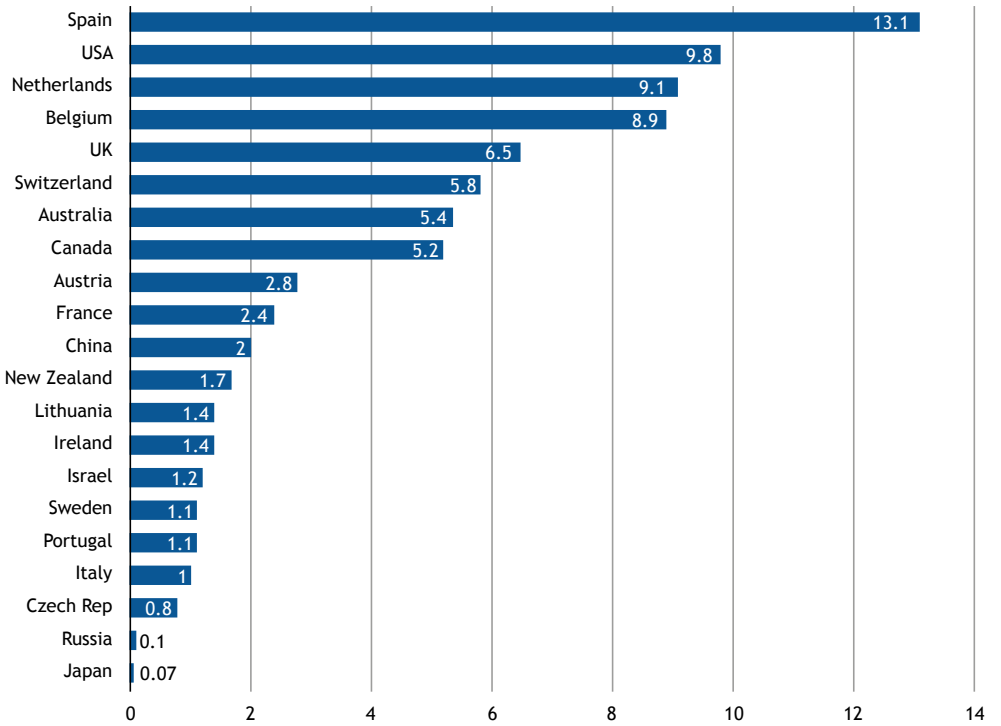

Figure 1. Rates of donation after circulatory death in various countries worldwide, as measured by donors per million population (pmp) in 2020. UK: United Kingdom.

In contrast to what is observed in developed countries, brain death rates are high and are not decreasing in Brazil. In the 1990s, it was estimated that there would be approximately 60 brain deaths pmp per year, and only a third of them (about 20 pmp) were reported as potential donors. This rate of notification of potential donors, which was 24.8 pmp in 2000, rose to 54.7 pmp in 2019, the year before the pandemic, which negatively impacted donation and transplant rates. In some Brazilian states (Paraná, Santa Catarina, and Mato Grosso do Sul), as well as in the Federal District, the annual notification rate of brain-dead cases is between 80 and 100 pmp.[19] Therefore, we currently estimate the brain death rate to be between 90 and 100 pmp in the country, which is the double that is observed in developed countries. Therefore, we can increase the notification rate of potential brain-dead donors by 50% in Brazil. In addition, the rate of effectiveness was 33% in 2019, and our goal is to reach up to 45%, which has already been the case in some states (Santa Catarina, Paraná, and Ceará).[19] On the basis of these data, we can estimate that we will reach a rate of DBD of 40 pmp (90 brain-dead individuals pmp and a 45% effectiveness rate) in 7 years.

It is necessary to improve the use of organs from brain-dead donors. Estimated rates of annual transplant demand and optimal utilization (in %) of the following organs are, respectively: kidney (70 pmp; 85%); liver (30 pmp; 80%); heart (8 pmp; 40%); and lung (8 pmp; 20%).[20] In 2019, the effective overall donor rate was 18.1 pmp—and the range of utilization was 30.1-71.0% (kidney); 10.8-55.0% (liver); 1.8-10.0% (heart); and 0.5-3.0% (lung).[20] It is believed that, in 2028, 40 donors pmp will be enough to meet the estimated need for all organs, except for the lung, if the needs remain at these levels. Therefore, although the use of DCD is an important and necessary strategy in many countries, other less complex and cheaper measures, such as DBD, will suffice in Brazil in the coming years.

AUTHOR CONTRIBUTIONS

VDG: article design, drafting, review, and approval of the final manuscript. PMPF and JM: review and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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Diagnosis of cystic fibrosis-related diabetes: too early or too late?

Aleksandar Sovtic[1,2]

Cystic fibrosis-related diabetes (CFRD) is the most common comorbidity associated with cystic fibrosis (CF). In its typical form, CFRD develops insidiously as the terminal event of glucose metabolism abnormalities, which begins with early insulinopenia causing glucose intolerance and finally results in clinical symptoms such as malnutrition, steep decline in lung function, changes in lung microbiota, and decreased quality of life and life expectancy.[1] The presence of glucose in bronchial secretion raises the risk for bacterial respiratory infections with methicillin-resistant *Staphylococcus aureus* and *Pseudomonas aeruginosa*, as well as more frequent pulmonary exacerbations. Metabolic stabilization after insulin treatment initiation leads to weight gain and improvement of lung function.

The etiology of CFRD is complex and primarily related to insulin deficiency, but some other processes contribute to it, mostly chronic inflammation and peripheral insulin resistance.[2] The prevalence of CFRD, according to the latest annual reports from Brazilian and European CF Society Registries,[3,4] is 4.3% in Brazil and 22.2% in Europe, and it has been increasing as the age of CF patients increases. This prevalence varies due to different time points when screening is performed and diverse diagnostic criteria in use.

The common methods for diagnosing diabetes mellitus, such as the determination of random or fasting plasma glucose (FPG) or glycated hemoglobin (HbA_1C) levels, are not sufficiently sensitive. FPG levels are normal in half of the patients with CFRD, and HbA_1C levels have demonstrated low predictive values.[2] Nevertheless, FPG levels ≥ 126 mg/dL (≥ 7.0 mmol/L) or random plasma glucose levels ≥ 200 mg/dL (≥ 11.1 mmol/L), as well as HbA_1C ≥ 6.5% are diagnostic criteria for CFRD.[5] The widely used 2-h 75-g oral glucose tolerance test (OGTT) has been recognized by the American Diabetes Association as a standard of care procedure and is recommended to be performed annually in CF patients ≥ 10 years of age.[2,5] The results allow to distinguish among normal glucose tolerance (< 7.8 mmol/L), impaired glucose tolerance (7.8-11.1 mmol/L), and CFRD (> 11.1 mmol/L).[6] In the last decade, it has become evident that OGTT underestimates early glucose tolerance abnormalities and practically shows a weak capacity to diagnose CFRD when compared with other diagnostic methods available.[7] In addition, the test itself is inconvenient for patients, leading to low annual screening adherence. Interestingly, the current data available have failed to confirm the beneficial effects of cystic fibrosis transmembrane conductance regulator (CFTR) modulator therapy (lumacaftor/ivacaftor) on glucose metabolism and insulin secretion over 1 year of follow-up.[8] Thus, it is of great importance to identify an alternative screening method that is practical, sensitive, and specific for diagnosing subtle glucose abnormalities that characterize the early stage of CFRD. It should independently correlate with improvements in lung function after insulin therapy initiation, regardless of eventual use of CFTR modulator therapy.

Continuous glucose monitoring (CGM) is a method that is primarily used in order to control the efficiency of insulin pump therapy in patients with diabetes mellitus type 1. It is validated for use in children, adolescents, and adults with CF as a valuable tool for early detection of glucose tolerance abnormalities. Placed subcutaneously, it measures glucose concentrations in the interstitial fluid every three to five minutes over time, mostly from three to seven days. CGM allows precise measurements of peaks and valleys of glucose concentrations, as well as the proportion of time that glucose levels are above pre-defined cutoff points.[9] Maximum CGM levels are directly correlated with the decline in lung function over time.[10,11]

In the current issue of the *Jornal Brasileiro de Pneumonogia*, Zorron et al.[12] reported the results of a longitudinal prospective study that evaluated the effectiveness of CGM to predict the onset of CFRD in 43 children and adolescents. At baseline, the CGM classification of the study participants was based on OGTT cutoff values, by analyzing the data collected from 36 h up to three days. After an average of 3 years of follow-up, OGTT was repeated, and 3 of the participants had developed CFRD over time. Interestingly, lower BMI z-scores at baseline and at follow-up were noted in the study participants who had glucose levels > 140 mg/dL on CGM. This major finding affirms the usefulness of CGM in the identification of glucose metabolism abnormalities not detected by OGTT. Finally, Zorron et al.[12] showed that none of the major variables obtained from CGM, such as peak/valley pattern, AUC, and percentage of time above cutoff values, were conclusive for CFRD diagnosis, showing no associations with the development of CFRD.

In conclusion, a better understanding of the etiology and the deleterious effects of insidious development of CFRD should lead to a more frequent use of reliable, practical, and simple tools, such as CGM, that are able to detect metabolic abnormalities that precede symptoms of CFRD. Beneficial effects of timely insulin replacement therapy initiation on the overall outcome should lead to prompt modifications of official recommendations of diagnostic criteria for CFRD.

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The air crescent sign

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

A 40-year-old man presented with a 3-month history of cough, fever, and weight loss, progressing to an episode of hemoptysis. A CT scan of the chest showed an intensely enhanced intracavitary nodule, with air interposed between the nodule and the cavity wall (the air crescent sign—ACS—Figure 1).

The ACS is a crescent– or half-moon–shaped collection of air in the periphery of an intracavitary nodule or mass, separating the nodule or mass from the cavity wall. The finding of a nodule in a lung cavity has important diagnostic and therapeutic implications. The most common cause of an ACS is a fungus ball, or aspergilloma, resulting from *Aspergillus* colonization of preexisting lung cavities. However, the ACS has been reported in association with a variety of lung diseases, including neoplasms (particularly bronchial carcinoma), recovery from angioinvasive aspergillosis, Rasmussen's aneurysm, and intracavitary clots. Other, rarer, causes include foreign bodies, thick pus, dehydrated caseous material, teratoma, and hydatid disease.[1,2]

A change in the position of the nodule in the cavity when patient position is changed, especially during CT examinations in the supine and prone positions, can be useful in the differential diagnosis. It is extremely important to determine whether the central mass is free or attached to the cavity wall because, unlike a fungus ball or a clot, cavitary lung cancer and Rasmussen's aneurysm present as masses that are fixed to the cavity wall; that is, they do not move when patient position is changed. Intense contrast enhancement of the nodule is seen in Rasmussen's aneurysm and can be useful in the differential diagnosis with aspergilloma, in which it is not.[1,2]

In the case reported here, the final diagnosis was Rasmussen's aneurysm in a patient with active tuberculosis. Rasmussen's aneurysms are pulmonary artery pseudoaneurysms secondary to pulmonary tuberculosis. In patients with Rasmussen's aneurysm, as well as in those with aspergilloma, hemoptysis is a common initial manifestation and can be fatal when massive. In conclusion, although aspergilloma is the most common cause of intracavitary nodules, other conditions should be considered in the differential diagnosis, including intracavitary tumors and Rasmussen's aneurysm. An accurate diagnosis is crucial and can have implications for disease management and prognosis.

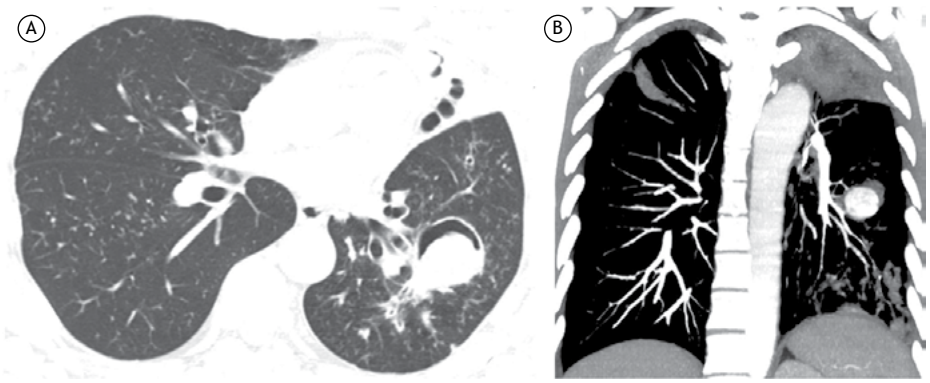

Figure 1. In A, axial CT scan of the chest with lung window settings, showing a nodule within a cavity, with air interposed between the nodule and the cavity wall (the air crescent sign), in the left lower lobe. Changes in patient position (not shown) resulted in no changes in the position of the nodule in the cavity. In B, coronal reconstruction showing intense contrast enhancement of the intracavitary nodule. Note the presence of small nodules in both lungs, as well as heterogeneous consolidation in the lingula, consistent with tuberculosis.

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How to write a curriculum vitae – advice for young researchers

Juliana Carvalho Ferreira[1,2]

PRACTICAL SCENARIO

A pulmonary fellow in Brazil is planning to apply for a position as a student in a prestigious doctoral program in another state. She consulted the program's website and learned that, in order to apply, in addition to other documentation, she needed a complete, updated version of her curriculum vitae (CV) at *Plataforma Lattes*. She realizes that her CV is one of the most important documents in the application process, since its content may be compared with that of other candidates to the doctoral position. Therefore, she seeks help to make sure that her CV at *Plataforma Lattes* is not only up to date, but that it helps her stand out as a good candidate for the graduate program as well.

WHAT IS PLATAFORMA LATTES

Plataforma Lattes is a nationwide electronic platform for academic CV adopted by most funding agencies, academic institutions, and research institutes in Brazil. It was launched in 1999 by the Brazilian *Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development) and is integrated with databases from other institutions, such as SciELO, Scopus, and CrossRef, as well as university databases, giving the platform user the possibility of accessing information from the researcher's CV, including his/her connections with academic institutions and prior funding.[1]

Given that the *Plataforma Lattes* system is almost universally adopted by academic institutions in Brazil and provides standardization of the process to include items in academic CV, anyone accessing the platform can consult a researcher's CV and use it to evaluate and compare researchers, students, and institutions.

WHY IS THE CV SO IMPORTANT IN ACADEMIC MEDICINE?

A CV is a professional portfolio of a researcher's academic career. In many situations, it is the first impression that a future academic supervisor, employer, or funding agency will have of the researcher. It tells the researcher's professional story, and even at first glance, it should present information in a way that highlights strengths and expertise that show that the candidate is the perfect match for the role he/she is applying for.

One of the most important parts of a CV is the personal statement—described as the "Summary" in the platform—containing from one to three paragraphs, in which the researcher summarizes his/her academic history, current job position, accomplishments, and interests. In some instances, the personal statement is longer and used to apply to specific grants.[2] *Plataforma Lattes* shows the personal statement as the first and, therefore, most visible item in the CV. The platform generates a standardized text automatically, extracting information from other standardized items, such as education/training and current job positions. However, researchers can (and should) edit this section periodically, making sure that the text is well written and tells their professional story in a way that conveys what makes them fit for the position they are applying for.

Table 1. Elements to include in a curriculum vitae: the model at *Plataforma Lattes*.

Item	What to include
Brief personal details	Name, professional address
Personal statement[a]	One to three paragraphs summarizing career story, current job position, accomplishments and interests
Education (most recent first)	Undergraduate degree, specialization, residency, and fellowship for clinicians
Job positions (most recent first)	It may be a fellow position for young researchers
Research projects and funding	Current and completed projects, including funding details
Awards and prizes (most recent first)	It may include undergraduate prizes
Publications	Peer-reviewed manuscripts, book chapters, and conference abstracts
Teaching experience	It may include informal teaching such as teaching interns
Conference attendance	National and international conferences

[a]For some specific awards and grants, the personal statement may be longer and more focused on the position being sought.[2]

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WHAT ARE THE ELEMENTS TO BE INCLUDED IN THE CV?

Even young researchers, with little or no prior research experience, can and should have an impressive CV that is compatible with the position they are applying for. An experienced researcher, applying for a large grant, will highlight publications, teaching appointments, and prior successes with academic funding. Young researchers such as the fellow in the practical scenario should highlight their education, including the institutions where they were trained; their motivation to learn, such as attendance to academic and medical conferences; community service, such as volunteering in academic projects; and technical skills, such as the ability to communicate in foreign languages. Table 1 shows the basic structure of an academic CV at *Plataforma Lattes*. There are other models, of course, but the general structure is more or less the same.

TIPS TO WRITE A GREAT CV

1. Make sure that the most important information comes first (usually in the personal statement) and is well written, brief, and easy to read.
2. Make sure that you include all the important items in the order required by the institution.
3. If you are not using a standardized platform such as *Plataforma Lattes*, format your CV in a way that it is consistent in its use of fonts, line breaks, bullet points, and other details.
4. Proofread your CV to correct spelling mistakes and grammatical errors.
5. Be honest and consistent. Lying on your CV gets you a bad reputation.

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Lung function: what constitutes (ab) normality?

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

BACKGROUND

Defining whether pulmonary function test (PFT) results are outside the expected range has obvious diagnostic implications. Many physicians assume that any value outside ± 20% of the predicted value or FEV_1/FVC < 0.7 indicates abnormality. Current guidelines strongly support the statistical "limits of normal" to classify test results as low—less than the lower limit of normal (LLN)—or high—greater than the upper limit of normal (ULN).[1] Does it really matter? If so, can we safely use across-the-board LLN/ULN criteria in clinical populations?

OVERVIEW

Table 1A shows that the fifth percentile for FEV_1 and FVC are systematically higher than 80% of the predicted value in younger men and women (LLN > 0.7 for FEV_1/FVC), and the opposite is seen in the elderly. In contrast, the LLN for "static" lung volumes and DL_{CO} are typically lower than 80%, regardless of age and sex. Table 1B shows spirometric results of a young non-smoking overweight woman who had reported recurrent episodes of dyspnea: 0.7 < FEV_1/FVC < LLN suggested an obstructive ventilatory defect. Table 1C shows spirometric results of an elderly former smoker woman reporting chronic dyspnea and productive cough. Her symptoms, her chest CT scans showing emphysema and bronchial wall thickening, and an FEV_1/FVC ratio < 0.7, despite the latter being above the LLN, were deemed consistent with obstruction. Both patients reported marked improvement with the use of inhaled formoterol/budesonide.

Our uncertainty on what constitutes normal FEV_1, FVC, and FEV_1/FVC increases with aging, that is, the LLN is far from the predicted values in the elderly (Table 1A). Thus, values < 80% of predicted might be well within the expected range in the elderly yet abnormal in the young. Sticking rigidly to the 80% or 120% threshold is even more problematic for lung volumes, markedly increasing the rate of false positives (Table 1A). This does not imply that the statistical limits of normal are immune to errors. The best example is the LLN threshold for FEV_1/FVC: up to a third of elderly subjects at risk for COPD with LLN < FEV_1/FVC < 0.7 showed a range of resting and exercise abnormalities consistent with COPD.[2] In fact, minimal variations in the cutoff value to define the threshold of normality for FEV_1/FVC have

Table 1. Panel 1A shows a comparison of the fifth percentile (5th p) of the lower limit of normal (LLN), expressed as absolute and percent of predicted (pred) values for several lung function parameters in four White subjects with different sexes and ages. Observe the potential bias (red columns) introduced if a fixed percent of pred threshold (e.g., 80% of pred) is used. Notwithstanding, while the 5th-p criterion can appropriately identify the state of disease in a young woman despite an FEV_1/FVC > 0.7 (Panel 1B), it failed to diagnose obstruction in a symptomatic elderly woman presenting with a value lower than the fixed threshold of 0.7 (Panel 1C). See the text for further elaboration. yo: years old; and FRC: functional residual capacity.

A	Young Male 20 yo/175 cm			Young Female 20 yo/165 cm			Elderly Male 70 yo/175 cm			Elderly Female 70 yo/165 cm		
	5th p	Pred	% Pred	5th p	Pred	% Pred	5th p	Pred	% Pred	5th p	Pred	% Pred
FVC	4.27	5.27	81.0	3.14	3.92	80.1	3.03	4.09	74.0	2.15	2.54	73.1
FEV_1	3.64	4.49	81.0	2.76	3.44	80.2	2.24	3.10	72.2	1.66	2.28	72.8
FEV_1/FVC	0.74	0.85	87.0	0.76	0.88	86.3	0.62	0.76	81.2	0.64	0.78	82.0
TLC	5.13	6.47	79.3	4.05	5.03	80.5	5.45	6.89	79.1	4.08	5.15	79.2
FRC	2.14	3.12	68.6	1.79	2.54	70.4	2.56	3.68	69.6	2.05	2.89	70.9
RV	0.57	1.37	41.6	0.48	1.09	44.0	1.45	2.43	59.6	1.21	2.01	60.2
DL_{CO}	25.1	31.7	79.1	17.7	22.4	79.0	18.4	25.1	73.3	14.6	19.4	75.2

B ♀, 17 yo 149 cm	Measured	% Pred	LLN	Z-Score
FVC, L	2.13	69.8	2.45	-2.545
FEV_1, L	1.63	59.4	2.21	-3.364
$FEV_1//FVC$	0.76	84.7	0.79	-1.916

C ♀, 85 yo 167 cm	Measured	% Pred	LLN	Z-Score
FVC, L	1.66	64.8	1.76	-1.849
FEV_1, L	1.11	57.8	1.31	-2.184
$FEV_1//FVC$	0.67	87.6	0.61	-1.046

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a marked impact on the proportion of all cases in the entire population that can be attributed to the exposure (smoking). This is particularly true in the elderly since, as mentioned, variability is larger; thus, a sizeable fraction of patients with COPD will show "preserved" FEV_1/FVC, that is, greater than the fifth percentile (Table 1C).[3] In many circumstances, values within the "grey zone" (e.g., between 80% of predicted and LLN; 120% of predicted and ULN; or LLN < FEV_1/FVC < 0.7) should be individually interpreted in the light of the pre-test likelihood of abnormality.[4]

CLINICAL MESSAGE

Using fixed thresholds (such as 80% or 120% of the predicted value) to classify PFT results as abnormal can lead to substantial mistakes, usually resulting in "under-calling" of disease in the young and "over-calling" of disease in the elderly. The statistical LLN, however, is far from being a panacea: interpretation of PFTs will always be an N = 1 study, requiring careful clinical correlation to judge the normalcy of values close to the proposed threshold.[5]

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Can continuous glucose monitoring predict cystic fibrosis-related diabetes and worse clinical outcome?

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ABSTRACT

Objective: To determine whether abnormal continuous glucose monitoring (CGM) readings (hypoglycemia/hyperglycemia) can predict the onset of cystic fibrosis-related diabetes (CFRD) and/or clinical impairment (decline in BMI and/or FEV_1) in pediatric patients with cystic fibrosis (CF). **Methods:** This was a longitudinal prospective cohort study involving CF patients without diabetes at baseline. The mean follow-up period was 3.1 years. The patients underwent 3-day CGM, performed oral glucose tolerance test (OGTT), and had FEV_1 and BMI determined at baseline. OGTT, FEV_1, and BMI were reassessed at the end of the follow-up period. **Results:** Thirty-nine CF patients (10-19 years of age) had valid CGM readings at baseline, and 34 completed the follow-up period (mean = 3.1 ± 0.5 years). None of the study variables predicted progression to CFRD or were associated with hypoglycemic events. CGM could detect glucose abnormalities not revealed by OGTT. Patients with glucose levels ≥ 140 mg/dL, as compared with those with lower levels, on CGM showed lower BMI values and z-scores at baseline—17.30 ± 3.91 kg/m^2 vs. 19.42 ± 2.07 kg/m^2; p = 0.043; and −1.55 ± 1.68 vs. −0.17 ± 0.88; p = 0.02, respectively—and at the end of follow-up—17.88 ± 3.63 kg/m^2 vs. 19.95 ± 2.56 kg/m^2; p = 0.039; and −1.65 ± 1.55 vs. −0.42 ± 1.08; p = 0.039. When comparing patients with and without CFRD, the former were found to have worse FEV_1 (in % of predicted)—22.67 ± 5.03 vs. 59.58 ± 28.92; p = 0.041—and a greater decline in FEV_1 (−36.00 ± 23.52 vs. −8.13 ± 17.18; p = 0.041) at the end of follow-up. **Conclusions:** CGM was able to identify glucose abnormalities not detected by OGTT that were related to early-stage decreases in BMI. CGM was ineffective in predicting the onset of diabetes in this CF population. Different diagnostic criteria for diabetes may be required for individuals with CF.

Keywords: Cystic fibrosis; Glucose intolerance; Glucose tolerance test; Diabetes mellitus.

INTRODUCTION

Cystic fibrosis-related diabetes (CFRD) is the commonest comorbidity in cystic fibrosis (CF). The pathophysiology of CFRD is theorized to involve insulin insufficiency, but unlike diabetes mellitus type 1, β-cell damage in CF is not caused by autoimmunity, and it is associated with some degree of insulin resistance due to inflammation and medications.[1]

CFRD is correlated with a progressive decline in pulmonary function and nutritional status, and, therefore, lower survival.[2,3] In accordance with recommendations from a consensus guideline publication,[4] the gold standard for CFRD screening is the oral glucose tolerance test (OGTT). The OGTT is a burdensome examination, as samples are collected over a long period, fasting is required before the test, and low gastrointestinal tolerability poses challenges to adherence.[5] OGTTs can induce hypoglycemic episodes following the glucose load.[6-8] Continuous glucose monitoring (CGM) could be a sensitive method to detect spontaneous hypoglycemia/hyperglycemia in CF patients, and this exam has been validated for use in children and adolescents with CF.[9,10]

Hypoglycemia in CF could be associated with a delayed first phase of insulin secretion paired with a diminished glucagon response, liver disease, undernourishment, gastrointestinal disorders, and other incretin dysfunctions. CFRD and hypoglycemia in CF share a similar pathophysiological basis.[11] For CGM, the cutoff values for hypoglycemia are classified into two levels applicable to type 1 and type 2 diabetes (in mg/dL): < 70 (level 1) and < 54 (level 2).[12]

Although the risk of microvascular complications exists, the main goal of CFRD management is to control lung bacterial growth, avoid a decline in pulmonary function and nutritional status, and ensure glycemic control.[13]

The present study aimed to determine whether abnormal CGM readings (hypoglycemia/hyperglycemia), when compared with the gold standard OGTT, could

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predict the onset of CFRD and/or clinical impairment (decline in BMI or FEV_1 in percentage of predicted values) in pediatric CF patients.

METHODS

Patients and study design

A prospective, single-center study was conducted between August of 2014 and January of 2019. All of the patients—from 10.0 to 19.9 years of age and with two pathogenic variants in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene and/or with two sweat chloride test results ≥ 60 mEq/L)— treated at an outpatient clinic of a CF referral center were invited to participate (N = 63).

The sweat test was conducted with a quantitative ionic analysis of sweat (iontophoresis) after pilocarpine stimulation of the skin.[14] Genetic testing was performed using genetic sequencing; the genotype was classified as homozygous or heterozygous for the p.Phe508del variant and by its severity based on *CFTR* mutation classes.

Data collection, data analysis, and outcome measures

The CF patients were followed up during their routine clinical quarterly visits. Two-time points were evaluated in this study: T0 (baseline), the time when participants underwent CGM and OGTT, and T1 (end of the follow-up period), the time of the routine visit closest to the first newly diagnosed cases of CFRD by OGTT in the cohort. For those who did not develop CFRD, T1 was determined as the last visit before study termination.

No participants were experiencing pulmonary exacerbations, were receiving systemic corticosteroid therapy, or were pregnant at the time of data collection. Individuals with improper CGM calibration, CGM readings performed in < 36 h, who did not complete OGTT, or who were diagnosed with diabetes based on the American Diabetes Association criteria[15] were excluded. No patient received enteral nutrition or therapy with CFTR modulators, or underwent lung transplantation during the follow-up period.

All study participants wore the CGMS Gold® (Medtronic MiniMed, Fridley, MN, USA) for a minimum of 36 h and up to 3 days at the start of the follow-up period. The number of peaks (≥ 140 mg/dL and ≥ 200 mg/dL) and valleys (< 54 mg/dL) was adjusted for CGM duration. CGM data were provided by MiniMed Solutions Software, version 1.7a (Medtronic Minimed). The numbers of peaks ≥ 140 mg/dL and ≥ 200 mg/dL (total and per day); number of valleys < 54 mg/dL (total and per day); proportion of time during which interstitial glucose values remained at < 54 mg/dL, ≥ 140 mg/dL, and ≥ 200 mg/dL; AUC for interstitial glucose values < 54 mg/dL, ≥ 140 mg/dL, and ≥ 200 mg/dL; and association of peaks (mg/dL) ≥ 200 mg/dL with valleys < 54 mg/dL were evaluated.

The patients were continuously instructed about the clinical signs of hypoglycemia (weakness, tremors, hunger, irritability, and others) during the appointments. For the study, they were instructed once again when the CGM device was placed. After removing the device, they answered a questionnaire about complications during CGM device use, in which they were actively asked about hypoglycemia (values < 70 mg/dL detected through capillary blood glucose measurements and/or clinical signs of hypoglycemia).

CGM classification was based on OGTT cutoff values for normal glucose tolerance (NGT; interstitial glucose < 140 mg/dL), impaired glucose tolerance (IGT; interstitial glucose between 140 and 199 mg/dL), and CFRD (interstitial glucose ≥ 200 mg/dL at least twice). Moreover, two subgroup analyses were performed by analyzing glucose abnormalities (CFRD+IGT) vs. NGT for both CGM and OGTTs.

An OGTT was requested annually as per guideline recommendations[4]; however, we only tracked the study variables at the two study time points (T0 and T1), because adherence was inadequate during follow-up. Based on the results of OGTT, performed according to the WHO protocol[16] and using the enzymatic colorimetric method, we classified participants according to the American Diabetes Association criteria[15]—NGT: fasting blood glucose (BG) < 126 mg/dL or BG < 140 mg/dL at 120 min; IGT: fasting BG < 126 mg/dL or BG of 140-199 mg/dL at 120 min; and diabetes: fasting BG ≥ 126 mg/dL or BG ≥ 200 mg/dL at 120 min (at least twice).

Spirometry was conducted in compliance with the standards of the American Thoracic Society and the European Respiratory Society.[17] FEV_1 in percentage of the predicted values was evaluated at T0 and T1.[18]

Two pediatric endocrinologists evaluated the weight, height, BMI, and pubertal stage of the participants at T0 and T1. BMI was presented as absolute values and z-scores based on the 2006 WHO child growth standards.[19] Pubertal stage was evaluated using Marshall & Tanner staging criteria.[20,21]

Exocrine pancreatic function (exocrine pancreatic insufficiency [PI] < 200 µg/g) was evaluated based on fecal elastase-1 levels at T0 using the Pancreatic Elastase 1 Stool Test (ScheBo, Giessen, Germany).[22]

The study protocol was approved by the Research Ethics Committee of the *Faculdade de Ciências Médicas*, *Universidade Estadual de Campinas* (Protocol no. 3.328.215). All participants or their legal guardians provided written informed consent for study participation. Minors provided written assent as well.

Statistical analysis

All analyses were performed with the IBM SPSS Statistics software package, version 20.0 (IBM Corp., Armonk, NY, USA). Differences were considered statistically significant at two-tailed $p < 0.05$. Qualitative variables were expressed as absolute and relative frequencies, and quantitative variables

were expressed as medians and minimum-maximum values. Mann-Whitney and Kruskal-Wallis tests were used in order to compare two and three or more independent groups, respectively. A nonparametric multiple comparison test was used to identify intergroup differences.

Associations with qualitative variables were analyzed by the Fisher's exact test or the Fisher-Freeman-Halton test, as appropriate. For paired evaluations, we used the McNemar-Bowker test and the Wilcoxon test.

A univariate logistic regression analysis was performed to identify CFRD predictors. Predictors with a $p < 0.2$ in the univariate analysis were included in the multivariate analysis by generalized estimating equation models.

RESULTS

Of the 63 patients recruited, 13 declined to participate, 1 had several pulmonary exacerbations, 2 provided CGM readings for < 36 h, and 8 were diagnosed with CFRD. Therefore, 39 nondiabetic patients with CF underwent a 3-day blinded CGM and were followed for a mean period of 3.1 ± 0.5 years. Among those, 34 participants completed the study follow-up (Figure 1). At T0, we were unable to know who would become diabetic, we only had the classification as having IGT or NGT according to OGTT results. In addition, all patients in the cohort had comparable lung function and nutritional status at T0. Three patients were classified as having CFRD by OGTT at T1.

Demographic data are shown in Table 1. During the follow-up period, the patients with PI showed no changes in clinical parameters, fecal fat balance, and steatocrit. Patients who remained with interstitial glucose levels < 140 mg/dL (n = 8) on CGM did not develop CFRD during the follow-up period, and only 1 experienced a single episode of asymptomatic hypoglycemia. All patients classified as having CFRD based on CGM had asymptomatic hypoglycemic episodes. None of the patients who progressed to CFRD had peaks ≥ 200 mg/dL during CGM evaluation. The relationship between OGTTs (at T0 and T1) and CGM is presented in Figure 2.

The peak/valley pattern (total and per day), AUC, and proportion of time during which the values (in mg/dL) were ≥ 140, ≥ 200, and < 54 on CGM showed no associations with the OGTT classification either at T0 or T1. Individual CGM variables are described in Table S1.

Eleven patients (32%)—7 were males, 7 were homozygous for p.Phe508del *CFTR* variant, and 7 presented with PI—had glucose levels < 54 mg/dL during CGM. There were no associations of BMI, FEV_1, OGTT results, sex, p.Phe508del genotype, and PI with hypoglycemia on CGM (at T0). None of the patients who experienced hypoglycemia needed intervention for recovery. None of analyzed clinical or laboratory variables were associated with hypoglycemic episodes or could predict the onset of CFRD (data not shown).

A secondary analysis was conducted by grouping hypoglycemic and hyperglycemic (≥ 200 mg/dL) episodes to determine whether this conjunction could be related to CFRD outcome; no significant association was found ($p = 0.664$).

Patients who developed CFRD, in comparison with those who did not, had worse FEV_1 (in % of predicted values)—22.67 ± 5.03 vs. 59.58 ± 28.92; $p = 0.041$—at T1 (Table 2).

BMI z-scores and crude BMI values are shown according to OGTT (at T1) and CGM (at T0) results in Table 2. Lower BMI values were noted in those who developed CFRD than in those who did not at T0 (14.37 ± 1.22 kg/m^2 vs. 18.13 ± 3.65 kg/m^2; $p = 0.049$) and at T1 (14.81 ± 0.67 kg/m^2 vs. 18.71 ± 3.46 kg/m^2; $p = 0.022$). The subgroup analysis regarding OGTT results at T1 between glucose abnormalities (CFRD+IGT) and NGT showed a significant difference in BMI values only at the end of the follow-up period. However, considering CGM-based classification at T0 (but not OGTT-based classification), the subgroup analysis showed significantly lower crude BMI values and BMI z-scores that were maintained from T0 to T1. Curiously, regarding the OGTT classification (IGT vs. NGT) at T0, no significant differences were noted in FEV_1 or BMI (Table S2).

A logistic regression analysis was conducted to ascertain the effect of time, adjusted for independent variables, on CFRD development. Participants classified as having IGT (on OGTT) had a higher chance of developing CFRD (OR = 21.67; 95% CI: 7.03-67.36; $p < 0.01$), whereas that chance was lower among the participants having NGT (OR = 1.84; 95% CI: 1.06-3.19; $p = 0.031$). According to the univariate logistic analysis, male sex, p.Phe508del homozygous

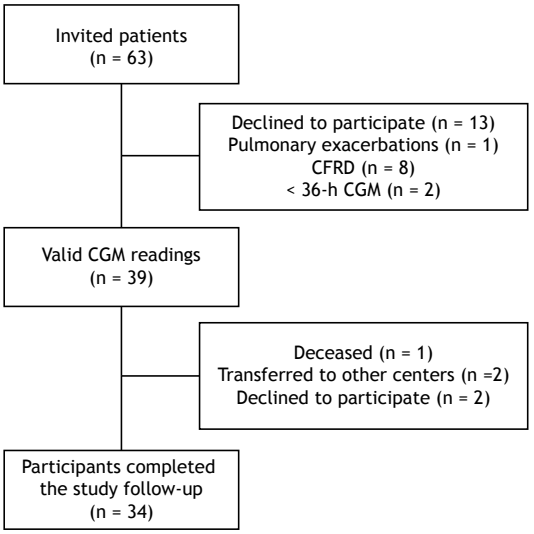

Figure 1. Flow chart of patient selection process. CFRD: cystic fibrosis-related diabetes; and CGM: continuous glucose monitoring.

Table 1. Clinical and demographic data of the patients with cystic fibrosis enrolled in the study.[a]

Variable	Time point		p*
	T0	T1	
Sex			
Male	16/34; 47.1		N/A
Female	18/34; 52.9		
Pubertal stage[20,21]			
Prepubertal	4/34; 11.8	None	N/A
Pubertal	30/34; 88.2	34/34; 100	
OGTT			
NGT	24/34; 70.6	20/34; 58.8	N/A
IGT	10/34; 29.4	11/34; 32.4	
CFRD	None	3/34; 8.8	
Pancreatic insufficiency	23/34; 70.6		N/A
BMI, kg/m^2	17.35 (12.39-30.18)	17.58 (14.04-31.04)	0.025
FEV_1, % of predicted	71 (18-113)	55 (16-112)	0.001
Age, years	16.10 (10.8-19.5)	18.80 (13.6-23.3)	N/A
CFTR pathogenic variants			
p.Phe508del/p.Phe508del	15/34; 44.12		N/A
p.Phe508del/p.Gly542Ter	5/34; 14.71		
p.Phe508del/Unknown	2/34; 5.88		
p.Phe508del/p.Gln890Ter	1/34; 2.94		
p.Phe508del/p.Arg553Ter	1/34; 2.94		
p.Phe508del/621+1G>T	1/34; 2.94		
p.Phe508del/1716+18672 A>G	1/34; 2.94		
p.Phe508del/p.Lys684SerfsX38	1/34; 2.94		
p.Phe508del/1717-1G>A	1/34; 2.94		
p.Phe508del/p.Arg1066Cys	1/34; 2.94		
p.Phe508del/p.Asn1303Lys	1/34; 2.94		
p.Gly542Ter/p.Arg1162Ter	1/34; 2.94		
p.Gly542Ter/Unknown	1/34; 2.94		

OGTT: oral glucose tolerance test; NGT: normal glucose tolerance; IGT: impaired glucose tolerance; CFRD: cystic fibrosis-related diabetes; *CFTR*: cystic fibrosis transmembrane regulator; T0: baseline; and T1: end of the follow-up period.[a]Values expressed as n/N; % or median (minimum-maximum values). *Wilcoxon test (α = 0.05).

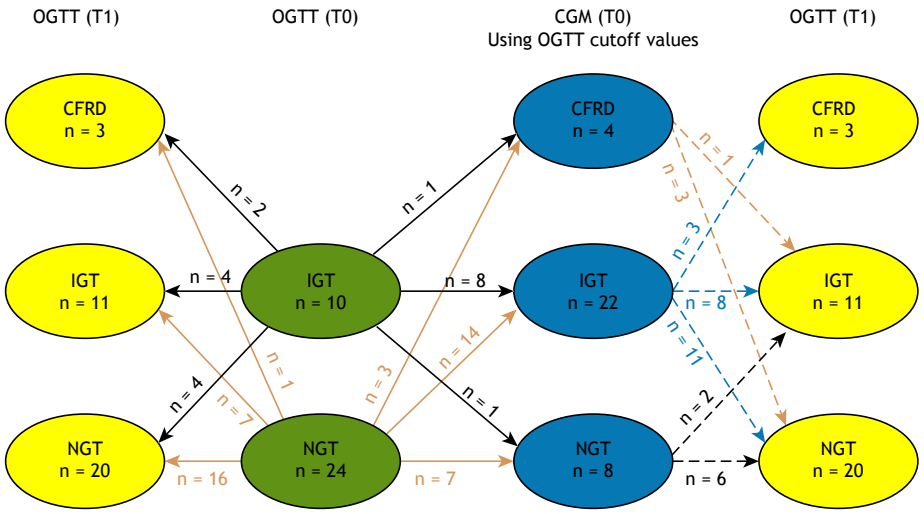

Figure 2. Relationship of oral glucose tolerance test (OGTT) at baseline (T0) and at the end of the follow-up period (T1) with continuous glucose monitoring (CGM) at T0 using OGTT cutoff values in accordance with the American Diabetes Association[15] criteria—normal glucose tolerance (NGT): interstitial glucose < 140 mg/dL; impaired glucose tolerance (IGT): interstitial glucose between 140 and 199 mg/dL; cystic fibrosis-related diabetes (CFRD): interstitial glucose ≥ 200 mg/dL at least twice.

Table 2. Correlation of FEV_1 (in % of the predicted values) and BMI (in kg/m² and z-score) with oral glucose tolerance test at the end of the follow-up period (T1) and continuous glucose monitoring at baseline (T0) results.[a]

Oral glucose tolerance test (at T1)										
Variable	CFRD (n = 3)	IGT (n = 11)	NGT (n = 20)	p*	CFRD (n = 3)	IGT + NGT (n = 31)	p*	CFRD + IGT (n = 14)	NGT (n = 20)	p*
FEV_1 (T0)	70 (31-75)	63 (20-113)	76.5 (18-108)	0.399	70 (31-75)	72 (18-113)	0.524	65.50 (20-113)	76.5 (18-108)	0.180
FEV_1 (T1)	22 (18-28)	55 (17-104)	59.5 (16-112)	0.116	22 (18-28)	56 (16-112)	0.041	45.50 (17-104)	59.5 (16-112)	0.274
FEV_1 (T1 – T0)	−47 (−52 to −9)	−3 (−21 to 24)	−2.5 (−63 to 19)	0.146	−47 (−52 to −9)	−3 (−63 to 24)	0.041	−9 (−52 to 24)	−2.5 (−63 to 19)	0.522
BMI z-test (T0)	−3.08 (−3.46 to −2.12)	−2.01 (−5.03 to 0.69)	−0.53 (−3.30 to 2.21)	0.027⁺	−3.08 (−3.46 to −2.12)	−0.75 (−5.03 to 2.21)	0.041	−2.09 (−5.03 to 0.69)	−0.53 (−3.30 to −2.21)	0.017
BMI z-test (T1)	−3.42 (−3.87 to −3.03)	−2.03 (−3.76 to 0.15)	−0.67 (−3.09 to 2.24)	0.030⁺	−3.42 (−3.87 to −3.03)	−1.25 (−3.76 to 2.24)	0.014	−2.88 (−3.87 to 0.15)	−0.67 (−3.09 to 2.24)	0.010
BMI z-test (T1 – T0)	−0.41 (−0.91 to −0.34)	−0.03 (−2.22 to 1.58)	−0.01 (−1.37 to 1.59)	0.324	−0.41 (−0.91 to −0.34)	−0.03 (−2.22 to 1.59)	0.172	−0.15 (−2.22 to 1.58)	0.01 (−1.37 to 1.59)	0.341
BMI (T0)	14.53 (13.07-15.51)	17.31 (12.81-23.81)	18.96 (12.39-30.17)	0.072	14.53 (13.07-15.51)	17.72 (12.39-30.17)	0.049	16.20 (12.81-23.81)	18.96 (12.39-30.17)	0.083
BMI (T1)	15.13 (14.05-15.26)	17.49 (14.34-21.89)	19.39 (14.05-31.04)	0.013⁺⁺	15.13 (14.05-15.26)	18.08 (14.05-31.04)	0.022	15.77 (14.05-21.89)	19.39 (14.05-31.04)	0.015
BMI (T1 – T0)	0.73 (−0.38 to 0.97)	0.21 (−3.53 to 2.16)	1.03 (−2.24 to 4.29)	0.307	0.73 (−0.38 to 0.97)	0.57 (−3.53 to 4.29)	0.909	0.25 (−3.53 to 2.16)	1.03 (−2.24 to 4.29)	0.478
Continuous glucose monitoring at T0 (using OGTT cutoff values)										
Variable	CFRD (n = 4)	IGT (n = 22)	NGT (n = 8)	p	CFRD (n = 4)	IGT + NGT (n = 30)	p	CFRD + IGT (n = 26)	NGT (n = 8)	p
FEV_1 (T0)	69 (43-80)	68 (20-113)	79.50 (18-108)	0.441	69 (43-80)	71 (18-113)	0.817	68 (20-113)	79.50 (18-108)	0.205
FEV_1 (T1)	47 (33-67)	54 (16-112)	70 (16-105)	0.650	47 (33-67)	55 (16-112)	0.738	54 (16-112)	70 (16-105)	0.368
FEV_1 (T1 - T0)	−24.50 (−42 to 24)	−7 (−52 to 17)	−2.5 (−63 to 19)	0.969	−24.50 (−42 to 24)	−3 (−63 to 19)	0.310	−9 (−52 to 24)	−2.5 (−63 to 19)	0.858
BMI z-test (T0)	−1.44 (−5.03 to −0.44)	−1.38 (−4.19 to 2.21)	−0.04 (−1.48 to 1.12)	0.059	−1.44 (−5.03 to −0.44)	−0.78 (−4.19 to 2.21)	0.336	−1.38 (−5.03 to 2.21)	−0.04 (−1.48 to 1.12)	0.02
BMI z-test (T1)	−1.55 (−3.45 to −1.43)	−1.64 (−3.87 to 2.24)	−0.40 (−1.86 to 0.83)	0.103	−1.55 (−3.45 to 1.43)	−1.10 (−3.87 to 2.24)	0.392	−1.60 (−3.87 to 2.24)	−0.40 (−1.86 to 0.83)	0.039
BMI z-test (T1 – T0)	−0.09 (−1.04 to 1.58)	0.03 (−2.22 to 1.59)	−0.09 (−1.11 to 0.17)	0.841	−0.09 (−1.04 to 1.58)	0.01 (−2.22 to 1.59)	0.777	0.03 (−2.22 to 1.59)	−0.09 (−1.11 to 0.17)	0.591
BMI (T0)	15.39 (12.81-19.92)	16.86 (12.39-30.18)	19.05 (15.77-22.30)	0.090	15.39 (12.81-19.92)	17.54 (12.39-30.17)	0.239	16.32 (12.39-30.17)	19.05 (15.77-22.30)	0.043
BMI (T1)	16.60 (14.97-17.58)	17.53 (14.05-31.04)	20.33 (16.78-22.85)	0.083	16.60 (14.97-17.58)	18.14 (14.05-31.04)	0.239	17.42 (14.05-31.04)	20.33 (16.78-22.85)	0.039
BMI (T1 – T0)	01.21 (−2.34 to 2.16)	0.65 (−3.53 to 4.29)	0.34 (−2.11 to 2.88)	0.881	1.21 (−2.34 to 2.16)	00.56 (−3.53 to 4.29)	0.738	0.67 (−3.53 to 4.29)	0.34 (−2.11 to 2.88)	0.796

CFRD: cystic fibrosis-related diabetes; IGT: impaired glucose tolerance; and NGT: normal glucose tolerance. [a]Values expressed as median (minimum-maximum values). *Kruskal-Wallis and Mann-Whitney tests (α = 0.05). ⁺NGT (nonparametric multiple comparison test) showed a statistically significant value. ⁺⁺CFRD ≠ NGT (nonparametric multiple comparison test) showed a statistically significant value.

Table 3. Univariate logistic analysis with variables to predict cystic fibrosis-related diabetes.

Variable	OR	95% CI	p*
Age	1.1	0.94 to 1.29	0.223
Male sex	4.99	1.63 to 15.18	0.005
p.Phe508del homozygous[a]	4.62	1.55 to 13.74	0.006
Pancreatic insufficiency	1.51	0.41 to 5.53	0.539
BMI, kg/m^2	0.78	0.63 to 0.97	0.028
FEV_1 (% of predicted values)	0.98	0.96 to 1.0	0.09
Peak ≥ 140 mg/dL/day (CGM-T0)	1.09	0.75 to 1.58	0.655
Valley < 54 mg/dL/day (CGM-T0)	0.93	0.29 to 3.03	0.906

CGM: continuous glucose monitoring; T0: baseline. [a]p.Phe508del classification was used because it is the only pathogenic variant routinely screened in our center. *Generalized estimating equation (α = 0.05).

status, and BMI were significantly related to CFRD development (Table 3). However, the multivariate logistic regression analysis showed no significant associations (data not shown).

DISCUSSION

This single-center study was conducted to compare the ability of OGTT with that of CGM in predicting the onset of CFRD and clinical impairment in CF patients. In the study population, abnormal CGM results based on the American Diabetes Association OGTT cutoff points[15] were not associated with an increased rate of CFRD or a decline in FEV_1 over a mean of 3.1 years of follow-up.

Although OGTT is the recommended gold standard for CFRD diagnosis, it is not an optimal tool, as the cutoff values are extrapolated from adult type 2 diabetes model based on the prevention of microvascular complications, which are not the leading causes of death in individuals with CF. Moreover, type 2 diabetes is not the same as CFRD.[23] A considerable lack of adherence to OGTTs has been reported.[5] Therefore, alternative screening methods are being investigated, especially those that could be related to the clinical outcomes of CF patients.

A study showed that CGM was useful for CFRD diagnosis and as an indication for early insulin therapy initiation, even though OGTT results were not confirmative.[24] Our study could not show this relationship, although dysglycemia detected by CGM readings was able to identify early BMI impairment in our patients. This difference may have occurred because of the shorter follow-up period in our study, as well as the shorter time of CGM use due to the model of the device used in our cohort.

In our study, when glucose abnormalities (CFRD and IGT) were grouped, lower BMI values and z-scores at baseline and at the end of the follow-up period were identified through CGM but not through baseline OGTT results. A study reported decreased pulmonary function and an increased rate of *Pseudomonas aeruginosa* infections among patients with CGM peaks of ≥ 200 mg/dL, although there was no detectable difference in BMI.[25]

Another study evaluated 25 children with CF and found that a proportion of time ≥ 4.5% with glucose levels > 140 mg/dL on CGM was associated with a decline in pulmonary function and weight gain in the previous 12 months.[26] Our study included a more robust case series with a longer follow-up period and detected lower BMI on patients with peaks ≥ 140 mg/dL during CGM; however, no associations were found of peaks, peaks per day, AUC, and proportion of time with glucose levels ≥ 140 mg/dL with FEV_1. The deterioration of FEV_1 and nutritional status occurs years before the diagnosis of CFRD.[2] In this context, we identified that patients who developed CFRD showed poorer FEV_1 at T1 but not at T0, as well as lower BMI at both T0 and T1 in our sample. Although the metric > 10% of the time with glucose levels ≥ 140 mg/dL on CGM is being used, it has yet to be incorporated into the guidelines, and thus it has not been considered for evaluation.

Despite the lack of significant differences, all patients who developed CFRD had a p.Phe508del homozygous status and PI and were classified as having "severe" disease (≤ 40% of predicted FEV_1) on spirometry and as being under weight (BMI) at T1. This is consistent with the literature available.[1] Furthermore, the decline in FEV_1 between T1 and T0 was greater in those classified as having CFRD according to the CGM classification than in those classified as having NGT and IGT. However, this decline was not significant in our study, which could be due to the small sample size.

Being female is considered a risk factor for CFRD, although the pathophysiology related to it is not well understood.[1] All patients who developed CFRD were male; thus, according to the univariate logistic regression analysis, being male seemed to be a potential predictor. However, in the multivariate analysis, the significance disappeared after adjustment.

Hypoglycemia during OGTT may indicate dysregulation of insulin secretion and could represent a stage preceding the onset of CFRD.[27] Our CGM study results showed that hypoglycemic events were unrelated to an increased risk of CFRD during the mean 3.1-year follow-up period. Radike et al. reported similar findings.[7] However, the prevalence of hypoglycemia was higher (32%) in our study.

The prevalence of hypoglycemia (< 50 mg/dL) in CF patients during an OGTT was reported to be 15%,[6] although this percentage could be attributed to the lower cutoff values used in that study. Furthermore, the age of the patients ranged from 8 to 31 years, whereas it ranged from 10.0 to 19.9 years in our study. Therefore, the discrepancies in cutoff values and methods could have contributed to the higher prevalence rates in our study.

Despite the higher sensitivity of CGM, its accuracy has been questioned regarding its precision in detecting consistent hypoglycemia and the lack of consensus guidelines, because no data are linking CGM to long-term outcomes in CF patients.[28] Although CGM was unable to predict the onset of CFRD based on the extrapolation of the criteria used for the OGTT,[15] 4 patients with glycemic values ≥ 200 mg/dL were identified by CGM but not by OGTT, and none of the participants who remained with interstitial glucose values < 140 mg/dL on CGM progressed to CFRD during the study period, leaving an open question of whether these patients might skip an OGTT. Gojsina et al.[24] showed that CGM could have higher sensitivity, since CFRD patients diagnosed by CGM had significantly lower hemoglobin A1c levels when compared with those diagnosed by OGTT.

Given its cost, CGM may not be available in all services for routine use and could be considered in individuals who are unable to undergo OGTT and in symptomatic NGT patients. CGM is a valid tool for the detection of dysglycemia in the CF population, and previous studies with a longer duration of CGM were able to demonstrate an association between dysglycemia detected by CGM and CF clinical outcomes.[24] CGM deals with the daily life and not with a controlled situation as does OGTT. CGM for the determination of glucose metabolism could be equated to 24-h ambulatory blood pressure monitoring for hypertension.

CGM can detect glucose abnormalities not detected by OGTT.[23,24] In our study, those abnormalities were associated with early BMI impairment, although they were not related to the current definition of the onset of CFRD based on the OGTT classification.[15] Perhaps, the reason why CGM could not predict the onset of CFRD was that the OGTT cutoff values[15] adopted might have been inadequate and/or the fact that CGM and OGTT are different tools from technical and interpretive standpoints. Moreover, according to the Endocrine Society, there is insufficient evidence for the establishment of an optimal postprandial blood glucose value.[24,29]

Only 3 of our participants developed CFRD; thus, it was not possible to make any statement about cutoff values, but we recommend that future multicenter studies evaluate CGM values between 140 and 200 mg/dL to determine appropriate cutoff values, since there are studies showing associations between values within this range and clinical outcomes.[30,31] It remains unclear whether a single CGM variable or a combination of these variables could predict clinically significant CF outcomes and potentially reformulate the CFRD concept. Additionally, CFRD patients are known to need insulin, but it is unknown if CF patients without overt diabetes but with CGM-detected glucose abnormalities could benefit from insulin use.[32] However, Gojsina et al.[24] showed that CFRD patients diagnosed by CGM benefit from insulin therapy with improvements in BMI z-score.

To clinical practice, the ideal tool would be able to predict a worse clinical evolution in short/medium terms, and, in our opinion, the adopted follow-up period fulfills this objective. Then, the same diagnostic criteria should not be used for CF individuals and those without CF, because the major cause of mortality in CF patients is not related to microvascular complications but rather to the worsening of the lung disease. The establishment of a tool that is correlated with clinical impairment in CF, mainly pulmonary function and BMI, could allow for early intervention and lead to savings related to public health care costs, as deteriorating clinical conditions lead to a greater number of hospitalizations, more aggressive therapies, and an increased need for oxygen therapy and lung transplants, in addition to the implications for quality of life and survival of CF patients.

The strengths of our study include the large sample size from a single CF referral center, the prospective design, the standardized data collection, and a pubertal pediatric cohort with high miscegenation. However, certain limitations must be recognized. Since CFRD is age related, a longer follow-up period would increase the number of patients diagnosed with this entity. The arbitrary use of OGTT cutoff values to classify CGM results is another limitation. Ideally, CGM should be performed during and at the end of the follow-up period, but, unfortunately, we were unable to do that. The CGM device available for the study was the CGMS Gold® (Medtronic Minimed), which allowed readings for a short period. Although the sample size is large for a single-center study, the small number of patients who developed CFRD during the follow-up period limited our ability to conduct multivariate regression analysis with the current dataset.

In conclusion, CGM can identify glucose abnormalities not detected by OGTT and may be more sensitive for the early detection of decreases in BMI. However, based on our data, we were unable to identify early predictors for the onset of CFRD among the variables studied. Individuals with interstitial glucose levels < 140 mg/dL on CGM might not need to perform OGTT in the short/medium term. Furthermore, we could have an alternative tool for those patients who are unable to perform OGTT and for those classified as having NGT on OGTT but with poor clinical evolution. Different diagnostic criteria for diabetes may be required for the CF population.

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AUTHOR CONTRIBUTIONS

MZ: conceptualization, data curation; formal analysis; investigation; methodology; project administration; drafting, reviewing, and editing of the manuscript. FALM: formal analysis; methodology; review and editing of the manuscript. AMM: formal analysis; review and editing of the manuscript. ACG: data curation; review and editing of the manuscript. MSEB: data curation; review and editing of the manuscript. JDR: conceptualization; methodology; project administration; drafting, reviewing, and editing of the manuscript. and AFR: conceptualization; methodology; project administration; drafting, reviewing, and editing of the manuscript. All of the authors gave final approval of the version to be published and agreed to be accountable for all aspects of the study, ensuring that questions related to the accuracy or integrity of any of its parts have been appropriately investigated and resolved.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Impact of prone positioning on patients with COVID-19 and ARDS on invasive mechanical ventilation: a multicenter cohort study

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Study carried out at the Hospital das Clínicas, Faculdade de Medicina, Universidade de São Paulo, São Paulo (SP); Irmandade Santa Casa de Misericórdia de Porto Alegre, Porto Alegre (RS); Hospital Tacchini, Bento Gonçalves (RS); Hospital Universitário de Santa Maria, Universidade Federal de Santa Maria, Santa Maria (RS); Hospital Universitário Polydoro Ernani de São Thiago, Universidade Federal de Santa Catarina, Florianópolis (SC); and Santa Casa de Misericórdia de Belo Horizonte, Belo Horizonte (MG) Brasil.

ABSTRACT

Objective: To identify factors that lead to a positive oxygenation response and predictive factors of mortality after prone positioning. **Methods:** This was a retrospective, multicenter, cohort study involving seven hospitals in Brazil. Inclusion criteria were being > 18 years of age with a suspected or confirmed diagnosis of COVID-19, being on invasive mechanical ventilation, having a PaO_2/FIO_2 ratio < 150 mmHg, and being submitted to prone positioning. After the first prone positioning session, a 20 mmHg improvement in the PaO_2/FIO_2 ratio was defined as a positive response. **Results:** The study involved 574 patients, 412 (72%) of whom responded positively to the first prone positioning session. Multiple logistic regression showed that responders had lower Simplified Acute Physiology Score III (SAPS III)/SOFA scores and lower D-dimer levels (p = 0.01; p = 0.04; and p = 0.04, respectively). It was suggested that initial SAPS III and initial PaO_2/FIO_2 were predictors of oxygenation response. The mortality rate was 69.3%. Increased risk of mortality was associated with age (OR = 1.04 [95 CI: 1.01-1.06]), time to first prone positioning session (OR = 1.18 [95 CI: 1.06-1.31]), number of sessions (OR = 1.31 [95% CI: 1.00-1.72]), proportion of pulmonary impairment (OR = 1.55 [95% CI: 1.02-2.35]), and immunosuppression (OR = 3.83 [95% CI: 1.35-10.86]). **Conclusions:** Our results show that most patients in our sample had a positive oxygenation response after the first prone positioning session. However, the mortality rate was high, probably due to the health status and the number of comorbidities of the patients, as well as the severity of their disease. Our results also suggest that SAPS III and the initial PaO_2/FIO_2 predict the oxygenation response; in addition, age, time to first prone positioning, number of sessions, pulmonary impairment, and immunosuppression can predict mortality.

Keywords: Respiratory distress syndrome; Coronavirus infections; Pulmonary medicine; COVID-19; Prone position; SARS-CoV-2.

INTRODUCTION

In severe COVID-19 cases, there is a cytokine storm characterized by a hyperinflammatory state, interstitial edema, hypoxemic respiratory failure, pulmonary perfusion impairment, and multiple organ failure.[1] A significant proportion of individuals with COVID-19 presents a deficit in ventilation-perfusion similar to moderate-to-severe ARDS but with an atypical and heterogeneous pathological pattern.[2-5]

COVID-19-related ARDS presents a spectrum of clinical phenotypes that vary in degrees of pulmonary infiltration, concomitant thrombotic injury, and lung recruitability and compliance; therefore, heterogeneous respiratory mechanics. Thus, some patients are more or less likely to respond to prone positioning, and subgroups tend to have different behaviors and high mortality.[6]

Prone positioning has been recommended as rescue therapy by the WHO and the Surviving Sepsis Campaign in refractory hypoxemia due to COVID-19-related

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ARDS.[7-9] The main effects of prone positioning are improvement in chest wall compliance, uniformity of pleural pressure gradient, recruitment of dorsal regions, and changes in the distribution of alveolar units.[10]

The recommendation is the association of prone positioning with protective ventilatory strategies, using low VT (6 mL/kg of predicted weight), plateau pressure of the respiratory system (Pplat) < 30 cmH_2O, and neuromuscular blocker infusion.[11,12] Furthermore, there is evidence that prone positioning provides better outcomes when applied earlier (within the first 48 h of disease onset) and maintained for at least 12-16 h.[1,9,11]

Since the beginning of the pandemic, researchers have shown that prone positioning is effective and safe in treating COVID-19-related ARDS. However, we sought to understand which patients would be more susceptible to a better response. The primary goal of the study was to identify factors that would lead to a positive oxygenation response after the use of the prone positioning maneuver. The secondary goal was to identify predictive factors of mortality.

METHODS

This retrospective multicenter study was conducted in seven Brazilian hospitals involving a cohort of 574 intubated, mechanically ventilated patients with severe COVID-19-related ARDS. The clinical research ethics committees of all hospitals involved approved the study (Protocol no. 31881520.3.1001.5335). Patient consent was waived because of the retrospective nature of the study.

Data collection was conducted between the 1st of June and the 30th of December, 2020. The authors had access to electronic medical records of their affiliated institutions. Data were collected using standardized forms, safeguarding the identification of each patient. The main goals were to identify predictive factors of oxygenation improvement and mortality among the patients placed in prone positioning.

Inclusion criteria were individuals having suspected or confirmed COVID-19, requiring invasive mechanical ventilation, presenting with severe ARDS (PaO_2/FIO_2 < 150 mmHg), and being ≥ 18 years of age. Confirmed diagnosis of COVID-19 was based on clinical symptoms and a positive RT-PCR test; highly suspected diagnosis of COVID-19 was based on presenting with a negative RT-PCR test but showing COVID-19 clinical signs such as flu-like symptoms, progressive dyspnea, compatible pulmonary radiological images, and positive epidemiology.

Patients with negative RT-PCR were included due to the high probability of false-negative results. However, patients who were submitted to prone positioning when awake, without invasive mechanical ventilation support, were excluded.

All patients were divided into two groups according to oxygenation response. The PaO_2/FIO_2 ratio was calculated before and after the first prone positioning session. Patients who presented an increase in the PaO_2/FIO_2 ratio ≥ 20 mmHg after the session were allocated in the responder group, whereas those with an increase < 20 mmHg after the session were allocated in the nonresponder group.

The overload caused by the initial peak of the disease in Brazil made laboratory sample collection unfeasible in due time. Therefore, it was not possible to perform blood gas analyses one hour after prone positioning, as recommended. The data considered in the study were the ones obtained closest to the beginning and end of the first prone positioning session. The patients included were followed until hospital discharge. The mortality outcome included the events that occurred during hospitalization.

Availability of study data

The datasets generated and analyzed during the current study are available in the Zenodo repository (https://zenodo.org/badge/DOI/10.5281/zenodo.4667698.svg).

Collected variables

The following data were collected: age, gender, race, comorbidities, and BMI. Pulmonary impairment was assessed by chest CT performed closer to the intubation period. According to the radiologist report in the medical records, the proportion of parenchymal impairment was classified as < 25%, 25-50%, 51-75%, or > 75%. Lung involvement was subclassified into I (< 25%), II (25-50%), III (51-75%), and IV (> 75%) to enable data analysis.

D-dimer levels were evaluated using the HemosIL HS-500 automated immunoassay (Instrumentation Laboratory Company, Bedford, MA, USA). The level considered for statistics was the one closest to the first prone positioning session if the patient had multiple measurements. The Simplified Acute Physiology Score III (SAPS III) and the SOFA score considered for analysis were collected at ICU admission.

The following comorbidities were reported: immunosuppression; arterial hypertension; diabetes; obesity; smoking and alcohol consumption; and neurological, hematological, respiratory, or cardiovascular diseases. Patients with a history of organ transplantation were considered immunosuppressed, as were those with chronic kidney disease, HIV/AIDS, and those undergoing cancer treatment.

Data on ventilator settings, respiratory mechanics (i.e., driving pressure, Pplat, and static compliance of the respiratory system), and arterial blood gas analysis were collected before and after the first prone positioning session. Time to first prone positioning session was defined as the time between the first intubation procedure and the first prone positioning session.

Total duration of the first prone positioning session (in h), number of sessions, and adverse effects were

recorded. Patient outcomes were also recorded, including duration of invasive mechanical ventilation, length of ICU and hospital stay, reintubation, and survival.

Statistical analysis

Continuous and categorical variables were expressed as medians (interquartile ranges) and absolute and relative frequencies, respectively. Comparisons between the two groups (responders and nonresponders) were performed using an independent test or the Mann-Whitney test. Logistic regression was used in order to examine factors associated with the response to prone positioning and mortality. A forward stepwise regression was then performed to identify the clinical variables that correlated with the change of oxygenation level. After that, multicollinearity was assessed by examining the variance inflation factor (values > 2 were excluded). The results are presented as odds ratios and 95% confidence intervals. We used the IBM SPSS Statistics software package, version 26.0 (IBM Corp., Armonk, NY, USA) for statistical analysis. Significance was set at $p < 0.05$.

RESULTS

During the study period, 574 consecutive patients were included. The median age was 59 years. Male sex and White race were the most prevalent self-responses. The most common comorbidities in both groups were arterial hypertension and diabetes. Being overweight or obese was the third most prevalent comorbidity. The mean BMI was 29.4 kg/m^2 (Table 1).

The mean overall SAPS III was 65, and the mean overall SOFA score was 9. The degree of pulmonary involvement on chest CT was high; most patients were classified as grade III (51-75%). The mean overall D-dimer level was 9.6 µg/m. SAPS III, SOFA score, and D-dimer levels were significantly lower in the responder group. In general, patients had Pplat < 30 cmH_2O, and duration of prone positioning was greater than 12-16 h.

The median time to the first prone positioning session was 48 h (24-120 h) and 72 h (24-144 h) in the responder and nonresponder groups, respectively ($p = 0.02$). In general, patients required 2 (1-3) prone positioning sessions, and there was no difference in the number of sessions performed between the groups.

Most patients received vasoactive drugs and neuromuscular blockade infusion, and a small proportion required tracheostomy and/or reintubation during the follow-up period. The median length of ICU stay was 20 days and that of hospital stay was 27 days (Table 2).

Table 1. Baseline characteristics of patients with COVID-19-related ARDS at ICU admission.[a,b]

Variable	Whole sample	Group		p
		Responder	Nonresponder	
	(n = 574)	(n = 412)	(n = 162)	
Age, years	59 [49-69]	59 [49-69]	59 [50-70]	
Male gender	336 (58.5)	237 (57.5)	99 (61.1)	0.43
Self-reported race				
White	348 (60.6)	253 (61.4)	95 (58.6)	0.47
Brown	163 (28.4)	112 (27.2)	51 (31.5)	
Black	37 (6.4)	27 (6.6)	10 (6.2)	
Asian	4 (0.7)	3 (0.7)	1 (0.6)	
Comorbidities				
Arterial hypertension	334 (58.2)	237 (57.5)	97 (59.9)	0.60
Diabetes mellitus	225 (39.2)	161 (39.1)	64 (39.5)	0.88
Obesity	224 (39)	163 (39.6)	61 (37.7)	0.73
Smoker	115 (20)	78 (18.9)	37 (22.8)	0.26
Pneumopathy	75 (13.1)	54 (13.1)	21 (13.0)	0.98
Immunosuppression	62 (10.8)	48 (11.7)	14 (8.6)	0.31
SAPS III	65 [54-77]	63 [52-75]	68 [56-79]	0.01
SOFA score	9 [6-12]	9 [6-12]	10 [7-13]	0.04
Chest CT pulmonary findings				
I (< 25%)	7 (1.2)	6 (1.5)	1 (0.6)	0.91
II (25-50)	60 (10.5)	38 (9.2)	22 (13.6)	
III (51-75)	151 (26.3)	104 (25.2)	47 (29.0)	
IV (> 75%)	45 (7.8)	30 (7.3)	15 (9.3)	
BMI, kg/m^2	29.4 [24.8-32.6]	29.4 [24.8-32.7]	29.2 [24.4-32.3]	0.75
D-dimer, ng/mL	9,634 [943-5,426]	9,224 [891-4,452]	10,534 [1,146-6,376]	0.04

SAPS III: Simplified Acute Physiology Score III. [a]Values expressed as median [IQR] or n (%). [b]Missing data: diabetes mellitus (n = 1); obesity (n = 3); smoker (n = 2); pneumopathy (n = 1); immunosuppression (n = 2); SAPS III (n = 141); SOFA score (n = 159); chest CT (n = 310); BMI (n = 42); and D-dimer (n = 149).

Prone positioning and oxygenation improvement

The PaO_2/FIO_2 ratio improved in 412 patients (72%) after the first prone positioning session. The median difference in PaO_2/FIO_2 after the first prone positioning session was expressively greater in the responder group (84 [41-111] mmHg vs. −9.2 [−20.5 to 7.0] mmHg). As previously mentioned, SAPS III and SOFA scores, as well as D-dimer levels, were significantly lower in the responder group.

Among ventilator settings, the responder group presented lower RR, PaO_2, and $PaCO_2$ but no significant changes in arterial pH. In addition, the initial PaO_2/FIO_2 ratio was lower in the responder group. Regarding the nonresponder group, it was found that the time to the first prone positioning session was longer, and session duration was shorter.

The clinical variables related to oxygenation response studied were the following: SAPS III, number of sessions, static compliance of the respiratory system, baseline PaO_2/FIO_2 ratio, and D-dimer level. After multivariate logistic regression analysis, SAPS III and baseline PaO_2/FIO_2 ratio were significantly associated with oxygenation improvement (Table 3).

Prone positioning and mortality

More than half of the patients had an unfavorable outcome after prone positioning. Although no difference was observed between responders and nonresponders (p = 0.08), responders had lower mortality than did nonresponders (67.2% vs. 74.7%).

Mortality was associated with age, time to first prone positioning session, SOFA score, SAPS III, number of prone positioning sessions, extension of pulmonary

Table 2. Ventilator management, response to prone positioning, and outcomes in the patients studied.

Variable	Whole sample	Group		p*
		Responder	Nonresponder	
	(n = 574)	(n = 412)	(n = 162)	
Pre-prone ventilatory support				
PEEP, cmH_2O	11 [10-12]	11 [10-12]	11 [10-12]	0.66
FIO_2,%	80 [65-100]	80 [65-100]	80 [60-100]	0.11
RR, breaths/min	28 [24-32]	28 [24-32]	30 [25-34]	< 0.001
VT, mL	387 [335-435]	385 [330-440]	390 [350-420]	0.76
Driving pressure	13 [11-16]	13 [11-15]	14 [11-16]	0.69
Pplat, cmH_2O	24 [22-28]	24 [22-28]	24 [22-28]	0.82
Cst, mL/cmH_2O	31.2 [23.0-37.0]	31.2 [23.0-36.5]	31.0 [22.0-37.5]	0.75
Pre-prone blood gas analysis				
Arterial pH	7.31 [7.25-7.38]	7.32 [7.26-7.39]	7.30 [7.25-7.36]	0.05
PaO_2, mmHg	74.7 [64-83]	74 [63-82]	77 [65-84]	0.04
$PaCO_2$, mmHg	53.8 [45-60]	53 [43-59]	56 [47-61]	0.01
HCO_3, mEq/L	27 [23-30]	26.7 [23-30]	28 [23-30]	0.62
Initial PaO_2/FIO_2 ratio, mmHg	100 [79-120]	97 [77-118]	103 [83-123]	0.01
Time to 1st prone maneuver, days	2 (1-5)	2 [1-5]	3 [1-6]	0.02
Duration of 1st prone maneuver, h	18.3 (16.2-20.5)	18.6 [16.5-20.9]	17.6 [16.0-20.0]	0.04
Prone sessions, n	2 [1-3]	2 [1-3]	2 [1-2]	0.74
Post-prone oxygenation/ventilatory response				
$\Delta PaO_2/FIO_2$, mmHg	57.8 [14.7-90]	84 [41–111]	−9.2 [−21 to 7]	< 0.001
ΔPCO_2, mmHg	−3.0 [−10.0 to 5.0]	−2.5 [−9.4 to 5.1]	−3.8 [−11.5 to 4.0]	0.33
Complications	31 (5.4)	10 (2.4)	21 (13.0)	< 0.001
Drug interventions				
Anticoagulants	559 (97.4)	398 (96.6)	161 (99.4)	0.07
Vasopressors	509 (88.7)	361 (87.6)	148 (91.4)	0.16
Duration of MV, days	18 (9-23)	18 (9-22)	18 (10-24)	0.61
Length of ICU stay, days	20 [11-26]	21 [11-26]	20 [10-25]	0.49
Length of hospital stay, days	27[14-35]	28 [14-35]	26 [12-34]	0.05
Reintubation	76 (13.2)	54 (13.1)	22 (13.6)	0.89
Tracheotomy	115 (20.0)	85 (20.6)	30 (18.5)	0.61
In-hospital mortality	398 (69.3)	277 (67.2)	121 (74.7)	0.08

MV: mechanical ventilation; Pplat: plateau pressure of the respiratory system; Cst: static compliance of the respiratory system; and HCO_3: bicarbonate; [a]Values expressed as median [IQR] or n (%). [b]Missing data: PEEP (n = 1); RR (n = 5); VT (n = 4); driving pressure (n = 238); Pplat (n = 233); Cst (n = 253); duration of first prone maneuver (n = 2); complications (n = 8); anticoagulants (n = 1); vasopressors (n = 2); reintubation (n = 5); and tracheostomy (n = 2). *Mann-Whitney test for continuous variables and the chi-square test for categorical variables.

impairment on chest CT, immunosuppression, initial arterial pH, and $PaCO_2$. After multivariate logistic regression analysis, age, time to first session, number of sessions, extension of pulmonary impairment, immunosuppression, and initial arterial pH were independently associated with the risk of mortality (Table 3).

DISCUSSION

We performed a retrospective multicenter study involving seven Brazilian hospitals in a cohort of 574 intubated, mechanically ventilated patients with severe COVID-19-related ARDS. Our results showed that most patients (72%) had their oxygenation improved after the first prone positioning session, and this response was associated with SAPS III and PaO_2/FIO_2 ratio. We also observed a high mortality rate during ICU stays that was associated with age, time to the first prone positioning session, number of sessions, pulmonary impairment, and immunosuppression.

Patients were subdivided according to oxygenation improvement using a cutoff point of 20 in PaO_2/FIO_2. Although PaO_2/FIO_2 has been used to assess oxygenation response in patients with ARDS, no cutoff values have been well established. Most studies have used either an improvement of 10-20 mmHg in PaO_2 or a 10-20% increase in PaO_2/FIO_2.[13] In addition, we identified that the responder group presented lower SAPS III and SOFA score, as well as lower D-dimer levels. The SAPS III and SOFA scores are systems for predicting mortality in patients admitted to the ICU. Also, elevated D-dimer levels in patients with COVID-19 are associated with hemostatic abnormalities and poor outcomes and could predict mortality risk.[6,14-16] Taken together, our results reinforce the clinical relevance of using SAPS III/SOFA score and D-dimer levels to predict mortality in patients with COVID-19-related ARDS.

We found no significant reductions in mortality when comparing responder and nonresponder groups (67.2 vs. 74.7%; p = 0.08). Other studies were also unable to determine this correlation in patients with COVID-19-related ARDS. However, a retrospective study of 648 intubated patients with COVID-19-related ARDS placed in prone positioning showed that oxygenation response could reduce mortality.[10] Our results suggest that age, previous immunosuppression, extension of pulmonary involvement, time to start the first prone positioning session, number of prone sessions, and baseline arterial pH are predictors of mortality.

Overall mortality was 69.3%. We hypothesize that our patients had worse outcomes due to their socioeconomic status and health condition as accessed by age, comorbidities, SAPS III/SOFA score, D-dimer levels, and extension of pulmonary impairment. Weiss et al.[7] found a mortality rate of 21.4% among 42 patients requiring invasive mechanical ventilation and submitted to prone positioning. The mean age of the patients was 58.5 years, and the mean SOFA score was 6.8 at ICU admission. On the other hand, a less socioeconomically favored population neighborhood in New York City had a mortality rate > 75%.[17] Therefore, it is necessary to consider that the present study represents a population lacking resources in an underdeveloped country.

The high mortality rate can also be attributed to the overloaded health care system during the first pandemic peak in Brazil. The mortality rate in Brazil was approximately 80% among 250,000 patients hospitalized with COVID-19 on mechanical ventilation.[18] In addition, the median time to perform the first prone positioning session was 48 h (24-120 h) in the responder group and 72 h (24-144 h) in the nonresponder group. We were unable to identify the reasons why it took some patients a long time to be placed in the prone position.

The study had several limitations. First, because it is a retrospective study, it was not possible to find all of the data in the electronic medical records for analysis. Second, this is an observational study, and, contrary to a clinical trial, the decision and timing of prone positioning could not be controlled. Moreover, it was not possible to assess the strategies adopted by the teams during the prone positioning maneuver. Third, other treatments to improve response to

Table 3. Univariate logistic regression model analysis for predictors of oxygenation improvement and mortality.

Variable	OR	95% CI	p
Oxygenation response[a]			
SAPS III	0.98	0.96-0.99	0.04
Initial PaO_2/FIO_2 ratio, mmHg	0.98	0.97-0.98	< 0.001
Mortality risk[b]			
Age, years	1.04	1.01-1.06	< 0.001
Immunosuppression	3.83	1.35-10.86	0.01
Pulmonary impairment, % chest CT involvement			
Initial arterial pH	0.01	0.01-0.02	< 0.001
Time to first prone positioning session, days	1.18	1.06-1.31	0.01
Prone positioning sessions, n	1.31	1.00-1.72	0.04

SAPS III: Simplified Acute Physiology Score III. [a]Univariate analysis included the following data: SAPS III, number of sessions, static compliance of the respiratory system, initial PaO_2/FIO_2 ratio, and D-dimer level. [b]Univariate analysis included the following data: age, time to first prone positioning session, SOFA score, SAPS III, number of sessions, pulmonary impairment, immunosuppression, initial arterial pH, and $PaCO_2$.

prone positioning, such as the use of extracorporeal membrane oxygenation, hemodialysis, and alveolar recruitment, were not performed. Finally, the criteria that we used to assess the response to prone positioning are not universal; therefore, comparisons with other studies should be carried out with caution.

Our study showed that most patients with COVID-19-related ARDS experienced improved oxygenation after prone positioning. However, the mortality rate was high, probably due to the poor health status of the patients, disease severity, and high number of comorbidities of the patients, as well as the severity of their disease. These results highlight the usefulness of prone positioning to improve gas exchange for patients with COVID-19, mainly when performed early and in subjects with a better health status.

AUTHOR CONTRIBUTIONS

MCAC, JS, NCR, ACL, GNS, and LPI: study design, conception, and planning; data collection; interpretation of evidence; and drafting and revision of the manuscript. KRB, JEP, FF, LMF, RAC, AMVS, CCD, and RWW: study conception and planning; data collection; interpretation of evidence; revision of the manuscript; and approval of the final version. JCF, RDMP, and CRFC: study design, conception, and planning; interpretation of evidence; and revision of the manuscript.

CONFLICT OF INTEREST

None declared.

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Expiratory CT scanning in COVID-19 patients: can we add useful data?

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ABSTRACT

Objective: To evaluate small airway disease in COVID-19 patients using the prevalence of air trapping (AT) and correlating it with clinical outcomes. The relationship between CT-based opacities in small blood vessels and ventilation in patients with SARS-CoV-2 pneumonia was also assessed. **Methods:** We retrospectively included 53 patients with positive RT-PCR results for SARS-CoV-2 between March and April of 2020. All subjects underwent HRCT scanning, including inspiratory and expiratory acquisitions. Subjects were divided into two groups based on visual identification of AT. Small blood vessel volumes were estimated by means of cross-sectional areas < 5 mm^2 (BV5) derived from automated segmentation algorithms. Mixed-effect models were obtained to represent the BV5 as a function of CT-based lobar opacities and lobar ventilation. **Results:** Of the 53 participants, AT was identified in 23 (43.4%). The presence of AT was associated with increased SpO_2 at admission (OR = 1.25; 95% CI, 1.07-1.45; p = 0.004) and reduced D-dimer levels (OR = 0.99; 95% CI, 0.99-0.99; p = 0.039). Patients with AT were less likely to be hospitalized (OR = 0.27; 95% CI, 0.08-0.89; p = 0.032). There was a significant but weak inverse correlation between BV5 and CT-based lobar opacities (R^2 = 0.19; p = 0.03), as well as a nonsignificant and weak direct correlation between BV5 and lobar ventilation (R^2 = 0.08; p = 0.54). **Conclusions:** AT is a common finding in patients with COVID-19 that undergo expiratory CT scanning. The presence of AT may correlate with higher SpO_2 at admission, lower D-dimer levels, and fewer hospitalizations when compared with absence of AT. Also, the volume of small pulmonary vessels may negatively correlate with CT opacities but not with lobar ventilation.

Keywords: SARS-CoV-2; COVID-19; Tomography, X-ray.

INTRODUCTION

The SARS-CoV-2 pneumonia course is characterized by severe hypoxemia with preserved lung compliance.[1,2] The underlying causes of COVID-19-related acute respiratory failure are vascular injury and vasoconstriction, with microvascular injury causing the pulmonary exudate leak, which is characteristic of SARS-CoV-2 pneumonia.[1,2] The presence of inflammatory exudates in the airways leading to airway remodeling and destruction of alveolar walls has been described as the pathophysiology of other pulmonary diseases such as COPD and asthma. This damage to the small airways leads to airflow obstruction and air trapping (AT), which are markers of COVID-19 severity and prognosis.[3,4] AT has also been reported in pulmonary hypertension due to an increase in the caliber of arteries in areas of increased attenuation (hyperemia) when compared with smaller vessels in areas of low attenuation (oligemia).[5] A group of authors reported that the presence of AT was significantly more common in patients with COVID-19 admitted to the ICU or who died.[6] Thus, it is reasonable to question whether COVID-19 could result in small airway damage and AT and whether microvascular thrombosis may contribute to bronchiolar constriction or small airway disease.[7]

Chest CT has played a significant role in the COVID-19 evaluation, and abnormal CT findings have been reported in up to 90% of hospitalized patients.[8,9] The predominance of ground-glass opacities (GGO) is one of the most common patterns of SARS-CoV-2 pneumonia.[8,9] Although imaging cannot diagnose SARS-CoV-2, it can assess the severity and extension of lower respiratory tract involvement, as well as provide alternative diagnoses and concomitant pathologies, such as pulmonary embolism.[10,11] However, the role of expiratory CT acquisitions in COVID-19 remains unclear, and most imaging centers include only inspiratory phases to avoid patient exposure to additional radiation doses.[12] Thus, the prevalence of AT in COVID-19 patients might be underestimated. Some follow-up studies of SARS-CoV-2 pneumonia have demonstrated that AT may also be identified months after the infection.[13]

Quantitative CT imaging has been used to predict clinical outcomes of several pulmonary diseases, and the percentage of AT has been used as one of the

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quantitative CT tools in the evaluation of asthma, COPD, and interstitial lung diseases.[14-17] Regarding COVID-19, few articles have evaluated quantitative CT findings as markers of disease progression and prognosis. Increasing percentages of consolidation and GGO on chest CT have been found to estimate the risk of clinical deterioration or death in patients with COVID-19 pneumonia.[18] Also, a quantitative decrease in well-aerated lung volume has been reported to predict adverse outcomes in COVID-19.[19] Thus, the purpose of the present study was to evaluate small airway disease in COVID-19 patients by using the prevalence of AT and correlating it with clinical outcomes. The relationship between small blood vessels with CT opacities and ventilation in SARS-CoV-2 pneumonia patients was also assessed.

METHODS

The local institutional review board approved this cross-sectional retrospective study, and written consent was waived. We retrospectively included patients with positive SARS-CoV-2 RT-PCR results from throat swabs or lower respiratory tract samples between March 21, 2020 and April 20, 2020, in three hospitals. Patients should have undergone chest CT in the same period of a positive RT-PCR test.

Volumetric HRCT scans were obtained from all subjects, including acquisitions at full inspiration and the end of a normal expiration. The expiratory CT acquisition phase was already part of our institutional CT protocol to assess pulmonary infections before the COVID-19 pandemic. All CT scans were performed with a peak tube voltage of 120 kVp and a fixed tube current of 200 mAs for inspiratory CT and of 50 mAs for expiratory CT at a gantry rotation time of 0.5 s. The reconstructed slice thickness was 1.25 mm using a 64-slice CT scanner (LightSpeed VCT; GE Healthcare, Chicago, IL, USA).

Inspiratory and expiratory HRCT imaging datasets were analyzed using a digital database system (CARESTREAM Vue PACS, version 12.2.1.2; Carestream Health, Rochester, NY, USA), and the two radiologists (with 5 and 9 years of experience) who performed the analysis were blinded to clinical and laboratory results of the patients. The use of intravenous contrast media was requested at the discretion of the attending physician or radiologist. HRCT findings were described using the international standard nomenclature defined by the Fleischner Society glossary[20] and the British Society of Thoracic imaging classification of COVID-19 pneumonia (classic, probable, indeterminate, or non-COVID-19).[21] A semiquantitative score was used in order to estimate the parenchymal involvement with GGO and consolidation at inspiratory acquisitions by using the following lesion extension ranges: 0-24%; 25-49%; 50-74%; and 75-100%. Patients were divided into two groups based on the presence of AT, which was defined as parenchymal areas with less than the normal increase in attenuation and lack of volume reduction on end-expiration CT scans.[20] Regional AT was considered present when at least three secondary lobules were involved, as previously described.[22]

Data on airways and small vessels were also post-processed using functional respiratory imaging analysis, a technique to assess airway morphology that has been extensively validated in humans.[23-25] Three-dimensional reconstructions of the lung and pulmonary vasculature were created using a software program (FLUIDDA, Kontich, Belgium) approved by the US Food and Drug Administration. Using an automated blood vessel segmentation algorithm previously described,[26,27] we calculated the volume of blood contained in vessels in three ranges of cross-sectional areas: < 5 mm^3 (BV5); 5-10 mm^3 (BV5-BV10), and > 10 mm^3 (BV10). Three-dimensional visual representations of the blood vessels were created, and they were colored according to their size (Figures 1 and 2). From the data derived from gated inspiratory and expiratory CT scans, ventilation maps were created by assuming that regional changes in lung volume would relate to regional ventilation, as previously described.[28] Mixed-effect models were also obtained to represent the predicted percentage of BV5 as a function of volume of CT-based opacities within a lobe and lobar ventilation.

Demographic, clinical, and laboratory variables were collected from the electronic medical records of the institutions. Such parameters were based on previous investigations that found correlations between such variables and the severity of respiratory failure in patients with COVID-19.[29,30]

Data were presented as absolute and relative frequencies, as well as means and standard deviations or medians and interquartile ranges. The Shapiro-Wilk test was used to assess the normality of data distribution. We evaluated associations between variables with chi-squared tests. For comparing continuous variables, the Mann-Whitney test was used. The Student's t-test was used for continuous variables for two-group comparisons. All tests were two-tailed with a level of significance set at $p < 0.05$. Statistical analyses were performed using Stata statistical software package, version 15 (StataCorp LP, College Station, TX, USA).

RESULTS

In total, 53 patients were included, and AT was identified in 23 patients (43.4%). There were no significant differences between the patients with AT (AT group) and those without AT (non-AT group) regarding their baseline characteristics (Table 1). Both groups presented similar prevalences of comorbidities that cause AT, such as asthma and COPD. In accordance with the imaging classification of COVID-19 pneumonia,[21] the non-COVID-19 pattern was identified in 6 and 6 patients in the AT and non-AT groups, respectively (Table 1). Although most patients in both groups presented with the classic/probable COVID-19 pattern on CT (Figure 1), no significant differences were found in the prevalence of classic/probable or indeterminate

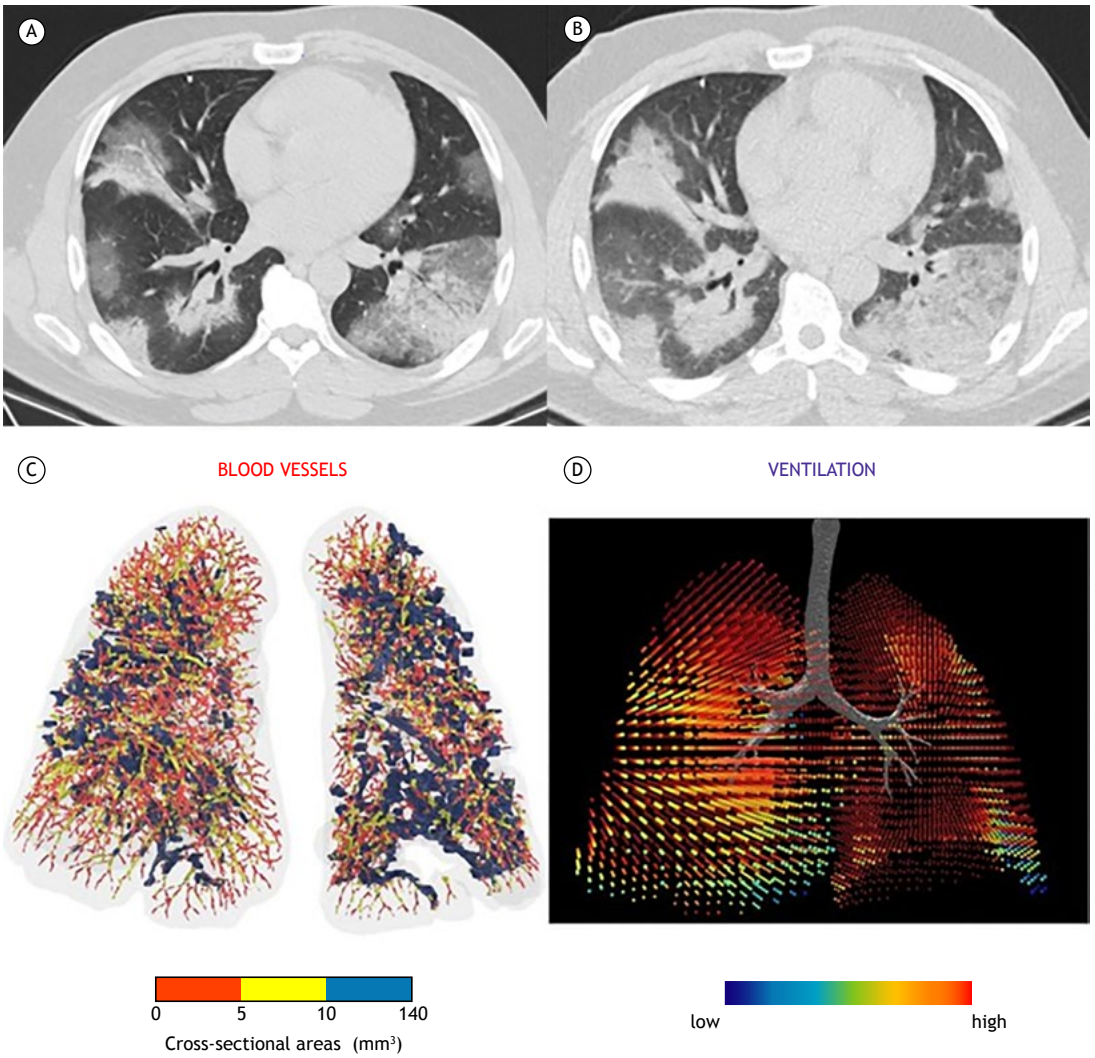

Figure 1. Typical appearance of COVID-19 (classic pattern)—50-74% parenchymal involvement. HRCT axial images obtained during inspiratory (in A) and expiratory (in B) acquisitions with no evidence of air trapping. In C, three-dimensional visual representation of blood vessels colored according to their size (red, yellow, and blue corresponding to small, mid-sized, and large vessels, respectively). Cross-sectional areas < 5 mm^3 are sparse throughout the lung, indicating severe diffuse vasoconstriction even in areas without consolidation. In the ventilation map (in D), most areas of the lung are colored red, representing a normal expansion of lobar volumes between inspiration and expiration, even in areas where there is severe vasoconstriction of small blood vessels.

COVID-19 patterns on CT between the groups (p = 0.196). Most patients included in our study presented with < 50% of lung involvement on their CT scans. Although the prevalences of lung involvement ≥ 50% were different between the groups, they were not statistically significant (p = 0.622).

Table 2 summarizes the comparison of outcomes between the groups. There were significant differences between the groups in SpO_2 at admission and D-dimer levels, as well as the need for hospitalization. In the initial evaluation, the non-AT group presented lower SpO_2 (p = 0.012) and higher D-dimer levels (p = 0.001) that did the AT group. A greater proportion of patients in the non-AT group required hospitalization when compared with those in the AT group (73.3% vs. 43.5%; p = 0.028).

The logistic regression univariate analysis compared the outcomes between the groups. The presence of AT was associated with a 25% increase in SpO_2 at admission (OR = 1.25; 95% CI, 1.07-1.45; p = 0.004) and lower D-dimer levels (OR = 0.99; 95% CI, 0.99-0.99; p = 0.039). Also, patients with AT were less likely to be hospitalized (OR = 0.27; 95% CI, 0.08-0.89; p = 0.032).

There was a significant but weak inverse correlation between BV5 and CT-based opacities (R^2 = 0.19; p = 0.03; Figure 3). Also, there was a nonsignificant and weak direct correlation between BV5 and lobar ventilation (R^2 = 0.08; p = 0.54; Figure 4).

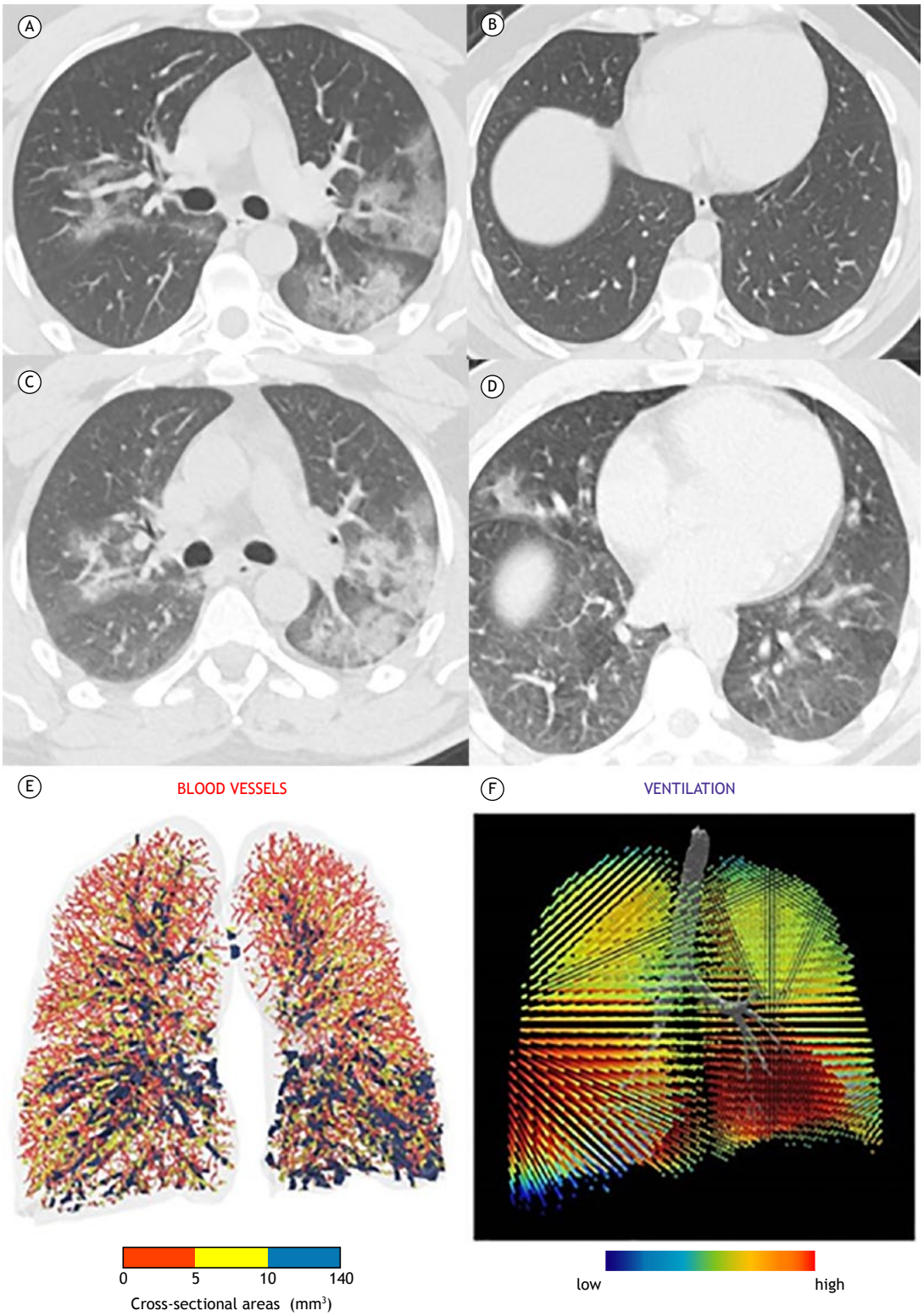

Figure 2. Typical appearance of COVID-19—25-49% parenchymal involvement. HRCT axial images obtained during inspiratory (in A and B) and expiratory (in C and D) acquisitions showing air trapping. In E, three-dimensional visual representation of blood vessels colored according to their size (red, yellow, and blue corresponding to small, mid-sized, and large vessels, respectively). Cross-sectional areas < 5 mm^3 are sparse throughout the lung, indicating severe diffuse vasoconstriction even in areas without consolidation. In the ventilation map (in F), most areas of the lung are colored red, representing a normal expansion of lobar volumes between inspiration and expiration, even in areas where there is severe vasoconstriction of small blood vessels.

Table 1. Characteristics of the patients at baseline (N = 53).[a]

Variable	Group		p
	Non-AT (n = 30)	AT (n = 23)	
Female	14 (46.7)	11 (47.8)	1.000
Age, years	55 ± 17	48 ± 15	0.091
Time to CT, days	4 [0-8]	4 [1-8]	0.483
Comorbidity			
Asthma	2 (6.7)	3 (13.0)	0.642
COPD	4 (13.3)	0 (0.0)	0.124
Diabetes mellitus	1 (3.3)	4 (17.4)	0.154
Hypertension	6 (20.0)	5 (21.7)	1.000
CT			
Imaging classification[21]			0.196
Non-COVID-19	6 (20.0)	6 (26.1)	
Classic/probable	21 (70.0)	11 (47.8)	
Indeterminate	3 (10.0)	6 (26.1)	
Grade, %			0.622
0-24	8 (33.3)	7 (41.2)	
25-49	8 (33.3)	7 (41.2)	
50-74	7 (29.2)	2 (11.8)	
75-100	1 (4.2)	1 (5.9)	
Symptoms			
Fever	18 (60.0)	14 (60.9)	1.000

AT: air trapping. [a]Values expressed as n (%), mean ± SD, or median [IQR].

Table 2. Comparison of outcomes between the groups (N = 53).[a]

Variable	Group		p
	Non-AT (n = 30)	AT (n = 23)	
SpO_2, %	92 ± 4	96 ± 2	0.012
D-dimer, ng/mL	959 [522-1,792]	367 [237-586]	0.001
Lymphopenia	13 (43.3)	8 (34.8)	0.581
Hospitalization	22 (73.3)	10 (43.5)	0.028
Length of hospital stay, days	9 [7-18]	8 [3-12]	0.172
Invasive mechanical ventilation	4 (15.4)	1 (4.3)	0.114
ICU admission	6 (25.0)	3 (13.6)	0.464

AT: air trapping. [a]Values expressed as n (%), mean ± SD, or median [IQR].

DISCUSSION

In the present study, we found that AT was a common finding among patients that underwent CT scanning with additional expiratory acquisitions. There was a significant difference between patients with and without AT in SpO_2 at admission, D-dimer levels, and hospitalization that was confirmed in the univariate regression analysis.

Previous studies have reported prevalences of AT up to 64% among subjects with normal pulmonary function.[31] Such a prevalence is comparable to the one found in our study (43.4%). Likewise, only 17% of the included patients had comorbidities that could lead to AT, such as asthma and COPD.

Loss of peripheral pulmonary vessels has been reported to correlate with worse clinical outcomes in asthma, COPD, and pulmonary hypertension.[32-35] On CT, peripheral vascular pruning can be represented as lower volumes of BV5. Our study found that the proportion of BV5 within a lung lobe was inversely correlated with the volume of CT-based lobar opacities but not with lobar ventilation. Hence, severely constricted areas were still well ventilated. This finding corroborates the hypothesis of hypoxia with preserved lung compliance. It also supports Lins et al.,[26] who suggested that COVID-19 is an infectious mimic of idiopathic pulmonary hypertension, since both diseases may present microvascular coagulopathy and increased muscularization of pulmonary arteries.

Serum D-dimer is a marker of microvascular injury. In patients with COVID-19, higher D-dimer levels are related to worse outcomes, respiratory failure, and pulmonary embolism.[29,30,36] This could be related to higher activation of blood coagulation secondary to a systemic inflammatory response syndrome or

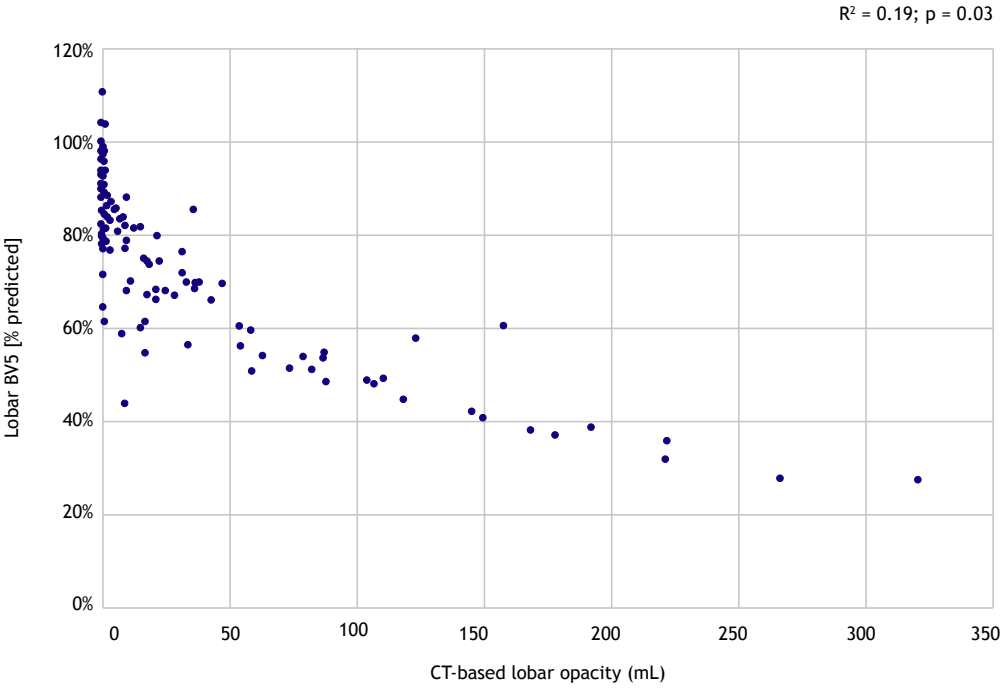

Figure 3. Mixed-effect model of blood volume in vessels with cross-sectional areas < 5 mm² (BV5) as a function of CT-based lobar opacity assessed per lobe.

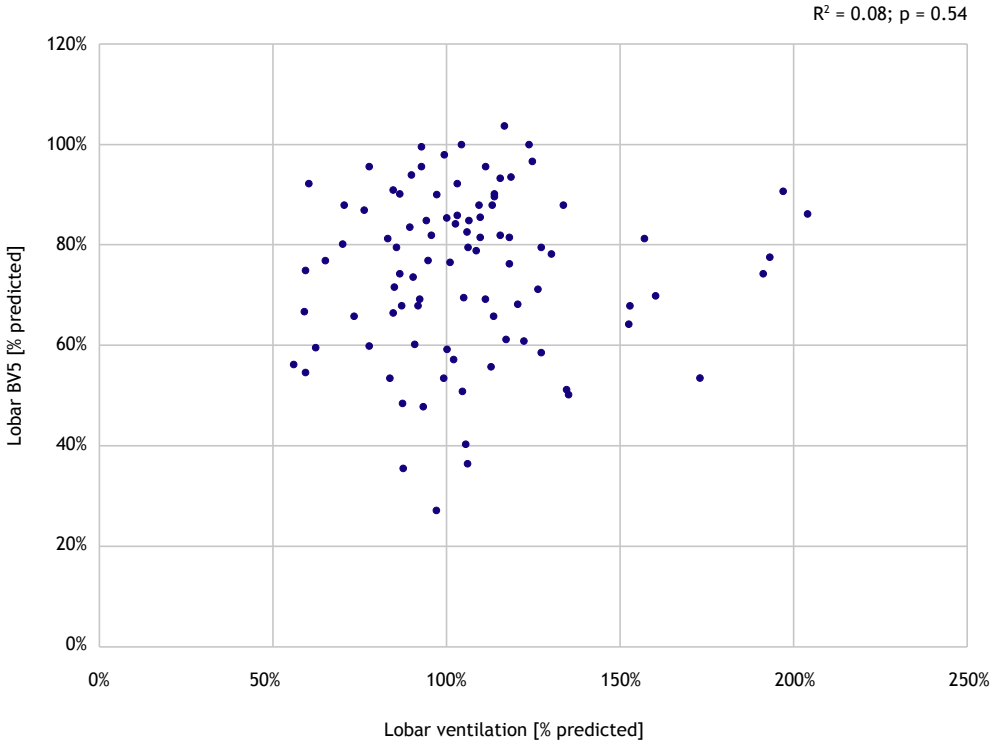

Figure 4. Mixed-effect model of blood volume in vessels with cross-sectional areas < 5 mm² (BV5) as a function of lobar ventilation assessed per lobe.

a direct consequence of the SARS-CoV-2 infection. Our data suggest that patients with AT have lower vascular damage and better outcomes. This could be related to the fact that patients with AT on chest CT have "more" airway disease than small vessel disease. Thus, we hypothesized that there might be two phenotypes of SARS-CoV-2 pneumonia. First, the small-vessel phenotype, characterized by severe

vasoconstriction and microvascular coagulopathy, which results in hypoxemia with preserved lung compliance. Second, the small-airway phenotype, characterized by small airway damage, represented on imaging by the presence of AT. These findings have to be further confirmed by larger studies, and it is still soon to make any recommendations on whether expiratory acquisitions should be included in CT scanning of all patients with COVID-19 pneumonia.

In a previous study of patients clinically diagnosed with COVID-19,[6] AT was more prevalent in those who had been admitted to the ICU or died. However, that study had several limitations that should be acknowledged, which might explain the difference between their results and ours. First, 34.4% of their sample had a negative SARS-CoV-2 RT-PCR test, which weakens the association between AT and worse outcomes because non-COVID-19 cases could have been included. In our study, all patients should have a positive SARS-CoV-2 RT-PCR result. Second, they included a small sample size of patients with poor outcomes.

Our study has some limitations. First, we acknowledge the preliminary nature of our findings, including the lack of a severe COVID-19 comparison group. Secondly, we could only include a small sample size, mainly due to concerns about the patients' exposure to additional radiation with no clear clinical benefits. These preliminary results might encourage further investigations with larger sample sizes to be carried out in the future.

In summary, we found that AT is a common finding in patients with COVID-19 who undergo expiratory CT acquisitions. The presence of AT may correlate with increased SpO_2 at admission, reduced serum D-dimer levels, and a decreased likelihood of hospitalization. Also, the volume of small pulmonary vessels may negatively correlate with CT opacities but not with lobar ventilation, suggesting that severely constricted areas are still well ventilated in COVID-19 patients.

AUTHOR CONTRIBUTIONS

BH: guarantor. RDC and BH: study design. RDC, NV, GW, TM, SPLA, MZ, JDB, BRL, EM, and BH: manuscript drafting. RDC, JDB, and BRL: data acquisition. RDC, NV, TM, SPLA, MZ, EM, BH GW, and BH: data interpretation. RDC, NV, GW, TM, SPLA, MZ, JDB, BRL, EM, and BH: critical review and approval of the final manuscript.

CONFLICT OF INTEREST

None declared.

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ORIGINAL ARTICLE

Prevalence of latent tuberculosis infection among patients with interstitial lung disease requiring immunosuppression

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Study carried out in the Complexo Hospital de Clínicas, Federal University of Paraná, Curitiba (PR), Brasil.

ABSTRACT

Objective: To characterize the prevalence of latent tuberculosis infection (LTBI) in patients with interstitial lung diseases (ILDs) requiring immunosuppression. Only 5 to 10% of individuals infected with *Mycobacterium tuberculosis* develop tuberculosis, and certain groups of patients have an increased risk of illness, such as the immunocompromised. Patients with ILDs are frequently treated with immunosuppressants and, therefore, might have a higher risk of developing the disease. **Methods:** Prospective study conducted at the ILD reference center of the Federal University of Paraná from January 2019 to December 2020. The screening of LTBI was performed with the use of the tuberculin skin test (TST). **Results:** The sample consisted of 88 patients, of whom 64.8% were women, with a mean age of 61.4 years. The most frequent diagnoses were autoimmune rheumatic disease ILD (38.6%) and hypersensitivity pneumonitis (35.2%). The most common immunosuppressant in use at the time of the TST was prednisone, either in combination with mycophenolate (19.3%) or alone (17.1%). The majority of participants had fibrotic lung disease, characterized by a reticular interstitial pattern on chest computed tomography (79.5%) and moderate to severe functional impairment (mean FVC 69.2%). A prevalence of LTBI of 9.1% (CI 95%, 2.1%-15.1%) was found, with a TST median of 13. **Conclusion:** Patients with ILD who are treated with immunosuppressants are not commonly screened for LTBI, despite being under a greater risk of progression to active disease. This study suggests the need for a more cautious approach to these patients.

Keywords: Latent tuberculosis infection; Interstitial lung diseases; Immunosuppression; Tuberculin test.

INTRODUCTION

Tuberculosis, a disease caused by *Mycobacterium tuberculosis* (Mtb), is a major public health issue and one of the leading global causes of death. In 2019, about 10 million cases of tuberculosis were reported and there were almost 1.5 million tuberculosis-related deaths worldwide.[1] The WHO lists Brazil as one of the priority countries regarding tuberculosis due to its high number of cases, as well as its high rate of HIV co-infection.[2] In 2019, approximately 74,000 cases of tuberculosis were reported[3] and there were close to 4,500 tuberculosis-related deaths countrywide,[4] with 2,209 cases[3] and 157 deaths[4] in the state of Paraná.

It is estimated that about a quarter of the world's population is infected with Mtb. However, most of the infected individuals do not develop active disease, exhibiting only a persistent immune response to Mtb antigens, a phenomenon known as latent tuberculosis infection (LTBI). Only 5 to 10% of infected individuals develop the illness during their lifetime and the risk of getting sick is higher for certain groups, such as the immunocompromised.[1] The diagnosis of LTBI is based on a response to Mtb antigens in the tuberculin skin test (TST) or an interferon-gamma release assay (IGRA).[5] Treating LTBI reduces the risk of progression to active disease by up to 90% and is one of the components of the WHO's End TB Strategy. Screening for LTBI should be considered for people with a higher risk of illness, such as people living with HIV,[6] as well as for patients initiating TNF inhibitors or systemic corticosteroids on a dose equal or equivalent to 15 mg of prednisone a day for more than 1 month.[5] Currently, there are no specific recommendations for patients on other immunosuppressants.

Interstitial lung diseases (ILDs) are a group of conditions characterized by inflammation and/or fibrosis of the lung tissue, whose treatment frequently includes the use of immunosuppressants, such as corticosteroids.[7] Hence, patients with ILD and LTBI under immunosuppression might have a higher risk of developing active tuberculosis. However, there are no studies investigating the prevalence

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of LTBI and the risk of progression to active disease in this population.

Given this gap in current knowledge, this study aimed to evaluate the prevalence of LTBI in patients with ILD about to initiate immunosuppressive therapy or already on one or more immunosuppressants using the TST. The participants were patients in follow-up at the ILD reference center of the Federal University of Paraná.

METHODS

This was a prospective study performed at the ILD reference center of the Federal University of Paraná from January 2019 to December 2020, approved by the Committee for Ethics in Research on Human Beings under the opinion 02458018.6.0000.0096.

We included patients who were 18 years old or older, had a diagnosis of ILD according to national and international guidelines,[8-11] were either about to initiate immunosuppressive therapy, or were already on one or more immunosuppressants, and agreed to participate in the study.

We excluded patients with silicosis, patients on TNF inhibitors, and people living with HIV, who are known to have a higher prevalence of tuberculosis, as well as people with a prior history of tuberculosis, who cannot undergo TST.

Participants were assessed for the presence of a BCG vaccination scar through direct visualization by one of the investigators. Those not previously tested underwent TST, performed using the Mantoux technique. Reactions equal to or larger than 5 millimeters were considered positive. Participants with a positive TST underwent clinical and radiological evaluation for active tuberculosis, and, when possible, sputum analysis. Those with no evidence of active disease were treated with a 6-month course of isoniazid. Demographic data, such as sex and age, and clinical data, such as type of ILD and comorbidities, were collected from medical records. Functional and radiological data were collected from spirometries and computed tomography (CT) scans performed at dates close to when TST was performed.

Data were stored and analyzed with the SPSS Statistics v. 22.0 software. The exploratory analysis included means, minimum values, maximum values, and standard deviations for quantitative variables, and frequencies and percentages for qualitative variables. Association analysis was performed through Fisher's Exact Test. Values of p under 0.05 were considered significant.

RESULTS

From January 2019 to December 2020, 474 patients were followed up at the ILD reference center, with 281 not meeting the inclusion criteria (53 had another diagnosis, 224 were not eligible for immunosuppression and 4 did not agree to participate) and 42 met the exclusion criteria (8 had silicosis, 24 were or had been on TNF inhibitors, 4 had HIV infection and 6 had a prior history of tuberculosis). Of the remaining 151 patients, 63 were not tested, either for failing to schedule the test or for not returning for the reading. Thus, 88 patients were included in the study. The study design, describing inclusion and exclusion criteria, is shown in Figure 1.

Participants (Table 1) were predominantly female (64.8%), with a mean age of 61.4 years old. The most frequent diagnoses were autoimmune rheumatic disease (AIRD)-ILD (38.6%) and hypersensitivity pneumonitis (35.2%). The most common immunosuppressant in use at the time of the TST was prednisone, either in combination with mycophenolate (19.3%) or alone

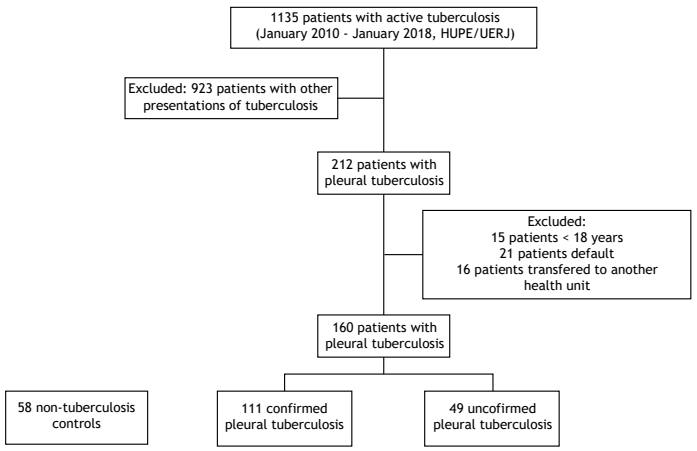

Figure 1. Included and excluded patients.

Table 1. Characteristics of the studied population.

Clinical-epidemiological characteristics [n = 88]	
Female sex, n (%)	57 (64.8)
Age in years, mean ± standard deviation	61.4 ± 12.5
Diabetes, n (%)	21 (23.9)
Current or previous smoking, n (%)	45 (51.5)
Presence of vaccination scar, n (%) [n = 70]	54 (77.1)
Type of ILD [n = 88]	
AIRD-ILD, n (%)	34 (38.6)
Hypersensitivity pneumonitis, n (%)	31 (35.2)
IPAF, n (%)	5 (5.7)
Sarcoidosis, n (%)	4 (4.5)
Undetermined, n (%)	11 (12.5)
Others*, n (%)	3 (3.4)
Type of AIRD [n = 34]	
Rheumatoid arthritis, n (%)	8 (23.5)
Systemic sclerosis, n (%)	7 (20.6)
Antisynthetase syndrome, n (%)	7 (20.6)
Sjögren's syndrome, n (%)	2 (5.9)
Dermatopolymyositis, n (%)	1 (2.9)
Others+, n (%)	9 (26.5)
Immunossuppressant(s) at the time of the TST [n = 88]	
None, n (%)	31 (35.2)
Prednisone and mycophenolate, n (%)	17 (19.3)
Prednisone, n (%)	15 (17.1)
Azathioprine, n (%)	4 (4.5)
Prednisone and azathioprine, n (%)	4 (4.5)
Prednisone and methotrexate, n (%)	4 (4.5)
Mycophenolate, n (%)	3 (3.5)
Cyclophosphamide, n (%)	2 (2.3)
Others, n (%)	8 (9.1)
Function characteristics [n = 82]	
Absolute FVC, mean ± standard deviation	2.09 ± 0.84
Relative FVC, mean ± standard deviation	69.2 ± 22.8
Tomographic findings [n = 88]	
Reticular interstitial pattern, n (%)	70 (79.5)
Ground-glass opacities, n (%)	54 (61.4)
Honeycombing, n (%)	12 (13.6)
Distribution of lesions on CT [n = 88]	
Peripheral, n (%)	48 (54.5)
Diffuse, n (%)	21 (23.9)
Peribronchovascular, n (%)	15 (17.0)

FVC = forced vital capacity; ILD = interstitial lung disease; AIRD = autoimmune rheumatic disease; IPAF = interstitial pneumonia with autoimmune features; CT = (chest) computed tomography. *: bronchiolitis obliterans [n = 1], hard metal lung disease [n = 1], pulmonary capillary hemangiomatosis [n = 1]; +: granulomatosis with polyangiitis [n = 3], eosinophilic granulomatosis with polyangiitis [n = 1], overlap of rheumatoid arthritis and Sjögren's syndrome [n = 1], overlap of rheumatoid arthritis and systemic lupus erythematosus [n = 1], overlap of systemic lupus erythematosus and Sjögren's syndrome [n = 1], overlap of systemic sclerosis and Sjögren's syndrome [n = 1], psoriatic arthritis [n = 1]; ++: patients with vasculitides or ILDs with airway-predominant disease, with no apparent tomographic findings; n = number of participants.

Table 1. Continued...

Not applicable++, n (%)	4 (4.5)
Predominance on CT [n = 88]	
Lower-lobe, n (%)	52 (59.1)
None, n (%)	22 (25.0)
Upper-lobe, n (%)	10 (11.4)
Not applicable++, n (%)	4 (4.5)

FVC = forced vital capacity; ILD = interstitial lung disease; AIRD = autoimmune rheumatic disease; IPAF = interstitial pneumonia with autoimmune features; CT = (chest) computed tomography. *: bronchiolitis obliterans [n = 1], hard metal lung disease [n = 1], pulmonary capillary hemangiomatosis [n = 1]; +: granulomatosis with polyangiitis [n = 3], eosinophilic granulomatosis with polyangiitis [n = 1], overlap of rheumatoid arthritis and Sjögren's syndrome [n = 1], overlap of rheumatoid arthritis and systemic lupus erythematosus [n = 1], overlap of systemic lupus erythematosus and Sjögren's syndrome [n = 1], overlap of systemic sclerosis and Sjögren's syndrome [n = 1], psoriatic arthritis [n = 1]; ++: patients with vasculitides or ILDs with airway-predominant disease, with no apparent tomographic findings; n = number of participants.

Table 2. Participants with a positive TST.

Participant	Sex	Age	BCG	Type of ILD	IS	FVC%	Fibrosis	TST
A. G. K.	F	75	yes	AIRD-ILD	PDN+MMF	64.8	no	15
D. S. A. N. L.	F	59	yes	AIRD-ILD	PDN	38.8	yes	7
F. M. F.	M	73	no	Undetermined	None	51.2	yes	14
G. A. G.	M	57	yes	Undetermined	None	68.4	yes	15
J. A. P.	M	68	no	AIRD-ILD	PDN+MMF	48.0	yes	10
J. M. R. C.	M	62	-	AIRD-ILD	PDN+MTX	37.4	yes	20
M. F. F. L.	F	68	yes	HP	None	64.0	yes	11
W. R. S.	M	65	-	Undetermined	None	-	yes	13

AIRD: autoimmune rheumatic disease; BCG: BCG vaccination scar; FVC%: relative FVC; HP: hypersensitivity pneumonitis; ILD: interstitial lung disease; IS: immunosuppressant(s); MMF: mycophenolate mofetil; MTX: methotrexate; PDN: prednisone; TST: tuberculin skin test; F = female, M = male.

Table 3. Associations between the studied variables and the TST.

	n	Negative TST	Positive TST	p
Diabetes, n (%)	21	19 (90.5)	2 (9.5)	1.000
Current or previous smoking, n (%)	45	38 (84.4)	7 (15.6)	0.059
Presence of vaccination scar, n (%)	54	50 (92.6)	4 (7.4)	0.614
TST while on immunosuppressant(s), n (%)	57	53 (93.0)	4 (7.0)	0.445
CT with reticular interstitial pattern, n (%)	70	63 (90.0)	7 (10.0)	1.000
CT with ground-glass opacities, n (%)	54	49 (90.7)	5 (9.3)	1.000
CT with honeycombing, n (%)	12	10 (83.3)	2 (16.7)	0.299

TST = tuberculin skin test; CT = (chest) computed tomography; n = number of participants, p = p value.

(17.1%). Most of the participants had moderate to severe functional impairment (mean FVC 69.2%). Some of them could not undergo spirometry (n = 6). The majority of participants had fibrotic lung disease, characterized by the presence of reticular pattern on chest CT (79.5%), though only some had extensive fibrosis with honeycombing (13.6%). The tomographic findings were predominantly of peripheral (54.5%) and lower-lobe (59.1%) distribution. Since the presence of a BCG vaccination scar was assessed by direct visualization, we were unable to assess participants evaluated remotely (n = 18).

We found 8 participants with a positive TST (Table 2), resulting in an LTBI prevalence of 9.1% (95% CI, 2.1%-15.1%). These individuals were mostly male (62.5%), older (mean age 65.9), and had moderate functional impairment (mean FVC 53.2%), with evidence of fibrotic lung disease (reticular pattern on chest CT in 87.5%). The TST median was 13 (minimum of 7, maximum of 20).

The frequency of positive reactions was slightly higher among individuals with a current or previous history of smoking, but this finding was not significant (p = 0.059). No significant association between prior BCG vaccination and positive reactions was found (p = 0.614). Though it is known that the use of immunosuppressants may lead to false-negative reactions, there was no association between immunosuppression and a negative TST (Table 3).

No active tuberculosis cases were observed among the participants during the study period.

DISCUSSION

The prevalence of LTBI found in the studied population (9.1%), though lower than that estimated for the world population (around 25%),[1] is similar to a study with people living with HIV, another at-risk population, in the state of Paraná (9.0%),[12] which might reflect the local prevalence of the infection. Data on LTBI in patients with ILDs are scarce in the literature. One study evaluated 62 patients with sarcoidosis and found a positive IGRA in 16 (25.8%) of them.[13] Another study evaluated 244 patients with coal workers' pneumoconiosis and found a positive IGRA in 162 (66.4%) of them.[14] There are no studies on LTBI in patients with other types of ILD. It is not possible to ascertain whether the prevalence found in our study reflects the true prevalence in this population. However, given that many of these patients have a higher risk of progressing to active disease due to immunosuppression, finding a prevalence of close to 10% in this group is extremely relevant, since identifying the infection and offering preventive treatment might diminish the risk of developing the illness.

Regarding risk factors for tuberculosis, smoking is one of the most well-established,[15] as well as diabetes.[16] In our study, neither smoking ($p = 0.059$) nor diabetes ($p = 1.000$) were significantly associated with a positive reaction. Since diabetes was only identified through data from medical records, underreported diagnoses might have interfered with this association.

Though BCG vaccination is frequently associated with false-positive reactions on the TST, implying low specificity for vaccinated individuals,[17] several authors affirm that vaccination in childhood has little impact on TST in adulthood.[18-20] However, a recent study found data suggesting otherwise.[21] It is recommended that people who were vaccinated late, that is, after the first few years of life, be screened with IGRAs.[22] In Brazil, BCG vaccination, which is available free of charge in the Brazilian public health system, is universal and administered on the first few days of life, making it unlikely to interfere with TST's results in adults. Corroborating these data, we did not find an association between the presence of BCG vaccination scar and positive TST ($p = 0.614$).

Patients with AIRDs have a higher rate of false-negative TSTs.[23] Furthermore, the chronic use of prednisone, which is one of the most prescribed corticosteroids for treating these diseases, negatively impacts the response to PPD,[21,24] especially in doses higher than 15 mg a day.[25] However, the effect of other immunosuppressants on TST and IGRAs is scarcely described in the literature and there is no consensus on the best method for diagnosing LTBI in immunocompromised patients,[26] although IGRAs seem to have higher sensibility and specificity than TST in this population.[23,24] Some authors suggest that TST and an IGRA should be performed concomitantly.[26] Although the majority (64.8%) of participants in this study underwent TST when already on one or more immunosuppressants, the association between being tested while immunosuppressed and a negative reaction was not statistically significant ($p = 0.445$). It is suggested to screen these patients before starting treatment, if possible.[22] Currently, the only available method for LTBI detection in the Brazilian public health system is the TST.[20] The incorporation of IGRAs into Brazil's public health system was recently approved, but only for people living with HIV, for children who are tuberculosis contacts, and for patients receiving hematological transplantation.[27]

Patients with ILDs have a higher risk of tuberculosis,[28,29] especially those with silicosis,[30] as well as patients with AIRDs,[31] in particular when associated with ILD.[32] The use of immunosuppressants such as corticosteroids,[33-35] azathioprine,[36] cyclophosphamide,[31] and TNF inhibitors[35] is also, by itself, associated with a higher risk of tuberculosis. The diagnosis of tuberculosis in patients with ILDs is more difficult due to parenchymal abnormalities related to the interstitial disease.[30] The participants of this study had several of those risk factors, however, none developed active tuberculosis during the study period.

In a study with another at-risk population, renal transplantation recipients, the participants with an initial negative TST were tested a second time to evaluate immune response reactivation,[37] a strategy recommended by some authors for immunocompromised patients.[22] In Brazil, this is usually performed in a periodic screening of health care workers[38] and was not performed in this study. However, in case of contact with an active tuberculosis patient after the initial investigation, the test should be repeated.[39]

This was one of the first studies to screen LTBI on patients with different ILDs, an at-risk population that is little addressed. The choice to screen only patients requiring immunosuppression prevents the generalization of the findings for all patients with ILD; however, it is justified by the fact that these individuals are the ones with a higher risk of developing tuberculosis. Since the screening was performed with TST, which can be more affected by immunosuppression, the prevalence found in this study might have been underestimated. Unfortunately, IGRAs are not currently offered by the Brazilian public health system, and though they are soon to be included, they will not be available for patients on immunosuppressants. There might have also been confounding biases related to other variables associated with the risk of tuberculosis, such as family income.

Early detection of LTBI is of vital importance, to allow for prompt indication of preventive treatment, as recommended by the WHO's End TB Strategy. Patients with ILD who are treated with immunosuppressants

are not commonly screened for this infection, despite being under a greater risk of progression to active disease. This study showed a prevalence of LTBI of 9.1% in a sample of such individuals, suggesting the need for a more cautious approach to these patients. Further research is needed to establish a more thorough definition of the role of LTBI screening in this population.

AUTHOR CONTRIBUTIONS

Both authors actively participated in all stages of the development of this manuscript.

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ORIGINAL ARTICLE

Hyporexia and cellular/biochemical characteristics of pleural fluid as predictive variables on a model for pleural tuberculosis diagnosis

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ABSTRACT

Objectives: Pleural tuberculosis (PlTB) diagnosis is a challenge due to its paucibacillary nature and to the need of invasive procedures. This study aimed to identify easily available variables and build a predictive model for PlTB diagnosis which may allow earlier and affordable alternative strategy to be used in basic health care units. **Methods:** An observational cross-sectional study compared PlTB and non-TB patients followed at a tertiary Brazilian hospital between 2010 and 2018. Unconditional logistic regression analysis was performed and a Decision Tree Classifier (DTC) model was validated and applied in additional PlTB patients with empiric diagnosis. The accuracy (Acc), sensitivity (Se), specificity (Sp), positive and negative predictive values were calculated. **Results:** From 1,135 TB patients, 160 were considered for analysis (111 confirmed PlTB and 49 unconfirmed PlTB). Indeed, 58 non-TB patients were enrolled as controls. Hyporexia [adjusted *odds ratio* (aOR) 27.39 (95% CI 6.26 – 119.89)] and cellular/biochemical characteristics on pleural fluid (PF) (polimorphonuclear in two categories: 3-14% aOR 26.22, 95% CI 7.11 – 96.68 and < 3% aOR 28.67, 95% CI 5.51 – 149.25; and protein ≥ 5g/dL aOR 7.24, 95% CI 3.07 – 17.11) were associated with higher risk for TB. The DTC constructed using these variables showed Acc=87.6%, Se=89.2%, Sp=84.5% for PlTB diagnosis and was successfully applied in unconfirmed PlTB patients. **Conclusion:** The DTC model showed an excellent performance for PlTB diagnosis and can be considered as an alternative diagnostic strategy by using clinical patterns in association with PF cellular/biochemical characteristics, which were affordable and easily performed in basic health care units.

Keywords: Pleural tuberculosis; Diagnosis; Decision tree classifier.

INTRODUCTION

Tuberculosis (TB) is a major public health problem worldwide.[1] Pleural tuberculosis (PlTB) is the commonest extrapulmonary TB presentation, representing 42% of all extrapulmonary cases.[2,3] In addition to its frequency, PlTB diagnosis can be a challenge due to the paucibacillary nature of patients' biological samples and to the need for invasive procedures.[4]

The Ziehl Neelsen (ZN) stain and the mycobacterial culture of pleural fluid (PF) and/or pleural tissue are the gold standard methods for tuberculous pleural effusion diagnosis, but their success rates are relatively poor.[5] The identification of granuloma in histopathological examination of the pleural tissue is also considered as diagnostic criteria.[6] However, besides being invasive, the pleural biopsy is operator-dependent, relatively expensive, may be limited by clinical contraindications and is associated with complications.[7-9] Adenosine deaminase (ADA) measurement in pleural fluid can provide a putative diagnosis of PlTB in high prevalence settings, considering that high ADA levels can also be observed in other infectious, inflammatory or malignant diseases.[6,10,11] In addition, the evaluation of biomarkers on pleural effusion configures an alternative for TB diagnosis.[12-14] Recently, our research group have shown that interferon-gamma (IFN-γ) was an excellent rule-in and rule-out test compared to other two biomarkers (IFN-γ inducible protein 10 kD and ADA) and that the combination of IFN-γ and ADA, in a reviewed cut-off point, showed to be particularly useful to PlTB confirmation.[15] However, these methods can be available only at reference centers, whereas basic health care units cannot count on them.

In order to surpass the limitations stated forementioned, which compels the practice of a not uncommon empiric diagnosis based on clinical and radiological criteria, as

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previously published,[16-19] our research group proposed the application of conventional biochemical and cellular parameters of pleural fluid, which lacks specificity when isolated considered,[4] but when in combination with each-other or with clinical features could discriminate between tuberculous pleural effusion or not. For this purpose, a predictive model for PlTB diagnosis was validated by us based on hyporexia, polymorphonuclear cells (PMN cells) and protein levels on pleural fluid, which was applied on empiric PlTB cases to perform an internal validation.

METHODS

Study design

A cross-sectional study was conducted based on medical records of patients with pleural effusion under investigation attended between January 2010 and January 2018 at Pedro Ernesto University Hospital from Rio de Janeiro State University (*Hospital Universitário Pedro Ernesto/Universidade do Estado do Rio de Janeiro* (HUPE/UERJ)), in the city of Rio de Janeiro (RJ), Brazil. Patients at least 18 years and who attended the Outpatient Clinic of Tuberculosis of HUPE with PlTB diagnosis were included. Those patients whose TB treatment outcomes were unknown (loss of follow-up) were excluded. Patients with non-TB pleural effusion were considered controls and were drawn from the Outpatient Clinic of Pleural Diseases of the same hospital.

The ethics committee approved the study of the institution under protocol #2612/2010.

Diagnostic criteria

PlTB was stratified as follows: i) *Confirmed PlTB (C-PlTB)*: ZN stain positive or isolation of *Mycobacterium tuberculosis* on the respiratory specimen, pleural fluid or pleural tissue, or identification of granuloma on histopathological analysis, or patients with clinical manifestations of PlTB and a lymphocytic and exudative pleural effusion with ADA dosage above 40 IU/L that fully recover after at least six months of antituberculosis treatment; ii) *Unconfirmed PlTB (UC-PlTB)*: cases with clinical manifestations of PlTB that did not fulfill the C-PlTB and fully recovered after at least six months of antituberculosis treatment.

Non-tuberculosis (Non-TB): patients were defined as those with pleural or pleuropulmonary diseases other than TB in which the diagnose was concluded based on clinical, laboratory, radiological, microbiological, or cytopathological/histopathological features.

Data collection

The medical records of all patients were reviewed in order to evaluate physical, clinical, and demographic information, medical history, and laboratory data. According to subjective reported presence and duration, signs and symptoms such as cough, fever, chest pain, dyspnea, night sweats, hyporexia, and weight loss were included. The Human Immunodeficiency Virus (HIV) status and other comorbidities were also recorded. Data on PF routine diagnostic tests, including a chemistry panel, total and differential cell count, ADA measurement, cytopathology, and microbiological analysis (ZN and solid media culture) were registered. In those cases where pleural biopsy with Cope's needle was performed, histopathology analysis, ZN stain, and mycobacterial culture results were registered.

Statistical analysis

For statistical analysis, categorical and continuous data were presented in frequency (percentage) and median and interquartile range (IQR), respectively. Fisher Exact Test and T-test were used for group comparisons. Simple and multiple unconditional logistic regression analyses were performed, and *odds ratios* (OR) and adjusted OR (aOR) with its 95% Confidence Interval (95% CI) were calculated. The level of significance used was 0.05.

Decision Trees Classifier (DTC) was selected as a predictive model because it allows a straightforward and easy interpretation of the rules, and it was built with an implementation of the Quinlan's C4.5 algorithm available in the packages 'rpart' version 4.1-10 for the open-source software R version 3.3.1.[20] The DTC was built with cases of C-PlTB and non-TB in a subset of nine [viral hepatitis, fever, dyspnea, hyporexia, weight loss, percentage of PMN cells, percentage of mononuclear cells (MN cells), protein and albumin on pleural fluid] of 22 variables pre-selected (age, diabetes mellitus, renal failure, cardiac failure, cancer, previous transplant, viral hepatitis, autoimmune disease, immunosuppressive treatment, fever, cough, chest pain, dyspnea, weight loss, hyporexia, night sweating, chest X-ray, percentage of PMN cells, percentage of MN cells, protein and albumin on pleural fluid) by successively eliminating at least 20% important variables (with importance as returned from random forest) using the out-of-bag error as minimization criterion from random forest (number of trees equal to 1,000) classifiers implemented in the R package 'varSelRF' version 0.7-5. The fitted tree was pruned to minimize the expected 10-fold cross-validation prediction accuracy. Pruning included a complexity parameter of 0.25, informing the algorithm that any split that does not improve the fit by 25% will likely be pruned off by 10-fold cross-validation. Hence, the algorithm needs not to pursue it. In addition, the performance of the built DTC was estimated by its leave-one-out cross-validation accuracy (Acc), sensitivity (Se), specificity (Sp), Positive Predictive Value (PPV) and Negative Predictive Value (NPV), and false-positive and negative ratios with 95% CI and area under the Receiver Operating Characteristics (ROC) and the Area Under the Curve (AUC).

RESULTS

From January 2010 to January 2018, 1,135 patients were diagnosed with active TB at HUPE/UERJ. Of these, 397 had an extrapulmonary presentation of TB, and

212 (53%) had PlTB, being 160 patients considered for analysis. The other 52 patients were excluded according to the exclusion criteria. The 58 non-TB cases included 34 malignancies (16 adenocarcinomas, four lymphomas, two carcinomas, one spindle epithelial, and 11 non-specified cell types), 11 renal/cardiac failures, four empyema, two systemic lupus erythematosus, one hepatic disease, one chylothorax and five cases of undefined pleural effusion (Figure 1).

The sociodemographic and clinical characteristics from all patients are shown in Table 1. PlTB patients were younger than non-TB and were less likely to present other comorbidities such as cancer, cardiac failure, viral hepatitis, and previous transplant. In addition, fever, chest pain, hyporexia, weight loss, and night sweats were more frequently observed in PlTB cases and higher levels of ADA measurement, MN cells frequency, total protein, and albumin levels, and reduced PMN cells frequency. Confirmed and unconfirmed PlTB were homogeneous unless for age (Table 1). Compared to non-TB, younger patients presented a higher risk for TB diagnosis (30 – 44 years: OR 4.6, 95% CI 1.63 – 12.99; 18 – 29 years: OR 6.16, 95% CI 1.79 – 21.16). This association persisted in multiple unconditional logistic analyses adjusting for gender, comorbidities, signs/symptoms, radiological appearance and cytological, and biochemical pleural fluid analyses (Table 2).

Fever, chest pain, weight loss, and hyporexia were the signs/symptoms considered risk factors for confirmed PlTB. Of these, hyporexia showed the highest aOR [27.39 (95% CI 6.26 – 119.89)]. Cytological characteristics on PF showed a reverse behavior once a reduced frequency of PMN cells has exhibited a greater chance of being diagnosed with PlTB (PMN cells 3 – 14%: aOR 8.78, 95% CI 3.35-22.97 and PMN cells < 3%: aOR 28.67, 95% CI 5.51-149.25) and the higher the percentage range of MN cells the greater the chance of PlTB diagnosis (MN cells 85 – 97.5%: aOR 9.04, 95% CI 3.34 – 24.42 and MN cells ≥ 97.5%: aOR 33.67, 95% CI 6.26 – 181.01). Protein levels above 5g/dL were also identified as a risk factor for the infectious disease (aOR 7.24, 95% CI 3.07 – 17.11) (Table 2).

From twenty-two pre-selected variables, our model chose nine to DTC building, which has included viral hepatitis, fever, dyspnea, hyporexia, weight loss, percentage of PMN cells, percentage of MN cells, protein, and albumin on PF. By the end of the analysis, the pruned DTC used only three predictive variables for PlTB discrimination: PMN cells and protein in PF and hyporexia.

Figure 2 depicts the DTC analysis built to discriminate confirmed PlTB from non-TB patients. Based on three variables' results (presence of hyporexia, PMN cells levels, and protein levels, both on PF), in 21 cases (12 PlTB and nine non-TB), the diagnostic classification of the DTC was mistaken. In these cases, the results of microbiological tests, pleural tissue biopsy, and ADA dosage were of extreme importance for differential diagnosis.

With an area under the ROC curve of 88.7%, the DTC proved to be 90.23% accurate with a Se of 92.47% (95% CI 88.99-95.95%) and a Sp of 87.6% (95% CI

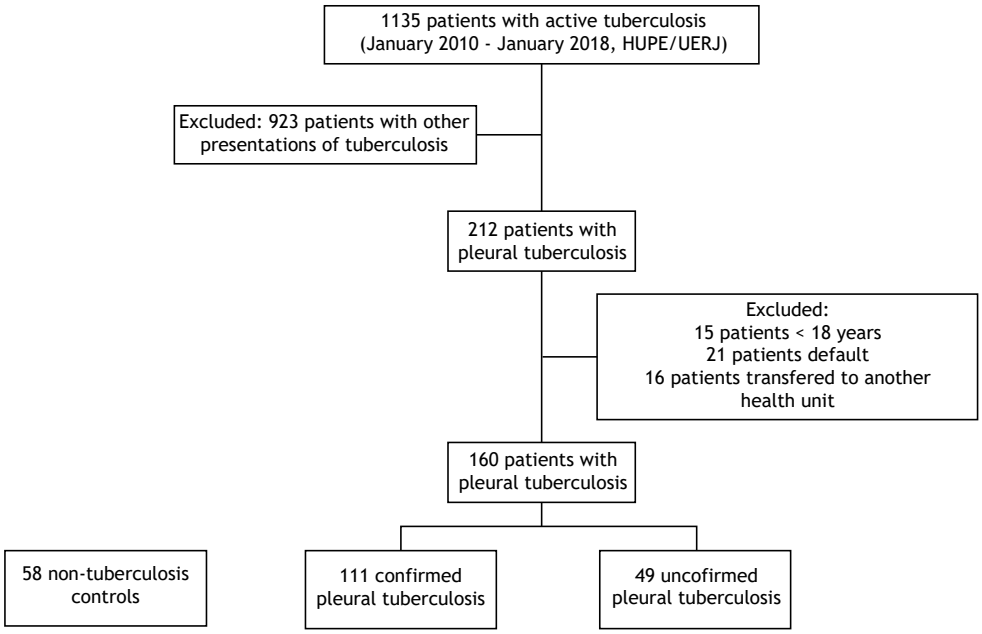

Figure 1. Flowchart of the study design. Pleural tuberculosis according to the eligibility criteria and non-TB cases considered as controls.

Table 1. Baseline characteristics of the study population. Univariate analysis was performed comparing PITB and non-TB groups. Also confirmed and unconfirmed PITB groups were compared.

	Non-TB	PITB		*p*	
		Confirmed	Unconfirmed		
	(58) N (%)	(111) N (%)	(49) N (%)	NTB *vs* TB	C-PITB *vs* NC-PITB
Gender, %					
Male	32 (55.2)	64 (57.7)	30 (61.2)		
Female	26 (44.8)	47 (42.3)	19 (38.8)	0.64	0.73
Age, years					
Median (IQR)	62 (49-73)	43 (30-53)	32 (25-48)	< 0.0001	0.004
HIV status, %					
Positive	2 (3.4)	1 (0.9)	3 (6.1)		
Negative	37 (63.8)	66 (59.5)	29 (59.2)		
Refuse testing	-	2 (1.8)	1 (2.0)	0.68	0.26
Unknown	19 (32.8)	42 (37.8)	16 (32.7)		
Previous comorbidities, %					
Arterial Hypertension	17 (29.3)	25 (22.5)	6 (12.2)	0.27	0.28
Diabetes mellitus	8 (13.8)	9 (8.1)	2 (4.1)	0.29	0.27
Chronic Renal Failure	4 (6.9)	4 (3.6)	2 (4.1)	0.59	0.83
Cancer	10 (17.2)	2 (1.8)	1 (2.0)	< 0.0001	0.83
Cardiac Failure	7 (12.1)	-	1 (2.0)	< 0.0001	0.26
COPD / Asthma	2 (3.4)	1 (0.9)	-	0.27	0.67
Previous transplant	4 (6.9)	-	1 (2.0)	0.02	0.26
Autoimmune disease	2 (3.4)	6 (5.4)	3 (6.1)	0.79	0.82
Viral hepatitis	5 (8.6)	-	1 (2.0)	0.006	0.26
Immunosuppressive therapy	5 (8.6)	5 (4.5)	6 (12.2)	0.91	0.07
Signs/symptoms, %					
Fever	13 (22.4)	83 (74.8)	36 (73.5)	< 0.0001	0.63
Cough	29 (50)	65 (58.6)	30 (61.2)	0.41	0.54
Chest pain	25 (43.1)	71 (64.0)	26 (53.1)	0.04	0.41
Dyspnea	43 (74.1)	66 (59.5)	28 (57.1)	0.09	0.47
Hyporexia	2 (3.4)	57 (51.4)	22 (44.9)	< 0.0001	0.56
Weight loss	20 (34.5)	69 (62.2)	35 (71.4)	< 0.0001	0.13
Night sweats	10 (17.2)	58 (52.3)	22 (44.9)	< 0.0001	0.53
Duration of signs/symptoms, Days					
Median (IQR)	75 (30-180)	30 (20-60)	30 (17-90)	0.001	0.94
PF Characteristics					
Median (IQR)					
Total cell count, mm^3	1135 (500-2600)	2305 (795-3875)	2435 (1300-3800)	0.72	0.65
Mononuclear (MN), %	78 (56-90)	95 (90-98)	85 (70-95)	< 0.0001	0.44
Polimorphonuclear (PMN), %	20 (10-41)	5 (2-10)	15 (5-30)	< 0.0001	0.43
Total protein, g/dL	4.2 (3.6-5.3)	5.5 (5.0-5.9)	5.5 (5.1-6.3)	< 0.0001	0.44
Albumin, g/dL	2.6 (2.0-3.1)	2.9 (2.6-3.2)	2.9 (2.9-3.3)	0.006	0.19
LDH, UI/L	210 (137-697)	411 (256-780)	513 (324-727)	0.25	0.73
ADA, IU/L					
Median (IQR)	39 (24.5-74.5)	71.5 (46.5-93.2)	-	0.008	-
Chest Xray					
UPE	41 (70.7)	73 (65.8)	32 (65.3)		
BPE	9 (15.5)	3 (2.7)	1 (2.0)		
UPE + Pulmonary infiltrates	6 (10.3)	28 (25.2)	15 (30.6)	0.001	0.78
BPE + Pulmonary infiltrates	1 (1.7)	1 (0.9)	-		
Missing data	1 (1.7)	6 (5.4)	1 (2.0)		

Table 2. Analysis of clinical, radiographic and laboratorial features in multiple unconditional logistic regression models for pleural tuberculosis.

Features	*Odds Ratio* (95%CI)	Adjusted *Odds Ratio* (95% CI)	*p*
Gender			
Male	1	1	
Female	0.9 (0.48-1.71)	1.09 (0.54-2.21)	0.80
Age			
60 - 74 years	1	1	
≥ 75 years	0.29 (0.08-1.06)	0.2 (0.05-0.82)	0.02
45 - 59 years	1.66 (0.68-4.04)	1.25 (0.47-3.34)	0.65
30 - 44 years	4.6 (1.63-12.99)	5.02 (1.53-16.54)	0.008
18 - 29 years	6.16 (1.79-21.16)	6.31 (1.54-25.93)	0.01
Comorbidities			
Diabetes Mellitus	0.55 (0.2-1.5)	0.53 (0.18-1.56)	0.25
Cancer	0.09 (0.02-0.41)	0.07 (0.01-0.36)	0.001
Autoimune disease	1.59 (0.31-8.12)	1.39 (0.27-7.23)	0.70
Renal failure	0.5 (0.12-2.08)	0.52 (0.11-2.5)	0.41
Immunossuppressive therapy	0.5 (0.14-1.79)	0.4 (0.11-1.47)	0.16
Fever	11.66 (5.37-25.3)	10.43 (4.62-23.58)	< 0.0001
Cough	0.7 (0.36-1.36)	0.67 (0.32-1.37)	0.27
Chest pain	2.51 (1.28-4.9)	3.32 (1.57-6.99)	0.002
Dyspnea	2.23 (1.05-4.71)	2.03 (0.89-4.61)	0.09
Weight loss	3.18 (1.61-6.25)	3.13 (1.51-6.49)	0.002
Hyporexia	30.83 (7.14-133.07)	27.39 (6.26-119.89)	< 0.0001
Night sweats	5.44 (2.48-11.92)	7.07 (2.87-17.43)	< 0.0001
Polimorphonuclear (PMN) % in PF			
≥ 15%	1	1	
3 - 14%	7.31 (3.1-17.2)	8.78 (3.35-22.97)	< 0.0001
< 3%	29.23 (6-142.5)	28.67 (5.51-149.25)	0.0001
Missing data	55.54 (11.73-262.99)	58.45 (11.34-301.32)	< 0.0001
Mononuclear (MN) % in PF			
< 85%	1	1	
85 - 97.4%	7.31 (3.02-17.67)	9.04 (3.34-24.42)	< 0.0001
≥ 97.5%	34 (6.76-171.04)	33.67 (6.26-181.01)	< 0.0001
Missing data	64.6 (13.21-315.85)	66.61 (12.65-350.84)	< 0.0001
Total protein in PF (g/dL)			
< 5.0	1	1	
≥ 5.0	6.32 (2.91-13.7)	7.24 (3.07-17.11)	< 0.0001
Missing data	86.32 (11.03-675.53)	69.69 (8.76-554.25)	0.0001

Table 3. Performance characteristics of the decision tree analysis for confirmed and unconfirmed PlTB cases.

	Confirmed Pleural Tuberculosis (95% CI)	Unconfirmed Pleural Tuberculosis (95% CI)
Accuracy	87.6 (84.4 - 90.7)	88.8 (84.8 - 92.8)
Sensitivity	89.2 (85.5 - 92.8)	93.9 (89.4 - 98.4)
Specificity	84.5 (78.5 - 90.4)	84.5 (78.2 - 90.7)
Positive Predictive Value (PPV)	91.7 (88.4 - 95)	83.6 (77.1 - 90.2)
Negative Predictive Value (NPV)	80.3 (74 - 86.7)	94.2 (90 - 98.5)
Area under ROC curve	88.7	90.1

CI: Confidence Interval; ROC: Receiver Operating Characteristic.

84.4-90.7) (Table 3). The performance of the DTC applied for unconfirmed PlTB classification to perform an internal validation was 88.8% accurate, 93.9% sensitive, and 84.5% specific (Table 3). Noteworthy, almost 90% of the cases would be correctly treated by applying the DTC as a diagnostic tool and using laboratory and clinical variables, which can be afforded and performed in a basic care health system.

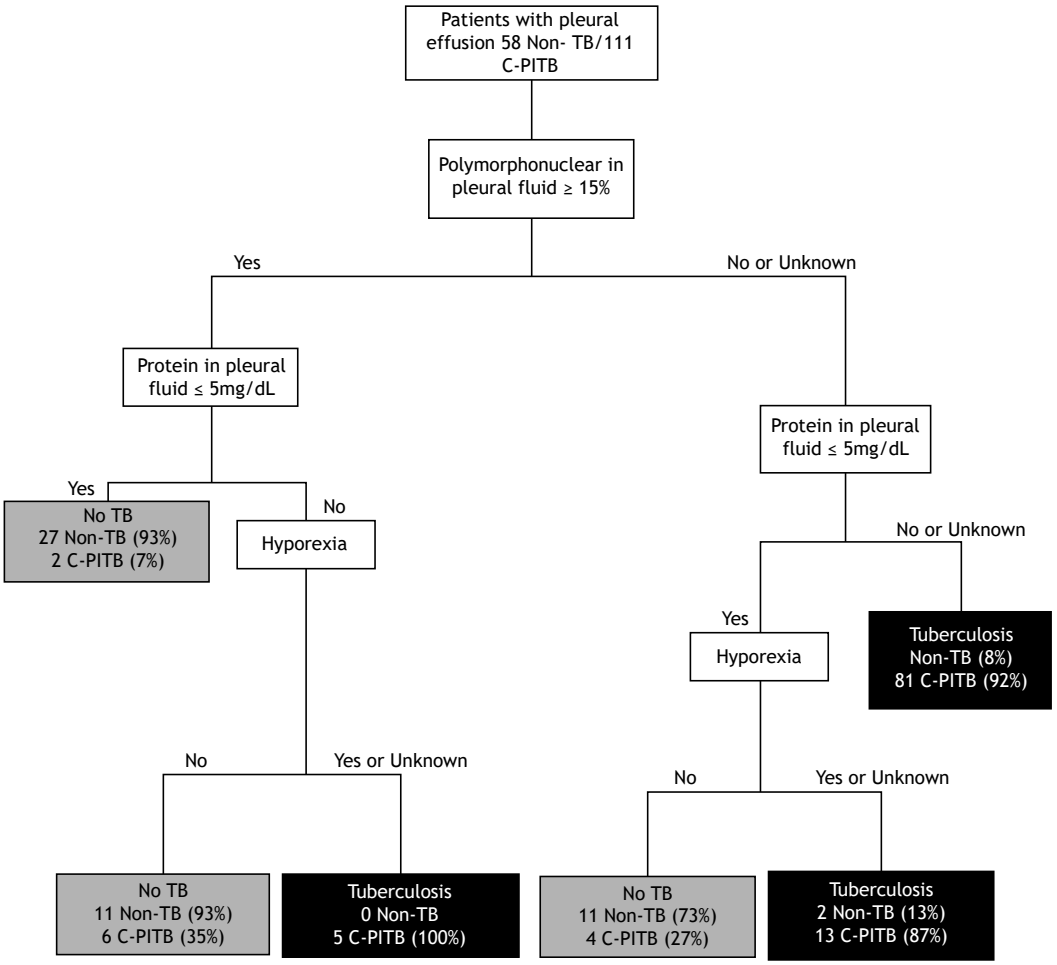

Figure 2. Discrimination between confirmed pleural tuberculosis and non-TB cases according to the decision tree classifier. Graphical representation of a decision tree classifier where the terminal branches filled gray were classified as non-TB and filled black terminal branches were classified as TB. The numbers inside the branches are the original diagnosis and their false positive results.

DISCUSSION

The challenge of differential diagnosis of tuberculous pleural effusion among a range of etiologies encouraged a great number of studies that employed efforts to develop tools for differentiating PlTB from other entities using scoring systems, DTC, and artificial intelligence neural networks.[21-27] Our DTC behaved as well as them, with excellent accuracy. Besides that, we consider our model, with only three predictive variables, and applied to a broad spectrum of patients, easier to use in clinical practice. Moreover, the DTC presented here was validated using an independent sample of patients, leading to almost 90% of cases being correctly classified.

In this study, a DTC model was built with excellent accuracy for discriminating PlTB in an area with a high incidence of TB. The performance of the DTC was similar when either applied on C-PlTB or unconfirmed PlTB cases, with sensitivity higher than 89%, for both groups. Noteworthy, the sensitivity of the proposed DTC model is much higher than either microbiological or histopathological analyses of pleural specimens for TB diagnosis.[5,28] Moreover, the decision tree presented here can also be considered an alternative to ADA dosage, given the various performances of ADA for PlTB diagnosis[11,29,30] and the lack of availability of the test in some scenarios. In addition, physicians would be more confident to initiate anti TB therapy in cases empirically diagnosed using this DTC in scenarios without other diagnostic methods available.

To the best of our knowledge, there are only two studies published that have proposed DTCs that could be used in clinical practice.[26,27] In 2008, a similar model was used to discriminate between tuberculous and malignant pleural effusions based on four parameters: age > 35 years, ADA > 38 IU/L, temperature, and DHL on pleural fluid.[26] This model was 92.2% sensitive and 98.3% specific, and the validation using an

independent sample showed a sensitivity of 85% and a specificity of 97%. Even though TB and cancer are the two most frequent causes of exudative pleural effusions,[31] other etiologies must be discarded during pleural diseases diagnosis. In our study, among the 58 non-TB patients, 41.4% had other etiologies than cancer. Valdés *et al.*[27] proposed a DTC to classify PF as tuberculous or non-tuberculous. The first proposed model included pleural fluid lymphocyte count > 31.5% and ADA > 35 IU/L with a mean accuracy of 99%. Then, to be applied in health care settings without the availability of ADA, a second model, including PF lymphocyte count > 31.5%, fever, and cough, showed to be less accurate than the first one. Only patients under 40 years old were included in that study, whereas our study population had patients from 18 to 89 years and more than 50% were older than 45.

Our statistical model identified PMN cells percentage instead of MN cells included in the DTC, although lymphocytic pleural effusions are most typical among tuberculous pleural fluid analyses.[9] However, in many cases, PMN rather than MN are the predominant cell type in the pleural effusion of TB cases, especially during the earlier phases of the pleural inflammatory process, as shown by Jeon *et al.*.[9] According to Lyadova,[32] neutrophils are probably the least understood among immune cell populations, playing a dual role during TB pathophysiology. It is already known that these cells participate in the acquired immunity and granuloma formation and may kill Mtb. Notwithstanding this characteristic, at the same time, neutrophils could support mycobacterial growth and have been implicated in the transition from infection to active TB, mediate tissue destruction, disease severity, and progression.[32] However, recently published studies[33-36] showed that TB disease alters the neutrophil population, leading to the accumulation of heterogeneous subsets of immature and activated dysfunctional cells with a decline in true neutrophils.

Based on the observations in the present study, it would be relevant not to reduce the importance of lymphocytes but to bring out the role of neutrophils in diagnosing TB. In our study, 13 confirmed PlTB cases (13/111; 12%) had a frequency of neutrophils higher than 15%. Lin *et al.*[37] showed that among 354 tuberculous pleural effusion, 39 (11%) presented a PMN predominance in the pleural fluid. Interestingly, these patients presented a high mortality rate and a high risk for transmission.

Moreover, in our study, the addition of total protein levels of pleural fluid on the DTC contributed to correct discrimination of PlTB, considering that according to Choi *et al.*,[38] PlTB with predominant PMN in PF showed a more intense inflammatory response with higher levels of total protein and albumin. As already indicated, since Light's criteria, an exudative pleural effusion is characteristic of inflammatory pleural diseases, including TB.[39] Our findings can be compared to those of Samanta *et al.*[30] that showed higher levels of total protein and albumin on the pleural effusion of TB patients than in lung cancer patients.

All of the most typical signs and symptoms of PlTB and other prevalent pleural diseases, namely fever, cough, chest pain, dyspnea, hyporexia, weight loss, and night sweat, were considered in the training of the DTC here proposed. Among them, just hyporexia was preserved in the final model. This symptom also showed the highest aOR for PlTB in the multiple unconditional logistic regression and was included in the DTC model (Figure 2). However, a literature search did not find any other publications that identified hyporexia as an essential clinical presentation for PlTB diagnosis and other classical signs/symptoms.

There were some limitations in our study, most of which were attributable to the use of the information from a retrospective cohort. We were dependent on documentation and interpretation of data in the medical records. However, data were reported in medical records according to standard questionnaires by the attending physicians of a university institution, where physicians, nurses, and students were trained to document data that could be used for research. In addition, many missing data regarding biochemical and cellular features of PF (40 cases) were identified. Besides that, the absence of data, which can happen in routine, was included in the DTC. Maybe, with more results available, our model could present a higher precision. Also, most non-TB cases had cancer (58.6%), with a minority of cases composed of less frequent pleural conditions such as empyema and autoimmune diseases. Our University Hospital is not a reference center for HIV patients, and this could explain the few cases of co-infected patients. Also, although some readers understand that hyporexia and protein levels in the DTC can be considered an incorporation bias, we comprehend that these isolated variables were not used to confirm or exclude TB diagnosis. Even if this bias could be found, it would not invalidate the results and only overestimate the DTC accuracy. Finally, but not a limitation of our study, but of the DTC model proposed itself, TB prevalence can affect the performance of this model in different scenarios and should be used with caution in low-prevalence settings.

Recently, clinical pathways have been used to optimize patient care for specific clinical conditions. Mummadi and Hahn[40] published their experience applying what they called the "pleural pathway" in an institution in the United States of America (USA). They concluded that this "pleural pathway" and a centralized pleural service are associated with reducing case charges, inpatient admissions, and length of stay for pleural conditions. We believe that the DTC proposed in this article could be included as a screening test to organize steps of diagnosis without neglecting the possibility of less frequent presentations of tuberculous pleural effusion.

The DTC based on pleural fluid cellular and biochemical characteristics does not replace microbiological tests for TB. Its disadvantage is associated with the failure to provide microbiological confirmation and antituberculosis sensitivity tests. Thus, we still advocate that pleural

fluid and the respiratory specimen should also be obtained whenever possible. Additionally, pathological analysis of pleural fluid and fragment may be indicated for cases with high suspicion of cancer.[26] However, the variables selected by this model can be readily available in primary health care units, which cannot count on ADA's dosage for PlTB diagnosis on a routine basis.

In conclusion, the DTC model proposed in this study could identify PlTB cases based on only three simple predictive variables readily available and collected in basic health care units, with a mean accuracy of almost 90%. ADA, microbiological and pathological analysis of pleural fluid should also be obtained whenever possible. Invasive diagnostic procedures, such as pleural biopsy may be reserved for specific cases considering their risks *versus* benefits.

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AUTHOR CONTRIBUTIONS

APS: idealization, investigation, data collection, writing of the paper. MRA: methodology, statistical analysis, writing of the paper. RC, IL, MAS e JL: data collection, writing of the paper. TTM: investigation, data collection, writing of the paper. LSR and RR: idealization, methodology, statistical analysis, final revision of the paper.

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ORIGINAL ARTICLE

Post-tuberculosis lung disease: a comparison of Brazilian, Italian, and Mexican cohorts

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ABSTRACT

Objective: To evaluate lung function in a cohort of patients with a history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung function over time and compare it with that observed in similar cohorts in Mexico and Italy. **Methods:** The three cohorts were compared in terms of age, smoking status, pulmonary function test results, six-minute walk test results, and arterial blood gas results. In the Brazilian cohort, pulmonary function test results, six-minute walk test results, and arterial blood gas results right after the end of tuberculosis treatment were compared with those obtained at the end of the follow-up period. **Results:** The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). Only 2 multidrug-resistant tuberculosis cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%). Mean PaO_2 and mean SaO_2 were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO_2 and SaO_2, respectively). In the Brazilian cohort, almost all functional parameters deteriorated over time. **Conclusions:** This study reinforces the importance of early and effective treatment of drug-susceptible tuberculosis patients, because multidrug-resistant tuberculosis increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if post-tuberculosis lung disease is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in these patients.

Keywords: Tuberculosis; Tuberculosis, multidrug-resistant; Spirometry; Rehabilitation.

INTRODUCTION

Tuberculosis is a serious public health concern and one of the leading causes of death worldwide. According to the latest report by the WHO, 5.8 million people were diagnosed with tuberculosis and 1.3 million tuberculosis deaths occurred in 2020. In addition, COVID-19 has impacted tuberculosis control.[1,2] The number of newly diagnosed tuberculosis cases fell from 7.1 million in 2019 to 5.8 million in 2020. In addition, reductions were observed in the number of people receiving multidrug-resistant tuberculosis (MDR-TB) treatment (a 15% reduction, from 177,100 people to 150,359 people) and tuberculosis preventive treatment (a 21% reduction, from 3.6 million people to 2.8 million people).[3]

Tuberculosis affects predominantly the lungs, and many patients, despite a bacteriologically confirmed cure, will have tuberculosis sequelae, with loss of lung function and chronic respiratory symptoms, as well as decreased exercise capacity and quality of life.[4-10] The prevalence of post-tuberculosis lung disease (PTLD) varies widely, from 18% to 87%,[11] depending on the population studied and the pulmonary function tests performed.

The International Union Against Tuberculosis and Lung Disease has recently published a core document on the importance of clinical evaluation of PTLD as soon as possible at the end of tuberculosis treatment.[12] According to the document, one of the key research priorities is to describe the frequency and severity of PTLD in different populations.[12] Indeed, although there is evidence that tuberculosis deteriorates lung function,[4-8] the evidence regarding the type of damage, the severity of PTLD, and patient prognosis is not clear, and between-cohort comparisons have never been done.

Therefore, the objective of the present study was to evaluate lung function in a cohort of patients with a

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history of pulmonary tuberculosis in Brazil, as well as to evaluate the decline in lung function over time and compare it with that observed in similar cohorts in Mexico and Italy.

METHODS

In this study we compared three different cohorts to identify elements to improve screening and rehabilitation of post-treatment tuberculosis patients: a Brazilian cohort (n = 114), an Italian cohort (n = 43), and a Mexican cohort (n = 59). The study was approved by the local research ethics committees (Protocol nos. 2018-0682, 2215 CE, and C17-14 in Brazil, Italy, and Mexico, respectively).

The Brazilian cohort consisted of outpatients who were over 18 years of age, had a history of bacteriologically confirmed pulmonary tuberculosis, were evaluated right after the end of tuberculosis treatment, and were followed for a mean of 8.3 ± 4.9 years at the *Hospital de Clínicas de Porto Alegre* Outpatient Clinic, located in the city of Porto Alegre, Brazil. We retrospectively reviewed pulmonary function test results, six-minute walk test (6MWT) results, and arterial blood gas results at two different time points: right after the end of tuberculosis treatment and at the end of the follow-up period. Spirometry, lung volume measurements, and DL_{CO} measurements were performed with a MasterScreen Body-PFT device (Jaeger, Würzburg, Germany). All tests were performed in accordance with recommended standards[13-15] and with the use of predicted values for the Brazilian population.[16-18] Ventilatory patterns (obstructive, restrictive, and mixed) were defined in accordance with the American Thoracic Society (ATS)/European Respiratory Society (ERS) interpretative strategies for lung function tests.[19] We also collected data on symptoms, BMI, smoking status, and bacteriological profile, as well as on radiological abnormalities, which were measured by using a scoring system proposed by Baez-Saldana et al.[20]

The Italian cohort consisted of patients with a history of pulmonary tuberculosis and successful treatment, admitted for pulmonary rehabilitation between 2004 and 2017. Details on the study population and the study itself have been presented elsewhere.[5] Pulmonary function tests were performed in accordance with the ATS guidelines[13-15] and the ATS/ERS interpretative strategies for lung function tests,[19] with the use of the ERS predicted values.[19]

In the Mexican cohort, as described previously,[6] all patients had bacteriologically confirmed tuberculosis, and the functional impact of post-treatment sequelae was evaluated in those who were over 18 years of age and who had drug-susceptible tuberculosis (DS-TB) or MDR-TB. Pulmonary function tests were performed in accordance with the ATS/ERS guidelines and the ATS/ERS interpretative strategies for lung function tests,[19] with the use of the National Health and Nutrition Examination Survey III reference values.[21]

Data analysis was performed with the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA). Data were presented as number of cases and percentage, mean ± SD, or median (IQR). The three cohorts were compared in terms of age, smoking status, pulmonary function test results, 6MWT results, and arterial blood gas results. Categorical variables were compared by Pearson's chi-square test. Continuous variables were compared by ANOVA. In the Brazilian cohort, pulmonary function test results, 6MWT results, and arterial blood gas results right after the end of tuberculosis treatment and at the end of the follow-up period were compared by a t-test for paired samples. A two-sided p-value < 0.05 was considered significant for all analyses.

RESULTS

Description of the cohorts

Table 1 shows the characteristics of the three cohorts of patients with tuberculosis sequelae. In all three cohorts, males predominated (58.8% in the Brazilian cohort, 55.8% in the Italian cohort, and 52.5% in the Mexican cohort). The Italian patients were older than the Mexicans patients (mean age, 72.3 ± 9.0 years vs. 41.1 ± 14.1 years, $p \leq 0.0001$). Current or past smoking was more common among the Italians (58.1%) and Brazilians (64.9%) than among the Mexicans (38.1%; $p = 0.011$).

Data on BMI and bacteriological profile were only available for the Brazilian and Mexican cohorts (Table 2). The mean BMI was 24.6 ± 4.9 kg/m^2 among the Brazilians and 25.6 ± 5.1 kg/m^2 among the Mexicans. Only 2 MDR-TB cases were included in the Brazilian cohort, whereas, in the Mexican cohort, 27 cases were included (45.8%).

Functional and radiological evaluation

The three cohorts were very different regarding pulmonary function test results. The most common ventilatory patterns in the Brazilian, Italian, and Mexican cohorts were an obstructive pattern, a mixed pattern, and a normal pattern (in 58 patients [50.9%], in 18 patients [41.9%], and in 26 patients [44.1%], respectively). DL_{CO} was lower in the Brazilian and Italian patients than in the Mexican patients ($p < 0.0001$). Mean PaO_2 and mean SaO_2 were lower in the Mexican cohort than in the Brazilian cohort ($p < 0.0001$ and $p < 0.002$ for PaO_2 and SaO_2, respectively). The Mexican cohort showed a significant decrease in SaO_2 during the 6MWT in comparison with the other cohorts ($p < 0.0001$).

Data on respiratory symptoms, as well as radiological scores, were available for the Brazilian and Mexican cohorts only (Table 2). Cough was present in 68 (59.6%) of the 114 patients in the Brazilian cohort and in 9 (15.3%) of the 59 patients in the Mexican cohort. Some degree of dyspnea was reported by 96 (84.2%) of the 114 patients in the Brazilian cohort

and by 17 (28.8%) of the 59 patients in the Mexican cohort. The median radiological score was 5.0 (IQR, 4.0-7.3) for the Brazilian cohort and 6.0 (IQR, 3.0-10.0) for the Mexican cohort.

Evaluation of lung function over time in the Brazilian cohort

Pulmonary function tests were performed after the initial evaluation, although only in the Brazilian cohort. The mean time elapsed between the first and last tests was 8.3 ± 4.9 years. No intervention (pulmonary rehabilitation or surgical procedure) was performed between the first and last tests. As can be seen in Table 3, all functional parameters deteriorated over time, with the exception of RV in L, PaO_2, and SaO_2, which decreased over time, albeit not significantly. Post-bronchodilator FEV_1 decreased from 1.7 ± 0.8 L to 1.4 ± 0.7 L ($p < 0.0001$). Post-bronchodilator FVC decreased from 2.6 ± 1.0 L to 2.3 ± 0.9 L ($p < 0.0001$). TLC decreased from 5.8 ± 1.8 L to 5.7 ± 1.7 L ($p < 0.0001$). DL_{CO} decreased from 49.1 ± 16.7% predicted to 41.8 ± 19.9% predicted ($p < 0.0001$). The six-minute walk distance decreased from 431.1 ± 105.3 m to 369.3 ± 107.9 m ($p < 0.0001$), and the lowest SaO_2 during the 6MWT decreased from 95.7 ± 2.2 to 94.6 ± 2.1 ($p < 0.0001$).

DISCUSSION

In the present study, tuberculosis was found to have a major impact on respiratory mechanics, gas exchange, and exercise tolerance in all cohorts. In the Brazilian cohort, all of the parameters evaluated were found to have decreased over time. To our knowledge, this is the first comparison of cohorts of patients with PTLD in very different settings (North America, South America, and Europe).

A variety of sequelae can occur after tuberculosis, and many patients can present with persistent symptoms and reduced quality of life, as reported in the Brazilian and Mexican cohorts. Late diagnosis, increased number of treatments, extensive disease, MDR-TB, and untreated tuberculosis are usually associated with chronic impairment of lung function.[4] However, even adequately treated patients (i.e., patients with microbiological cure) may be left with permanent pulmonary function abnormalities that will eventually impair exercise tolerance and quality of life, given the normal decline in lung volumes over the years.[22] Despite being young, the patients in the Mexican cohort were severely compromised, which

Table 2. Additional characteristics of the Brazilian and Mexican cohorts.

Characteristic	Cohort	
	Brazil (n = 114)	Mexico (n = 59)
BMI, kg/m²	24.6 ± 4.9	25.6 ± 5.1
Cough	68 (59.6)	9 (15.3)
Dyspnea	96 (84.2)	17 (28.8)
DS-TB	112 (98.2)	32 (54.2)
MDR-TB	2 (1.8)	27 (45.8)
Radiological score	5.0 (4.0-7.3)	6.0 (3.0-10.0)

DS-TB: drug-susceptible tuberculosis; and MDR-TB: multidrug-resistant tuberculosis.

Table 1. Characteristics of the three cohorts of patients with tuberculosis sequelae.[a]

Characteristic	Cohort			p
	Brazil (n = 114)	Italy (n = 43)	Mexico (n = 59)	
Age, years	65.3 ± 11.5[a]	72.3 ± 9.0[b]	41.1 ± 14.1[c]	< 0.0001
Male sex	67 (58.8)	24 (55.8)	31 (52.5)	0.732
Current or past smoking	74 (64.9)[a]	25 (58.1)[ab]	16 (38.1)[b]	0.011
Post-BD FEV_1, L	1.72 ± 0.83[a]	1.36 ±0.66[b]	2.36 ± 0.86[c]	< 0.0001
Post-BD FEV_1, % predicted	59.3 ± 25.4[a]	58.5 ± 24.5[a]	79.9 ± 23.5[b]	< 0.0001
Post-BD FVC, L	2.58 ± 1.04[a]	2.37 ± 0.90[a]	3.12 ± 1.06[b]	< 0.0001
Post-BD FVC, % predicted	71.9 ± 23.9[a]	77.9 ± 19.1[ab]	88.3 ± 23.2[b]	< 0.0001
Post-BD FEV_1/FVC	66.5 ± 17.3[a]	56.8 ± 17.3[b]	76.2 ± 10.7[c]	< 0.0001
Ventilatory pattern				
Obstructive	58 (50.9)[a]	11 (25.6)[b]	23 (39.0)[ab]	0.014
Restrictive	20 (17.5)	5 (11.6)	5 (8.5)	0.234
Mixed	15 (13.2)[ab]	18 (41.9)[a]	5 (8.5)[b]	< 0.0001
Normal	21 (18.4)[a]	9 (20.9)[ab]	26 (44.1)[b]	0.001
RV, % predicted	176.4 ± 78.8[b]	140.8 ± 40.6[a]	113.2 ± 41.6[a]	< 0.0001
DL_{CO}, % predicted	50.3 ± 18.2[a]	60.1 ± 20.5[a]	88.6 ± 24.5[b]	< 0.0001
PaO_2	78.6 ± 20.7[b]	70.4 ± 7.5[a]	65.3 ± 8.1[a]	< 0.0001
SaO_2	94.4 ± 5.3[a]	94.2 ± 2.3[a]	91.9 ± 3.0[b]	0.002
6MWD, m	430.6 ± 102.3[a]	378.1 ± 122.5[b]	536.7 ± 93.3[c]	< 0.0001
Lowest SaO_2 during the 6MWT	95.7 ± 2.1[a]	88.5 ± 5.2[b]	86.2 ± 4.4[c]	< 0.0001

BD: bronchodilator; 6MWD: six-minute walk distance; and 6MWT: six-minute walk test. [a]Equal letters mean no significant difference between cohorts, whereas different letters indicate a significant difference between cohorts.

Table 3. Decline in lung function over time in patients with tuberculosis sequelae in the Brazilian cohort.

Variable	Early follow-up	Late follow-up*	p
Pre-BD FEV_1, L	1.5 ± 0.8	1.3 ± 0.7	< 0.0001
Pre-BD FEV_1, % predicted	55.0 ± 25.0	48.9 ± 21.3	< 0.0001
Pre-BD FVC, L	2.4 ± 0.9	2.2 ± 0.9	< 0.0001
Pre-BD FVC, % predicted	66.9 ± 22.9	62.1 ± 20.0	< 0.0001
Pre-BD FEV_1/FVC	65.7 ± 16.8	61.3 ± 16.6	< 0.0001
Post-BD FEV_1, L	1.7 ± 0.8	1.4 ± 0.7	< 0.0001
Post-BD FEV_1, % predicted	59.2 ± 25.7	51.8 ± 21.8	< 0.0001
Post-BD FVC, L	2.6 ± 1.0	2.3 ± 0.9	< 0.0001
Post-BD FVC, % predicted	72.1 ± 24.1	65.5 ± 20.8	< 0.0001
Post-BD FEV_1/FVC	66.3 ± 17.2	62.1 ± 18.3	< 0.0001
TLC, L	5.8 ± 1.8	5.7 ± 1.7	< 0.0001
TLC, % predicted	103.8 ± 31.9	102.5 ± 27.5	< 0.0001
RV, L	4.3 ± 8.3	3.4 ± 1.4	0.089
RV, % predicted	178.6 ± 82.2	165.9 ± 70.4	< 0.0001
DL_{CO}, % predicted	49.1 ± 16.7	41.8 ± 19.9	<0.0001
PaO_2	71.1 ± 12.9	67.6 ± 16.5	0.125
SaO_2	93.1 ± 6.2	91.9 ± 6.9	0.999
6MWD, m	431.1 ± 105.3	369.3 ± 107.9	< 0.0001
Lowest SaO_2 during the 6MWT	95.7 ± 2.2	94.6 ± 2.1	0.007

*Mean time elapsed between the first and last tests: 8.3 ± 4.9 years. BD: bronchodilator; 6MWD: six-minute walk distance; and 6MWT: six-minute walk test.

is due to a high proportion of MDR-TB cases in that cohort. Although lung function was less compromised in the Mexican cohort than in the Italian and Brazilian cohorts, the Mexican cohort had more severe hypoxemia at rest and during exercise. Sometimes the combination of a restrictive pattern of sequelae (such as pulmonary fibrosis) with obstruction can lead to normal spirometry results or mild airway obstruction, with severe hypoxemia.[23]

The most prevalent abnormal ventilatory pattern was an obstructive pattern in the Brazilian and Mexican cohorts, whereas, in the Italian cohort, it was a mixed obstructive and restrictive pattern. There is a wide variability in pulmonary involvement of tuberculosis. Pulmonary function tests can range from normal to severe dysfunction.[24,25] The type of ventilatory defect is also quite heterogeneous.[24,26] Actually, several studies have shown that lung function impairment is typically obstructive but occasionally restrictive.[22,27-30] Host immune responses are probably a key component of this variable lung damage, but the specific factors associated with this damage remain unknown. An obstructive ventilatory pattern is related to excessive inflammation and, most frequently, to airway narrowing, pulmonary cavitation, and bronchiectasis. On the other hand, a restrictive ventilatory pattern is related to excessive fibrosis and presents radiologically as fibrotic bands, bronchovascular distortion, and pleural thickening.[11] Several studies have demonstrated that a history of treated tuberculosis is a risk factor for COPD.[26,28,31,32] In a population-based study involving 14,050 patients from 128 countries, previous tuberculosis was associated with a 2.5-fold increased risk of COPD.[28] Furthermore, in a meta-analysis, treated tuberculosis patients were shown to be approximately 3 times more likely to develop COPD.[26]

Our study has some limitations. First, we compared different settings and clinical profiles. However, this becomes an opportunity to discuss how better to apply the new clinical standards for the assessment, management, and rehabilitation of PTLD.[12] Second, it is difficult to estimate the role of smoking in lung function impairment because we had incomplete information on patient smoking habits (i.e., smoking history, in pack-years), which are difficult to assess because they are subject to memory bias. Despite these concerns, the strengths of our study are the completeness of functional evaluation in the three cohorts and the possibility (the first to our knowledge) to make an international comparison of PTLD patterns, including the evaluation of lung damage over time in one cohort.

In conclusion, the present study reinforces the importance of early and effective treatment of DS-TB patients, because MDR-TB increases lung damage. When patients complete their tuberculosis treatment, they should be evaluated as early as possible, and, if PTLD is diagnosed, they should be managed and offered pulmonary rehabilitation because there is evidence that it is effective in patients with PTLD.[5,22,33-35] Preliminary data have shown that there is a significant improvement in the six-minute walk distance, lung function parameters (FEV_1 and FVC), and median SaO_2 after implementation of a comprehensive pulmonary rehabilitation program.[5] Given that a decline in all lung function parameters was documented over a mean follow-up of 8.3 ± 4.9 years in the Brazilian cohort, additional prospective data are needed to determine whether pulmonary rehabilitation can improve the clinical history of PTLD.

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AUTHOR CONTRIBUTIONS

DRS: conceptualization, methodology, investigation, data curation, project administration, and drafting of the manuscript. AAF, ARG, LD, RC, MMT, and DV: conceptualization, methodology, investigation, and drafting and revision of the manuscript. GBM: conceptualization, methodology, investigation, data curation, supervision, and drafting of the manuscript.

CONFLICTS OF INTEREST

None declared.

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BRIEF COMMUNICATION

Country-specific lockdown measures in response to the COVID-19 pandemic and its impact on tuberculosis control: a global study

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ABSTRACT

The objective of this study was to describe country-specific lockdown measures and tuberculosis indicators collected during the first year of the COVID-19 pandemic. Data on lockdown/social restrictions (compulsory face masks and hand hygiene; international and local travel restrictions; restrictions to family visits, and school closures) were collected from 24 countries spanning five continents. The majority of the countries implemented multiple lockdowns with partial or full reopening. There was an overall decrease in active tuberculosis, drug-resistant tuberculosis, and latent tuberculosis cases. Although national lockdowns were effective in containing COVID-19 cases, several indicators of tuberculosis were affected during the pandemic.

Keywords: COVID-19; Tuberculosis; Physical distancing; Health policy; Global health; Communicable disease control.

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As the COVID-19 pandemic progressed, and due to the lack of readily available vaccines or treatments, public health measures intended to contain the spread of the disease were put in place. These included rapid diagnosis, rapid isolation of cases, physical distancing, use of face masks, school closures, smart working, travel restrictions, and closure of international borders. Countries worldwide implemented nationwide lockdowns to contain the spread of the virus and reduce the number of cases.[1] On the other hand, studies have demonstrated that the COVID-19 pandemic has substantially affected tuberculosis services in many countries.[2,3] We collected the lockdown measures adopted by various countries to manage the pandemic in order to gauge the best practices and lessons learned. We aimed to describe these country-specific lockdown measures and tuberculosis control indicators collected over the same period.

Invitations to participate in the study were sent to 24 countries (the study coordinators). Data were retrospectively collected from the beginning of lockdown measures until December 31, 2020. Data on lockdown and other social restrictions (compulsory use of face masks and hand hygiene; international and local travel restrictions; restrictions to family visits; and school closures) were collected, including dates and whether they were fully or partially implemented. Tuberculosis control indicators (total number of tuberculosis cases, drug-resistant tuberculosis cases, newly diagnosed tuberculosis cases, and latent tuberculosis cases) were also collected.

National preventive measures were collected from 24 countries spanning five continents: 10 in Europe (France, Greece, Italy, Kosovo, Lithuania, the Netherlands, Portugal, Russia, Spain, and the United Kingdom), 6 in Asia (Bhutan, Cambodia, India, Oman, the Philippines, and Singapore), 5 in America (Argentina, Brazil, Mexico, Paraguay, and the USA), 2 in Africa (Kenya and Niger), and 1 in Oceania (Australia). Tables 1 and 2 show such data, by continent and country.

Lockdown measures were implemented in all countries surveyed. The earliest lockdown was in Australia on February 1, 2020, and the latest was in Singapore on April 7, 2020. The majority of the countries implemented multiple lockdowns with partial or full reopening. Compulsory use of face masks was partial only in Mexico and Kenya. Compulsory hand hygiene was established as a full measure in all countries included in the study, except Kenya (only partially implemented). International traveling was partially restricted in Brazil, Cambodia, Lithuania, Russia, Singapore, the UK, and the USA. Local traveling was partially restricted in Brazil, Cambodia, Lithuania, and Niger. In the Netherlands, neither international nor local travels were restricted. In Mexico, no measure was taken with respect to local travels. The Philippines did not report international or local travel restrictions. Restrictions on family visits occurred in Australia, Cambodia, the Netherlands, Portugal, Russia, the UK, and the USA. In Brazil, Kenya, Mexico, and Niger no measure was taken with regard to family visits. Full school closures occurred in all countries included in the study, except Russia (only partial closures).

Tuberculosis cases decreased from 32,898 in 2019 to 16,396 in 2020 with a sudden decline in March of 2020 in the surveyed centers, concomitantly with the commencement of lockdowns in the majority of the countries. This decrease was observed in all countries included in this study, except in tuberculosis centers in Australia, Singapore, and the state of Virginia (USA). The number of drug-resistant tuberculosis cases also decreased (from 4,717 in 2019 to 1,527 in 2020), even in countries that have a smaller number of drug-resistant tuberculosis cases, such as Argentina, Brazil, India, Mexico, and Russia. Newly diagnosed tuberculosis cases in outpatient clinics decreased from 7,364 in 2019 to 5,703 in 2020, except for centers in Australia and in the state of Virginia (USA). In addition, fewer individuals were diagnosed with latent tuberculosis.

Several factors may contribute to explain the relationship of COVID-19 pandemic/lockdown measures with tuberculosis indicators. In the management of the pandemic, human and financial resources were reallocated from tuberculosis services to COVID-19 units, compromising tuberculosis care. In addition, for fear of leaving their home (fear of SARS-CoV-2 infection or fear of stigma), people avoided visiting tuberculosis services and health care centers/hospitals in general. Also, access to tuberculosis services was hampered due to restrictions on movement and reduced opening hours of health services. Indeed, there was a drastic reduction in the number of consultations and hospital admissions for various medical conditions. Emergency department (ED) admissions decreased by more than 50% in 2020, as compared with 2019.[4] EDs serve as the frontline for symptomatic respiratory patients in many countries, with a high number of tuberculosis cases diagnosed in this setting.[5] In a retrospective study in Nigeria,[6] pulmonary tuberculosis was diagnosed in almost 30% of adults presenting to EDs with respiratory complaints. In this sense, the reduction in ED visits may have contributed to a reduction in the number of tuberculosis cases diagnosed during the pandemic.

Tuberculosis testing and preventive therapy have also been impacted by the COVID-19 pandemic. Tuberculosis testing decreased in some of the countries included in the study, such as in the Philippines, Kenya, and Brazil. Relative declines in preventive therapy, ranging from 30% to 70%, were described in several tuberculosis centers such as in Brazil, Kenya, the Philippines, and Russia.[2]

A decline in the number of drug-resistant tuberculosis cases reported was observed in Argentina, Brazil, India, Mexico, and Russia. Globally, around 45% fewer people were tested for multidrug-resistant tuberculosis (MDR-TB).[7] In Brazil, there was a 14% reduction in the consumption of Xpert MTB/RIF Ultra

Table 1. Lockdown measures and dates instituted by each country in Africa and Europe.[a]

Country	F/P	Compulsory face mask use	International travel restriction	Local travel restriction	Restriction to family visits	School closure	Compulsory hand hygiene
France	F	07/20/2020-12/31/2020	03/17/2020-06/02/2020	03/17/2020-05/10/2020	03/17/2020-05/10/2020	03/12/2020-05/10/2020	02/28/2020-12/31/2020
			10/30/2020-12/15/2020	10/29/2020- 12/15/2020	10/30/2020-12/15/2020		
	P	03/17/2020-07/19/2020		05/11/2020-06/02/2020		10/30/20-12/31/20	
				12/16/2020-12/31/2020			
Greece	F	08/08/2020-06/24/2021	03/09/2020-05/18/2020	03/23/2020-05/04/2020		05/3/2020-18/5/2020 (high schools)	
		Since 06/24/21 (compulsory only in indoor spaces)		11/07/2020-01/11/2021		03/05/2020-06/01/2020 (elementary schools)	
						11/07/2020-01/11/2021 (elementary schools)	
						11/07/2020-02/01/2021 (high schools)	
	P		Since 11/26/2021				
Italy[b,c]	F	03/09/2020-05/04/2020	03/09/2020-06/21/2020	03/09/2020-05/31/2020	03/09/2020-05/18/2020	03/09/2020-05/18/2020	01/31/2020-ongoing
		10/13/2020-ongoing					
	P		05/19/2020-12/31/2020	11/01/2020-ongoing (regional variations)	10/24/2020-ongoing [b]	09/11/2020-ongoing (rotation by age groups)	
Kenya	F	04/05/2020-ongoing (mostly P)	03/25/2020-08/01/2020	03/25/2020-07/06/2020	No measures except in relation to domestic travel	03/15/2020-10/12/2020	Ongoing (P)
Kosovo	F	03/112020-ongoing (mostly P)	03/27/2020-06/02/2020	03/23/2020-06/01/2020	03/23/2020-06/012020	03/27/2020-06/27/2020 (all schools)	07/13/2020-ongoing (P)
			From that date-ongoing (P)			09/14/2020-ongoing (online e-learning only for heavily affected classrooms)	
Lithuania	F	03/14/2020-06/10/2020			12/14/2020-ongoing	03/14/2020-06/10/2020	01/31/2020-ongoing
		11/04/2020-ongoing					
	P		03/14/2020-06/10/2020	03/14/2020-06/10/2020		04/11/2020-ongoing	
			04/11/2020-ongoing	11/04/2020-ongoing			

Continue...▶

Table 1. Lockdown measures and dates instituted by each country in Africa and Europe.[a] (Continued...)

Country	F/P	Compulsory face mask use	International travel restriction	Local travel restriction	Restriction to family visits	School closure	Compulsory hand hygiene
Netherlands	F	12/01/2020-ongoing	None	None		03/23/2020-05/31/2020 12/17/2020-ongoing	03/23/2020-ongoing
	P	09/30/2020-11/30/2020 (recommendation only)	None	None	03/23/2020-05/31/2020 12/17/2020-ongoing		
Niger	F	01/22/2021-ongoing	03/19/2020-09/15/20		None	03/18/2020-05/31/2020	03/18/2020-ongoing
	P	03/18/2020-01/21/2021	09/15/2020-ongoing	03/27/2020-04/11/2020		10/01/2020-10/15/2020	
Portugal[b,c]	F	10/27/2020-ongoing	03/15/2020-05/22/2020	04/02/2020-05/18/2020		03/12/2020-09/14/2020[b]	03/18/2020-ongoing
	P	03/18/2020-10/26/2020	03/09/2020-ongoing	03/18/2020-05/22/2020	03/15/2020-05/04/2020	03/09/2020-05/18/2020	
Russia[b]	F	05/12/2020-07/12/20 (regional variations)		03/30/2020-06/08/2020			03/05/2020-ongoing
	P	03/27/2020-ongoing (regional variations)	03/05/2020-ongoing (regional variations)	06/09/2020-ongoing (individuals > 65 years of age and/or with chronic diseases)	03/27/2020-05/19/2020	03/21/2020-01/18/2021	
Spain[b,c]	F	05/21/2020-ongoing	03/14/2020-06/21/2020	03/19/2020-06/21/2020	03/14/2020-05/22/2020	03/14/2020-06/21/2020	03/14/2020-ongoing
	P		10/25/2020-ongoing	10/25/2020-ongoing			
United Kingdom	F	06/15/2020-ongoing (transportation) 07/24/2020-ongoing (shops)		03/23/2020-05/10/2020 12/19/2020-ongoing		03/20/2020-06/01/2020 12/18/2020-02/22/2021	03/04/2020-ongoing
	P	07/24/2020-12/31/2020	06/08/2020-ongoing		03/23/2020-06/05/2020 12/19/2020-05/17/2021		

F: full; and P: partial. [a]Ongoing as of December 31, 2020. [b]Local, provincial, or regional variations adopted. [c]Periods with full or partial restriction rotations.

Table 2. Lockdown measures and dates instituted by each country in the Americas, Asia, and Oceania.[a]

Country	F/P	Compulsory face mask use	International travel restriction	Local travel restriction	Restriction to family visits	School closure	Compulsory hand hygiene
Argentina	F	03/20/2020-ongoing	03/20/2020-11/06/2020	03/20/2020-11/06/2020	03/20/2020-11/06/2020	03/20/2020-02/17/2021	03/20/2020-ongoing
	P		11/06/2020-ongoing	11/06/2020-12/01/2020			
Australia[b,c]	F	06/30/2020-ongoing	03/27/2020-ongoing (2-week quarantine for all arrivals)	03/31/2020-11/07/2020		06/30/2020-11/22/2020	01/21/2020-ongoing[d]
	P		01/23/2021-ongoing (self-isolation for all overseas arrivals)	03/16/2020-ongoing	05/30/2020-ongoing (limited travels and number of visitors)	03/23/2020-05/25/2020 (children encouraged to stay at home)	
Bhutan	F	March to June 2020 (Govt. recommended use of face masks) 07/04/2020-ongoing (Govt. made use of face masks mandatory)	03/23/2020-08/30/2021 (restriction on tourist entry; mandatory 21-day facility quarantine) 08/30/2021-ongoing (mandatory 2-week quarantine for individuals with proof of full vaccination and 21-day quarantine for unvaccinated individuals)	09/11/2020-ongoing (mandatory 7-day facility quarantine for individuals wishing to travel from high-risk areas (southern districts) to other districts	02/07/2020-ongoing (no direct family visit restrictions; recommendations: avoiding mass gatherings; limiting travel visitors; businesses allowed to operate until 10 p.m.; public transportation, including taxis and buses, allowed to carry only 50% of capacity)	03/18/2020-12/31/2020 (preschool to grade 6) (03/18/2020-07/01/2020 (grades 7-11)	March 2020-ongoing (hand washing facilities made available in schools, hospitals, and public places)
Brazil[b]	F	04/18/2020-ongoing			None	03/21/2020-10/01/2020 (public and private schools)	03/13/2020-ongoing
	P	05/04/2020-ongoing	03/18/2020-ongoing	03/17/2020-ongoing		10/01/2020-ongoing (public and private schools)	
Cambodia	F	04/01/2020-ongoing				03/15/2020-08/31/2020 02/20/2021-10/01/2021	03/15/2020-ongoing
	P		04/16/2020-11/15/2021 (2-week quarantine for all international arrivals)	03/15/2020-04/01/2020 04/10/2021-10/31/2021 (by province)	04/15/2021-05/10/2021 (limited to 15 days or less)	11/01/2020-02/20/2021 10/01/2021-12/31/2021	

Continue...▶

Table 2. Lockdown measures and dates instituted by each country in the Americas, Asia, and Oceania.[a] (Continued...)

Country	F/P	Compulsory face mask use	International travel restriction	Local travel restriction	Restriction to family visits	School closure	Compulsory hand hygiene
India	F	03/25/2020-ongoing	03/25/2020-ongoing	03/31/2020-07/01/2020	03/25/2020-07/01/2020	03/25/2020-ongoing	03/21/2020-ongoing
	P			07/01/2020-ongoing			
Mexico[b]	F		03/15/2020-09/30/2020	None	None	03/14/2020-ongoing	02/28/2020-ongoing
	P	09/30/2020-ongoing					
Oman	F	05/18/2020-ongoing	03/29/2020-09/30/2020	04/01/2020-04/29/2020	03/15/2020-06/30/2020	03/15/2020-11/01/2020	01/01/2020-ongoing
				07/25/2020-08/08/2020			
	P				01/27/2021-ongoing		
Paraguay	F	11/27/2020-ongoing	03/17/2020-10/15/2020	03/17/2020-05/18/2020	07/20/2020-ongoing	03/10/2020-02/09/2021	03/10/2020-ongoing
	P		03/17/2020-ongoing			02/10/2020-ongoing	
Philippines		03/01/2020-ongoing	Not reported	Not reported	03/16/2020-10/30/2020	03/16/2020-ongoing	03/16/2020-ongoing
Singapore[b]	F	04/14/2020-ongoing		None	04/07/2020-06/01/2020	04/08/2020-05/18/2020	01/31/2020-ongoing
	P	04/03/2020-04/14/2020 (encouraged)	01/29/2020-ongoing (regional variations)		06/02/2020-06/17/2020 (2 visitors only)	05/19/2020-06/01/2020 (graduating cohort only)	
					06/18/2020-12/27/2020 (up to 5 visitors)		
USA[b] (State of Virginia)	F	05/26/2020-ongoing (indoors)		03/30/2020-06/10/2020		03/13/2020-06/30/2020	02/07/2020-ongoing
	P		02/28/2020-ongoing (CDC and US State Department only)	04/12/2020-12/21/2020	03/30/2020-ongoing (limited number of visitors)	9/15/2020-ongoing	

F: full; P: partial; Govt.: government; and CDC: Centers for Disease Control and Prevention. [a]Ongoing as of December 31, 2020. [b]Local, provincial, or regional variations adopted. [c]Periods with full or partial restriction rotations. [d]For travellers returning from Wuhan, China.

assay cartridges.[8] However, a declining consultation rate and a reduction in recognition and detection of diseases due to the pandemic could consequently cause delayed diagnosis and treatment,[9] contributing to the increase in the number of MDR-TB cases in the future.

In order to contain the spread of the new coronavirus, the public was instructed to stay at home. However, this policy may not be feasible in some settings. In developing countries, informal jobs make up the majority of employment: 54% in Latin America, 67% in Southeast Asia, and 86% in Africa.[10] These workers may not have the option to stay at home, and not all governments can provide emergency financial assistance to support them to stay at home. In some countries in Africa (Egypt, Kenya, Nigeria, and South Africa) and in Latin America (Peru, Brazil, Argentina, Mexico, and Colombia), the time to commute to work is significantly affected by the poverty level. A higher poverty level translates to a smaller reduction in commuting time.[11] In these lower-income areas, the number of COVID-19 cases could be higher, and, consequently, there might be fewer resources for and awareness of other diseases such as tuberculosis.

The adoption of stay-at-home measures and the use of face masks due to COVID-19, there could have reduced the transmission of other communicable

diseases such as tuberculosis. On the other hand, strict containment policies can facilitate the household spread of tuberculosis, since contact at the household level is one of the most important factors in the tuberculosis transmission chain.[12] However, the impact of increased household transmission will be noticed only in future years, because tuberculosis has a long incubation period.

In tuberculosis centers in Australia, Singapore, and the state of Virginia (USA), no reduction in the number of reported tuberculosis cases was observed. This finding may be attributable to increased surveillance of both tuberculosis and COVID-19 in these settings. In fact, the adoption of organizational changes was important to the maintenance of consultations for non-COVID-19-related problems.[9] For example, Bhutan set up walk-in flu clinics across the country to triage individuals with cough and fever to reduce the risk of COVID-19 transmission. Taking advantage of the infrastructure and investment, Bhutan also started tuberculosis screening at the flu clinics. This initiative supported the tuberculosis control efforts in intensifying the identification of tuberculosis cases and ensured the continuity of tuberculosis health care services without disruption during the COVID-19 pandemic. In addition, the use of telehealth/telemedicine may have prevented a reduction of diagnosing tuberculosis.[9] During the lockdown, many places implemented telehealth services; however, this is not widely available in all tuberculosis centers unfortunately.

The future consequences of the COVID-19 pandemic and lockdown measures are yet to be known. Cilloni et al.[13] estimated that a three-month interruption of tuberculosis services would cause an additional 1.19 million tuberculosis cases and 361,000 tuberculosis deaths in India, as well as 24,700 new tuberculosis cases and 12,500 tuberculosis deaths in Kenya. The WHO modeling suggests that the negative impacts on tuberculosis mortality and incidence in 2020 will become much worse in the coming years. Moreover, the COVID-19 pandemic is expected to have a negative impact on tuberculosis determinants, average income, and malnutrition rates. Considering that 30-50% of the incidence of tuberculosis is attributable to malnutrition, an increase in the prevalence of malnutrition may have an effect on tuberculosis incidence and mortality.[7] In addition, the Stop TB Partnership,[14] together with other institutions, conducted a modeling analysis to evaluate the potential impact of COVID-19 response on tuberculosis in high-burden countries; they suggested that there will be an additional 6.3 million cases of tuberculosis between 2020 and 2025, and an additional 1.4 million tuberculosis deaths in the same period.

In summary, although national lockdowns were effective in reducing COVID-19 cases, several indicators of tuberculosis were dramatically affected during the pandemic. Improvement of surveillance will be necessary, as an increase in the number of tuberculosis cases, drug-resistant tuberculosis cases, and tuberculosis deaths may be expected in future years.

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AUTHOR CONTRIBUTIONS

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

ETHICAL APPROVAL

The coordinating center and the participating centers had ethics clearance in abidance with their institutional regulations.

CONFLICT OF INTEREST

None declared.

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Donation after circulatory death and lung transplantation

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ABSTRACT

Lung transplantation is the most effective modality for the treatment of patients with end-stage lung diseases. Unfortunately, many people cannot benefit from this therapy due to insufficient donor availability. In this review and update article, we discuss donation after circulatory death (DCD), which is undoubtedly essential among the strategies developed to increase the donor pool. However, there are ethical and legislative considerations in the DCD process that are different from those of donation after brain death (DBD). Among others, the critical aspects of DCD are the concept of the end of life, cessation of futile treatments, and withdrawal of life-sustaining therapy. In addition, this review describes a rationale for using lungs from DCD donors and provides some important definitions, highlighting the key differences between DCD and DBD, including physiological aspects pertinent to each category. The unique ability of lungs to maintain cell viability without circulation, assuming that oxygen is supplied to the alveoli—an essential aspect of DCD—is also discussed. Furthermore, an updated review of the clinical experience with DCD for lung transplantation across international centers, recent advances in DCD, and some ethical dilemmas that deserve attention are also reported.

Keywords: Tissue and organ procurement; Brain death; Lung transplantation; Respiratory insufficiency.

RATIONALE

Lung transplantation (LTx) is a life-saving therapy for managing patients with end-stage lung diseases such as COPD, cystic fibrosis, and pulmonary fibrosis. Unfortunately, this modality of treatment cannot be offered to more patients because of the lack of suitable donors, highlighting the disproportion of patients currently waiting for an organ transplant compared with the number of people on the waiting list.[1]

For example, although a significant number of liver and kidney transplants are performed every year in Brazil, cardiothoracic transplantation is still much lower than what is seen in other countries according to the Brazilian Association for Organ Transplantation.[2] In this context, given the number of active lung transplant centers in Brazil, an increment in the number of procedures performed every year is paramount.

The process of donation is always long and complex; it is necessary to deal with the emotions of the family of the donor, logistics, and expectations of the recipient, and constant attention needs to be paid to every single detail for this entire equation to move forward successfully. Regarding lungs, specifically, optimal donor management is so critical because a potential organ can be lost due to many factors. Less than ideal management leads to high numbers of potential donors becoming unsuitable for LTx.

In contrast to other organs, additional criteria need to be fulfilled for LTx to be considered[3,4] and are critical for the success of the process. The lungs are also susceptible to many insults, such as the intravascular volume status of the donor or the suboptimal management of secretions in the airways. Chart 1 highlights the criteria for lung acceptance for clinical LTx and the particular challenges that need to be considered. Thus, to avoid post-transplant complications, the acceptance rate of a donor for clinical LTx is low, making the relative scarcity of donors combined with low utilization a real challenge.

As the number of patients on the waiting list continues to rise, several strategies have been developed to increase the number of lung transplants. This includes the use of extended-criteria donors,[5] living-donor lobar LTx,[6] and ex vivo lung perfusion (EVLP) for organ rehabilitation.[7]

Another potential source to alleviate the shortage of donors is donation after circulatory death (DCD). This donation process has progressively gained acceptance, not only for LTx but also for kidney, liver, pancreas, and even heart transplantation.[8] This modality of donation has been shown to contribute to an increment in the number of transplants worldwide and represents a shift in a paradigm, given that the standard is donation after brain death (DBD). However, the number of DBD donors seems insufficient for the demand of patients in need of a life-saving transplant.[9,10] Advancements in the knowledge about DCD have bolstered the number of LTx, resulting in progressive increments in the number of DCD every year.[11,12] In the USA, DCD donors has incrementally been contributing to benefit more patients, and, specifically regarding the lungs, the number of DCD used for clinical

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Chart 1. Criteria for acceptance and challenges in donor management.

Standard Criteria for Lung Accepetance for Clinical Transplantation
Age < 55 years
Clear chest X-ray
Adequate gas exchange PAO_2 > 300 mmHg and FiO_2 100%
Smoking history < 20 pack-years
No evidence of aspiration/purulent secretions on bronchoscopy
No history of primary pulmonary disease or active pulmonary infection
Absence of organisms on gram-stained sputum smear
Absence of chest trauma

Challenges—Donor management—Lungs
Attention to the volume status
Mechanical ventilation management
Hygiene of the airways
Potential infectious sources
Careful assessment of medical history
Continuous discussions with the family

LTx has steadily increased (Figure 1), impacting the overall number of lung transplants.

DEFINITIONS

The conventional modality of donation accepted is DBD, and several tests are performed to diagnose and confirm this status, such as the absence of circulation and no brainstem reflexes.[13] On the other hand, DCD involves a patient who has a permanent absence of circulation (blood pressure and pulse activity) and respiration.[14] Although these concepts are broad, in order to clarify this issue, a classification stratified DCD into categories (designated the Maastricht criteria),[15] with sequential updates in this classification (Chart 2).[14] Understanding this classification is paramount, especially considering a critical subdivision between categories I and II (uncontrolled DCD) and types III and IV (controlled DCD). Of note, a modified Maastricht classification encompasses patients submitted to euthanasia as potential donors (classified as category V). Categories I and II are considered "uncontrolled" DCD, implying that death has occurred suddenly. Examples are patients whose death occurred in the ER of a hospital or even at a pre-hospital stage. On the other hand, DCD categories III and IV are considered "controlled" DCD, because death is anticipated but has not happened yet. It usually occurs in ICUs and encompasses patients with nonrecoverable injuries who depend on life-sustaining therapies, however without meeting the criteria for brain death. Young patients with devastating brain injuries and irreversible damage who have not evolved to a brain dead status yet are a typical example of DCD category III and are commonly found in clinical practice. These patients, unfortunately, are so sick that imminent death after withdrawal of life-sustaining therapy (WLST) is expected, and cessation of futile therapies that are prolonging the life of a critical patient is part of the process.[16]

Most importantly, from the categories highlighted above, Maastricht III is currently the most studied and preferred type of DCD in many centers around the world. That is why the focus of this review primarily resides on this category.

In Maastricht III, logistics are critical for success once a donor is identified and matched to a recipient. WLST happens in a controlled environment (typically in ICUs), where comfort and compassionate care of the patient are paramount. In addition, it is extremely important to provide support to the family of the donor. Heparin is administered, ventilatory support is discontinued, extubation is performed in most places, and cessation of medications used to maintain hemodynamic support is also part of this process.

After WLST is performed, there is a planned interval of time, usually ranging from 60-90 min (that can be extended even up to 180 min), during which vital signs of the donor are checked continuously. This period is called the "agonal phase" and lasts until there is termination of circulation and respiration. When the potential donor has cardiac arrest within the planned interval, there is a stand-off period, ranging from 2-5 min, during which the absence of circulation and respiration must be determined by two physicians, who should not be related to the transplant teams. Typically, once death is determined, the donor is then transferred to the operating room, where intubation and ventilation are restarted and lungs are procured. Figure 2 summarizes the complex process involved in controlled DCD.

There are several steps described within this process[17] that should strictly be followed:

- Comfort measures are provided for the donor during the process.
- The family of the patient is being supported.
- As mentioned above, determination of death is critical after WLST is performed, as is the stand-off period, during which the potential donor can be declared dead after cessation of circulation and ventilation for an interval of 2-5 min.
- There are no conflicts of interest.

The surgical technique for procurement of lungs from such donors is essentially the same as for DBD. Briefly, sternotomy is performed. Once the chest is open, the pericardium is incised, and the heart is exposed. The pulmonary artery trunk is identified and cannulated. The left atrial appendage is also open. The preservation solution is perfused in an antegrade fashion from the pulmonary artery, and the output is drained from the left atrium. Lungs are continuously ventilated during the entire process. The technique has been described in detail elsewhere.[18]

After the lungs are removed from the chest in a semi-inflated state, quality is assessed, and a decision is made about the their condition before proceeding

to transplantation.[19] Figure 3 highlights the critical differences between the DCD and DBD processes for the donation of lungs.

In order to establish criteria for eligibility regarding DCD, we must remember that this concept has an intimate relationship to the concept of "end-of-life" care. Although it can provide the opportunity of a life-saving transplant, it is essential to maintain critical aspects, such as preserving dignity and respect for the donor, fulfilling the wishes of the patient and his/her family, and respecting their values. Also, focusing on alleviating any distress or pain, providing support, and avoiding unnecessary prolongation of the death process is paramount.[20]

DCD is still not utilized in many places due to logistics, lack of expertise of the transplant center, and ethical considerations, such as the acceptance of the concept of WLST.[21,22] In addition, there is no legislation regarding DCD in some countries (e.g., Brazil), which makes this process even more challenging.

In summary, there are many challenges to overcome in the DCD implementation process, as described in Figure 4. Many potential DCD donors are missed every year, and these donors could certainly and positively impact on patients waiting for a life-saving transplant.[23]

DIFFERENCES BETWEEN DCD AND DBD

Some differences between DBD and DCD have been discussed above, but two are critical and deserve special attention:

The first situation is the agonal phase. There are many definitions for this phase; in general, the most accepted concept is the interval between WLST and cardiac arrest. Here, a certain amount of time is expected for cardiac arrest to happen, usually ranging from a few minutes to 120 min.[24] The impact of the amount of time that the agonal phase represents and its relation to prognosis is undoubtedly an issue for discussion, given that intervals beyond 120 min have also been reported to be feasible in clinical transplantation.[25] This period is critical, and different patterns of injuries can happen due to the effects that WLST can have on the donor, such as hypotension, hypoxia, and aspiration.

The second issue is the duration of the warm ischemic time (WIT). WIT is generally the interval between the donor's systolic blood pressure < 50 mmHg and lung perfusion with a cold preservation solution via pulmonary artery flush.[26] In comparison with DCD, DBD has the WIT minimized as much as possible. Although this interval is deemed safe when it lasts < 60 min, the fact that the duration of WIT can potentially impair a patient's prognosis is still a matter of discussion and becomes critical for DCD, considering the different pathways that this type of donor follows.[27] In the opposite direction, it is important to discuss the fact that the brain dead status is associated with a process that involves complex pathophysiology in which inflammatory, sympathetic, and hemodynamic mechanisms can ultimately lead to lung injury.[28] These injuries can lead to neurogenic lung edema that can negatively impact on the outcome of LTx, especially

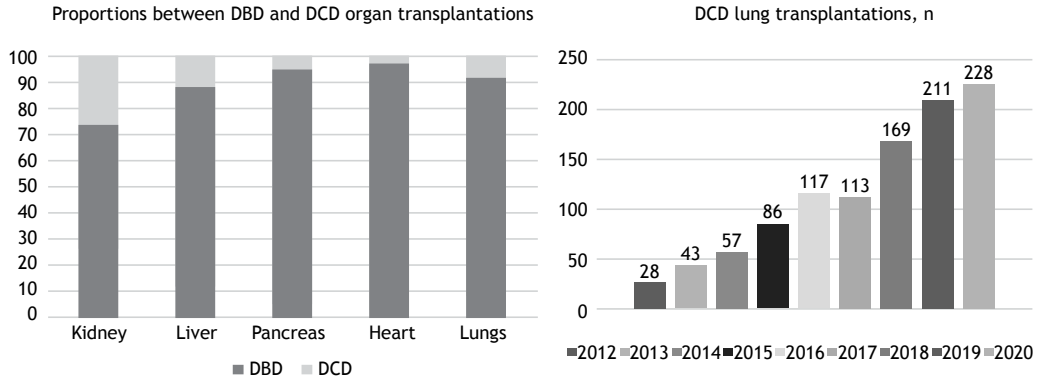

Figure 1. Proportions between donation after brain death (DBD) and donation after circulatory death (DCD) organ transplantations in 2020 and number of DCD lung transplantations between 2012 and 2020.*
*In accordance with data retrieved from the U.S. United Network for Organ Sharing website.

Chart 2. Donation after circulatory death classification.

Categories	Maastricht	Modified Maastricht
I	Dead on arrival at hospital	Found dead IA - Out of hospital IB - In-hospital
II	Death with unsuccessful resuscitation	Witnessed cardiac arrest IIA - Out of hospital IIB - In-hospital
III	Awaiting cardiac death	Withdrawal of life-sustaining therapy
IV	Cardiac arrest while brain dead	Cardiac arrest in a brain-dead patient prior to organ recovery
V		Euthanasia

Categories I and II - Uncontrolled donation after circulatory death
Categories III, IV and V - Controlled donation after circulatory death

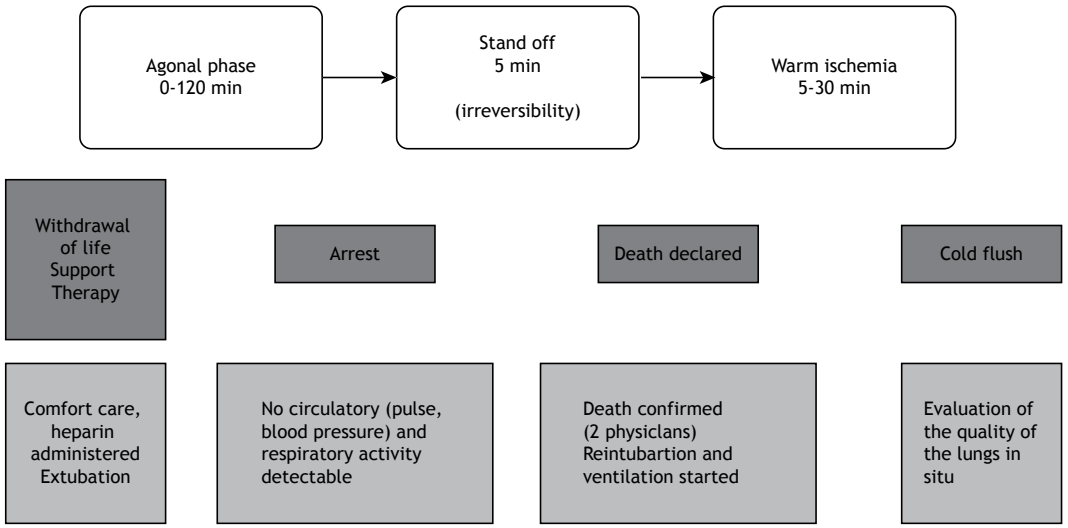

Figure 2. Process of donation after circulatory death.

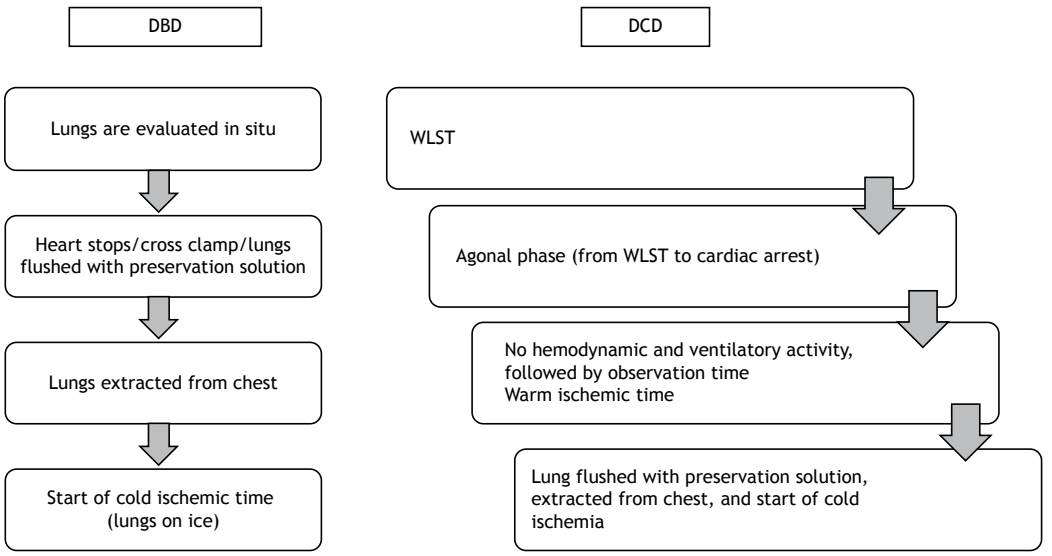

Figure 3. Donation process: donation after brain death (DBD) and donation after circulatory death (DCD). WLST: withdrawal of life-sustaining therapy.

in the early process of brain death.[29] Hence, DCD is potentially spared from this phenomenon since such donors are not exposed to the whole pathophysiological process involved in the brain death mechanism and its associated consequences.

More evidence has described the different pathways that DCD and DBD follow, which are also demonstrated in gene expression profiles. It appears that DBD has more commonly been associated with inflammatory profiles,[30] whereas DCD has shown donor-specific genetic signatures more associated with apoptosis and necrosis.[31]

HOW LONG CAN LUNG CELLS SURVIVE WITHOUT CIRCULATION?

Considering the DCD principles, a fundamental question related to this donation process is certainly for how long lung cells can survive so that the organ can be used for transplantation, since DCD implies a period during which lungs remain without circulation. To address this critical concept, an understanding of lung physiology is mandatory, and it is necessary to understand the lungs' particular capacity to maintain cell viability during WIT. Although this critical time can significantly impair the function of organs such as the liver, heart, kidney, and lungs, the latter can maintain cell viability when there is oxygen in the alveoli. Hence, even in the absence of circulation, ventilation of the lungs becomes paramount for the maintenance of cell viability. This concept is called aerobic lung preservation.[32]

After circulatory arrest, experimental data have shown that a state of atelectasis can be tolerated for 60 min at most without additional damage.[33] In this sense, it

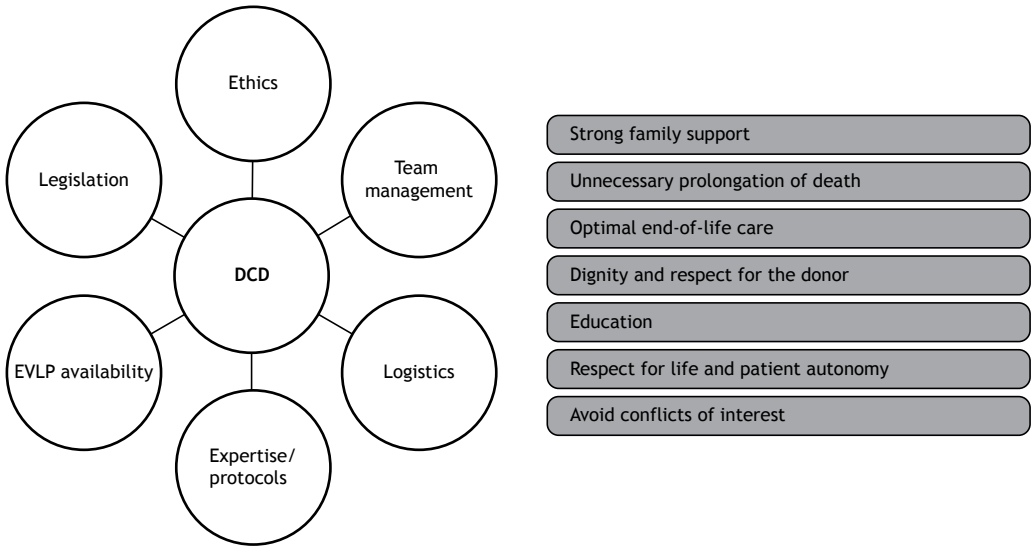

Figure 4. Potential barriers for donation after circulatory death (DCD) implementation and key principles. EVLP: ex vivo lung perfusion.

becomes critical to avoid collapse and atelectasis of the lungs, and its prevention appears to attenuate warm ischemic injury.[34,35] Also, the inflation of the lungs with oxygen seems to be a key component of preservation, because maintaining a reserve of oxygen in the alveoli can potentially minimize the effects of WIT.[36]

Having this in mind, a critical question is when lung cells start to die after cessation of circulation. In small animal models, the simple postmortem ventilation of lungs with oxygen seemed to attenuate ischemic injury to cells. In nonventilated rats, nonviable cells were 36%, 52%, and 77%, respectively, at 2, 4, and 12 h after death. Similar results were found in lungs ventilated with nitrogen. However, oxygen-ventilated cadaver rats had many less nonviable lung cells at the same time points: 13%, 10%, and 26%, respectively ($p < 0.01$), demonstrating that postmortem mechanical ventilation with oxygen can delay cell death.[37] The same research group also showed that, after 4-8 h from death, ultrastructural deterioration was significantly attenuated when oxygen ventilation was provided when compared with rats whose lungs were not ventilated.[38]

These data explain how lungs from DCD donors have the potential to maintain cell viability after cessation of circulation if ventilation/oxygen is provided, conferring a critical topic to be understood when we address this type of donation for clinical transplantation.

RESULTS OF CLINICAL EXPERIENCE WITH LTX USING DCD

A retrospective analysis carried out using the International Society for Heart and Lung Transplantation (ISHLT) circulatory death registry was published,[39] highlighting the experiences of many centers and their practices in the management of DCD, totalizing 306 LTx, between January of 2003 and June of 2013. The control group was constituted by DBD individuals available during the same period.

Most DCD donors were Maastricht category III, and several centers have reported their results with DCD LTx. When DCD and DBD were compared, there were no significant differences in 30-day mortality (96% vs. 97%), 1-year mortality (89% vs. 88%), or 5-year survival (61% vs. 61%).

A follow-up from the same ISHLT registry has been recently reported,[40] this time including more centers, involving patients submitted to LTx between 2003 and 2017 (1,090 DCD-related LTx), and equivalent long-term results were found between DCD and DBD.

These data show that DCD can be a safe resource to alleviate the waiting list of patients who desperately need a life-saving lung transplant. However, these reports addressed no critical perioperative data, such as incidence of primary graft dysfunction (PGD) and ICU length of stay (LOS). To address these issues, a review of retrospective single-center experiences focusing on these data is reported in Table 1.

These compiled data, in which DCD Maastricht category III was by far the most commonly used, also demonstrated no difference between medium- (1-year) or long-term survival, when DCD and DBD were compared regarding LTx.[25,41-45]

PGD is undoubtedly one of the critical factors that can influence the prognosis of patients submitted to LTx and is graded in accordance with the ISHLT classification.[46] Higher grades of PGD, especially at 72 h after LTx, are critical. However, DCD and DBD did not differ in the incidence of this complication at this time point. In addition, ICU LOS was equivalent, and hospital LOS also showed no differences, except for one report[45] that showed a longer hospital LOS in the DCD group.

Some of these studies also evaluated chronic lung allograft dysfunction (CLAD) or bronchiolitis obliterans syndrome (BOS). De Oliveira et al.[41] reported a 5-year

freedom-from-BOS rate of 72.3% for DCD and of 58.0% for DBD (p = 0.59). At one year after LTx, Van de Wauer et al.[42] described a significant advantage in the DCD group when compared with the DBD group. A favorable trend towards DCD was described by Ruttens et al.,[44] with a 5-year freedom from CLAD reported at 79.2% for DCD and 67.8% for DBD (p = 0.86). On the other hand, Sabashnikov et al.[43] reported a higher incidence of postoperative BOS in the DCD group (23.5%) than in the DBD group (11.7%; p = 0.049). Further analyses are necessary to clarify the relationship between DCD and CLAD.

Krutsinger et al.[47] reported his results using a systematic review and meta-analysis approach for comparison and found no differences in 1-year mortality, PGD, and acute rejection episodes when DCD and DBD groups were compared. More recently and using the same approach, Palleschi et al.[48] found no differences in 1-year survival, grade 2-3 PGD rates, or 1-year freedom from CLAD, but airway complications were more commonly found in the DCD group.

ETHICAL DILEMMAS

In some countries, the discussion about the use of controlled DCD is extremely complex because it involves WLST, end-of-life care, and cessation of futile therapies. In fact, in many instances, there is not even legislation that discusses DCD. This makes the dissemination of this process of donation even more challenging.

Although DCD Maastricht III is most commonly used for clinical transplantation, we need to understand that this type of DCD, together with Maastricht IV, comprises a situation in which the potential donor is so severely sick that death is anticipated, and this is not an easy issue to be accepted, understood, and respected in many places where there are different laws, ethical concerns, and religious beliefs. Unfortunately, the final product is that this potential pool of donors is restricted.

These "regulatory" boundaries potentially affect other DCD (uncontrolled Maastricht I and II categories). However, for other types of DCD to be used, other issues need to be tackled, such as the understanding of death and the irreversibility of situations. Taking this concept into consideration regarding uncontrolled DCD, when things can abruptly happen, such as a donor who dies at the arrival in the hospital or one who unfortunately dies after unsuccessful resuscitation efforts, may represent a different challenge for the families and the whole team involved in donation and transplantation. Education of the entire team involved in the donation process seems critical for developing a DCD program.[49] From a medical perspective, the challenge is undoubtedly a thorough understanding of the concept of death. The traditional standard of death remains the permanent cessation of circulation and respiration.[50]

Due to the nature of the events that can happen in these donation processes, it is paramount to educate the population and give support to the families when they are facing the most challenging times of their lives, dealing with the loss of a loved one. Hence, it is essential to understand the uncertainty about the timing of death and recognize efforts to optimize donation respecting the ethical boundaries.

Another critical point is that the introduction of DCD does not jeopardize the potential number of DBD donors. In fact, DCD seems to impact positively on the numbers of transplants and increase the number of DBD donors, potentially resulting from better donor referral policies, among others, which may play a role in this activity.[51]

Many people wish to donate their organs if, unfortunately, death happens; however, ultimately, the family will play a significant role in this critical decision, and the DCD process is different than that of conventional DBD.

DCD is, above all, an effort to save lives, and sometimes this type of donation can be unsuccessful for many reasons; for example, when the quality of the organ is not ideal or when the donor does not

Table 1. Perioperative data—donation after circulatory death vs. donation after brain death for lung transplantation.

Author	Year	DCD/DBD cases	DCD/DBD 1-year survival, %	DCD/DBD 5-year survival, %	DCD/DBD PGD, %[c]	ICU LOS	Hospital LOS
De Oliveira et al.[41]	2010	18/282	88/87	81.9/63.3	PGD Grade 2 or 3 within 72 h: 33.3/26.1	4/6	17/20
Van De Wauver et al.[42]	2011	35/77	91/91	73/66	PGD Grade 3 at 72 h: 6/11	4/5	32/33
Sabashnikov et al.[43]	2015	60/120	86.1/84.2	50.8/66.4	PGD Grade 3 at 72 h: 5/9	5/6	30/32
Ruttens et al.[44]	2017	59/331	87.3/90.9	70.9/78	Highest PGD < 72 h: 44.1/47.7	16.3/14.4	41.1/38.1
Costa et al.[45]	2018	46/237	91/92	78/75[a]	PGD Grade 3 at 72 h: 13/17	N/A	22/18*
Qaqish et al.[25]	2021	180/1088	N/A	8.0/6.9[b]	PGD Grade 2 and 3 at 72 h: 17.2 and 13.9/9, respectively	4.0	23/25

DCD: donation after circulatory death; DBD: donation after brain death; PGD: primary graft dysfunction; and LOS: length of stay. [a]Last follow-up three years after lung transplantation. [b]Values expressed as median of survival in years (p = 0.79). [c]In accordance with Snell et al.[46] *Statistically significant.

have cardiac arrest within a suitable time after WLST. However, even families of donors after circulatory death whose donation was unsuccessful appreciate the donation attempt. Families have reported that unsuccessful donation drawbacks are the waste of an organ highly needed, a lost opportunity to honor their loved one, and the loss of a way to ease their grief.[52]

A comprehensive education process for those involved in these types of donations is necessary to avoid potential conflicts in any possible step within the organ donation process. Education is vital to be tailored appropriately for each component of the decision making and management of DCD. Perceptions of the process can differ according to the family's perspective and the professionals involved in the transplant process.[53]

ADVANCES IN THE DCD—UNCONTROLLED DCD

The progressive acceptance of DCD has been important in order to increment the number of transplants and, as a result, save more lives. To move this discussion to the next phase, uncontrolled DCD is undoubtedly an area that needs to be addressed, considering the significant pool of donors in these categories.

Although uncontrolled DCD was not associated with the expected outcomes in the past,[54] recent data have shown promising results[55] and demonstrated some exciting concepts that potentially contributed to the reported outcomes and can undoubtedly benefit and help disseminate uncontrolled DCD.

Regarding lung preservation, a simple maneuver such as in situ lung inflation using a CPAP of 20 cmH_2O could protect an extended WIT (which, in the authors' experience,[55] was reported to be 2.8 h), creating critical time for the whole process of donation to happen. This period of time is significant for the lungs to be deprived of blood nourishment and to depend on aerobic lung preservation for maintenance of cell viability. In addition, the importance of EVLP was critical. During uncontrolled donation, many injuries can occur to the lungs, and EVLP would work to stratify better lungs that can maintain adequate function. With the anticipated expanded WIT intervals for uncontrolled DCD, the use of EVLP becomes an essential tool for organ usage.[56]

Despite the conflicting results presented with uncontrolled DCD, the development of standard protocols for donor management is critical to a better determination of outcomes, eventually disseminating this pool of donors.[57]

Ethical concerns such as the determination of irreversibility of cardiac arrest, the extension of resuscitation beyond futility, and the determination of death, as well as how to approach family members about uncontrolled DCD, are all areas that need to be taken into consideration to promote this mode of donation further.[58] However, it is undeniable that this modality can be a valuable resource for patients on the waiting list for a life-saving transplant.[59]

In summary, DCD does have the potential to impact significantly on the number of transplants. Clinical results to date have demonstrated excellent outcomes, at least equivalent to those of DBD. Ethical, cultural, and legislative barriers need to be further addressed in countries such as Brazil, so that this valuable source of organ donors can be fully utilized.

AUTHOR CONTRIBUTIONS

PARS: article design; drafting and review of the manuscript; final approval of the manuscript. DMMN, PJZT, and MC: review and final approval of the manuscript.

CONFLICT OF INTEREST

None declared.

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Bedaquiline-containing regimens and multidrug-resistant tuberculosis: a systematic review and meta-analysis

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ABSTRACT

Objective: Multidrug-resistant tuberculosis (MDR-TB) is a life-threatening infectious disease. Treatment requires multiple antimicrobial agents used for extended periods of time. The present study sought to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients. **Methods:** This was a systematic review and meta-analysis of studies published up to March 15, 2021. The pooled treatment success rates and 95% CIs were assessed with the fixed-effect model or the random-effects model. Values of $p < 0.05$ were considered significant for publication bias. **Results:** A total of 2,679 articles were retrieved by database searching. Of those, 29 met the inclusion criteria. Of those, 25 were observational studies (including a total of 3,536 patients) and 4 were experimental studies (including a total of 440 patients). The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0) in the observational studies and 86.1% (95% CI, 76.8-92.1; $p = 0.00$; $I^2 = 75\%$) in the experimental studies. There was no evidence of publication bias ($p > 0.05$). **Conclusions:** In patients with MDR-TB receiving bedaquiline, culture conversion and treatment success rates are high even in cases of extensive resistance.

Keywords: Tuberculosis; Drug resistance; Tuberculosis, multidrug-resistant; Efficacy.

INTRODUCTION

Tuberculosis is a life-threatening infectious disease. In 2020, the WHO estimated a total of 10 million tuberculosis cases, 1,400,000 deaths (including 208,000 deaths among people living with HIV), and 465,000 cases of drug-resistant tuberculosis.[1]

Over the last two decades, the global epidemiology of mycobacterial drug resistance has deteriorated, especially with the emergence and spread of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB).[1] MDR-TB is caused by *Mycobacterium tuberculosis* strains resistant to at least isoniazid and rifampin. MDR-TB with further resistance to any fluoroquinolone and at least one of the three injectable second-line drugs, i.e., kanamycin, amikacin, and capreomycin, was initially defined as XDR-TB.[2] However, the WHO has recently modified the definition of XDR-TB, focusing on resistance to group A drugs, which include bedaquiline.[3,4] The WHO has also introduced the definition of pre-XDR-TB, i.e., MDR-TB strains with additional resistance to fluoroquinolones.[4]

MDR-TB treatment outcomes are poor, with approximately 50% of patients achieving treatment success. A significant factor contributing to treatment failure in many settings is the lack of effective drugs to manage MDR-TB and XDR-TB.[1] Moreover, MDR-TB treatment is long and expensive. Numerous efforts have been made to shorten the therapeutic courses and develop more effective medications. Thus, several new drugs for tuberculosis treatment have been evaluated, including linezolid and some new drugs with novel mechanisms of action, such as bedaquiline and delamanid.[5]

The WHO has recommended bedaquiline and delamanid for the treatment of MDR-TB.[6] Bedaquiline, a diarylquinoline that inhibits mycobacterial ATP synthase, is the first antituberculosis drug in 40 years to be approved for MDR-TB patients.[7-9]

The 2018 WHO guidelines recommend bedaquiline as the first drug in an all-oral regimen designed to maximize treatment outcomes while minimizing the toxicity of injectable agents.[6]

Over the last few years, several studies have assessed the efficacy of bedaquiline.[3,10,11] However, a

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comprehensive analysis has not yet been performed. Thus, the objective of the present study was to evaluate the treatment success rate of bedaquiline-based regimens in MDR-TB patients.

METHODS

Search strategy

We searched MEDLINE (PubMed), EMBASE, and Cochrane Library for studies reporting the efficacy of individualized regimens containing bedaquiline in patients with culture- and drug susceptibility testing-confirmed MDR/XDR-TB, published up to March 15, 2021. The search terms were as follows: ((tuberculosis(Title/Abstract)) AND (bedaquiline(Title/Abstract)) AND (efficacy(Title/Abstract) OR effectiveness(Title/Abstract))). Only studies written in English were selected. This study was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement.[12]

Study selection

The records found through database searching were merged, and the duplicates were removed using EndNote X7 (Thomson Reuters, Toronto, ON, Canada). Two reviewers independently screened the records by title/abstract and full text to exclude those unrelated to the study topic. Included studies met the following criteria: (i) patients diagnosed with MDR-TB on the basis of the WHO criteria[1]; (ii) patients treated with bedaquiline-containing regimens; and (iii) treatment success (i.e., culture conversion). Conference abstracts, editorials, reviews, experimental studies on animal models, and articles describing tuberculosis patients recruited without a confirmed bacteriological diagnosis were excluded.

Pre-XDR-TB was defined as tuberculosis caused by *M. tuberculosis* strains that fulfill the definition of MDR-TB/rifampin-resistant tuberculosis and that are also resistant to any fluoroquinolone, whereas XDR-TB was defined as tuberculosis caused by *M. tuberculosis* strains that fulfill the definition of MDR-TB/rifampin-resistant tuberculosis and are also resistant to any fluoroquinolone and at least one additional group A drug.[4]

Treatment outcomes were recorded in accordance with adapted definitions of those given in the WHO guidelines, as follows: treatment success, defined as the combination of the number of patients who were cured and that of those who completed treatment; death, defined as death from any cause while on treatment; and treatment failure, defined as unsuccessful treatment, as determined by positive cultures at the end of the treatment regimen.[13]

Data extraction

Two reviewers designed a data extraction form and extracted data from all eligible studies, with differences being resolved by consensus. The following data were extracted: first author's name; year of publication; study duration; type of study; country or countries where the study was conducted; number of patients with MDR-TB; patient age; treatment protocols (treatment regimens and duration of treatment); HIV history; demographics; adverse effects; drug resistance status; and outcomes.

Quality assessment

Two blinded reviewers assessed the quality of the studies using two different assessment tools (checklists): one for observational studies and one for experimental studies.[14] Items such as study population, measure of exposures, confounding factors, extent of outcomes, follow-up data, and statistical analysis were evaluated.

Data analysis

Statistical analyses were performed with Comprehensive Meta-Analysis software, version 2.0 (Biostat Inc., Englewood, NJ, USA). The pooled success rate with 95% CI was assessed using the random-effects model or the fixed-effect model. The random-effects model was used because of the estimated heterogeneity of the true effect sizes. Between-study heterogeneity was assessed by Cochran's Q test and the I^2 statistic. Subgroup analyses stratified by type of study and treatment regimen (bedaquiline-based regimen, delamanid-based regimen, or both) were performed to minimize heterogeneity. Publication bias was statistically assessed by using Egger's test and Begg's test, as well as funnel plots, a value of $p < 0.05$ being considered indicative of statistically significant publication bias and funnel plot asymmetry being suggestive of bias.[15]

RESULTS

The article selection process is shown in Figure 1. A total of 2,679 articles were found by database searching; after the removal of duplicates, the titles and abstracts of 1,946 articles were screened. Of those, 44 met the inclusion criteria and were selected for a full-text review. After the full-text review, 29 were chosen. The studies[10,11,16-42] were divided into two groups: 25 observational studies, including a total of 3,536 patients, and 4 experimental studies, including a total of 440 patients (Table 1). The earliest study was published in 2014, and the latest studies were published in 2021. The mean age of the patients was 39.0 years.

Quality of the included studies

The checklist for observational studies[14] showed that the included observational studies had a low risk of bias (Table 2). In contrast, the checklist for experimental studies[14] showed that the included experimental studies had a high risk of bias for randomization, group concealment, participant assignment, and assessor blinding (Table 3).

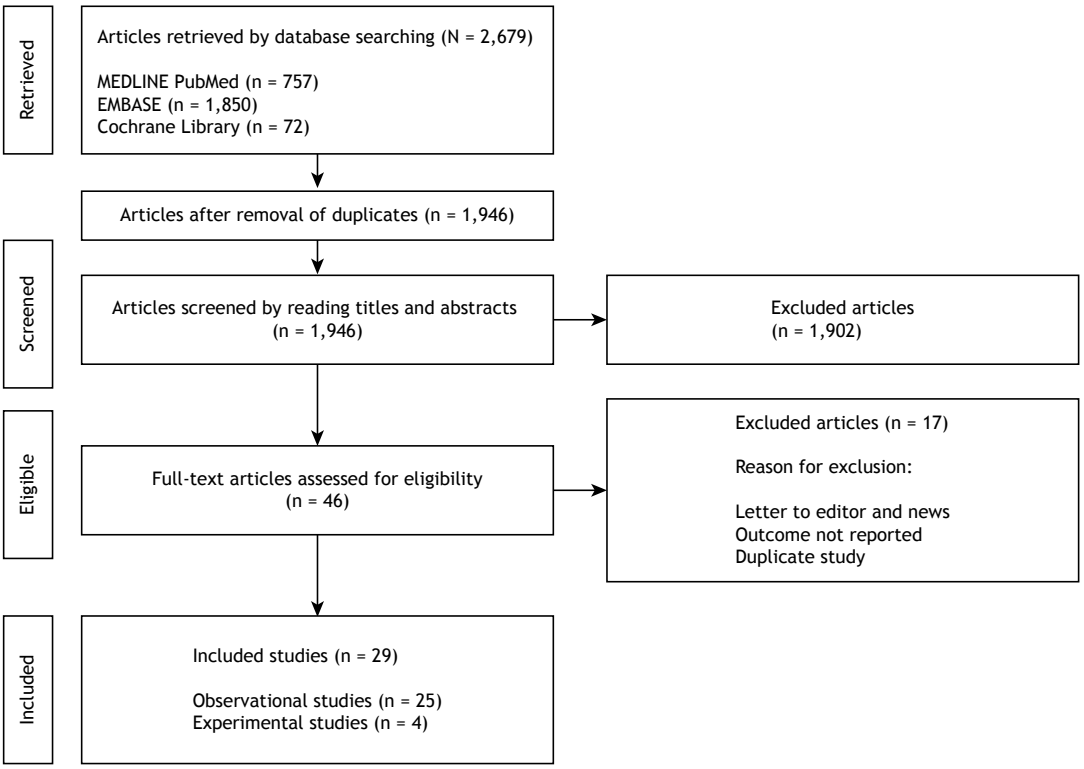

Figure 1. Flow chart of study selection for inclusion in the systematic review and meta-analysis.

Outcomes in the observational studies

The pooled treatment success rate was 74.7% (95% CI, 69.8-79.0; I^2 = 86%; Figure 2). There was no evidence of publication bias ($p > 0.05$).

The pooled death and treatment failure rates were 9.0% (95% CI, 6.8-12.0; I^2 = 75%) and 5.7% (95% CI, 3.6-8.9; I^2 = 85%), respectively.

Outcomes in the experimental studies

The pooled treatment success rate was 86.1% (95% CI, 76.8-92.1; p = 0.00; I^2 = 75%; Figure 3). There was no evidence of publication bias ($p > 0.05$).

Mortality rates were reported in 2 studies, and the pooled death rate was 3.6% (95% CI, 0.6-9.2). Only 1 study reported a treatment failure rate, which was 1.8%.

Adverse effects

Most of the adverse events potentially attributed to bedaquiline-containing regimens were gastrointestinal symptoms (15.3%), peripheral neuropathy (13.8%), and hematological disorders (13.6%; Table 4). Although there was limited information on how many patients interrupted bedaquiline treatment because of an increase in the Fridericia-corrected QT interval, 283 of 2,611 patients experienced Fridericia-corrected QT interval prolongation (pooled rate, 10.4%).

Subgroup analysis

Table 5 shows the subgroup analysis of the studies based on the treatment regimen and type of study. The treatment success rate in patients receiving bedaquiline-containing regimens was 74.5%. For patients receiving treatment with bedaquiline and delamanid, the treatment success rate was 73.9%. The treatment success rates in the observational and experimental studies included in the meta-analysis were 74.7% and 86.1%, respectively.

DISCUSSION

Drug-resistant tuberculosis treatment has severe limitations, such as extensive drug resistance limiting the number of effective drugs, a high risk of adverse events, and a high treatment failure rate. In 2020 the WHO introduced a new approach to managing drug-resistant tuberculosis and a new drug classification.[4] According to the WHO recommendations, bedaquiline is the first drug in an all-oral regimen to optimize treatment outcomes while minimizing the toxicity associated with injectable medicines.[6] Although some studies have been conducted on bedaquiline and delamanid to discuss their benefits and drawbacks, no systematic reviews and meta-analyses have recently been published on this topic.

In the current study, we screened 2,679 articles and finally selected 29 studies reporting on 3,929 patients and describing the treatment outcomes of bedaquiline-containing regimens. A pooled treatment success rate of 74.7% was found for bedaquiline-containing regimens in the observational studies. In the experimental studies, the pooled treatment success rate was 86.1%.

Table 1. Observational and experimental studies included in the meta-analysis.

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Koirala et al.[11]	2021	Multicenter	PC	39	27 (5.7)	329	MDR/XDR	383	WHO-recommended regimen	6	284	11	25
Kwon et al.[16]	2021	South Korea	RC	49	0	19	Pre-XDR/ XDR	28	DLM+LZD+CFZ+MEM/CLV+CYC	6	23	2	1
Shi et al.[17]	2021	China	RC	49.8	N/R	186	MDR	72	FLQs+LZD+CFZ+CYC	6	197	4	0
							pre-XDR	78					
							XDR	64					
Gao et al.[18]	2021	China	RC	40	1 (0.6)	168	MDR	39	FLQs+LZD+CFZ+CYC	6	151	23	3
							pre-XDR	56					
							XDR	82					
Barvaliya et al.[19]	2020	India	PC	31	N/R	110	Pre-XDR	87	FLQs+LZD+CFZ	5.5	102	10	14
							XDR	40					
Kashongwe et al.[20]	2020	Congo	RC	32.4	3 (9.4)	23	Pre-XDR	29	FLQs+LZD+CFZ+CYC	20	17	0	15
							XDR	3					
Das et al.[21]	2020	India	RC	Children/ adolescents	0	N/R	Pre-XDR/ XDR	13	DLM+ LZD+CFZ	22	12 or 13	N/R	N/R
Lee et al.[22]	2020	South Korea	RC	49.8	1 (1.4)	49	MDR	13	DLM+FLQs+ LZD+CFZ+CYC	5.5	42	1	4
							Pre-XDR	41					
							XDR	20					
Kim et al.[23]	2020	South Korea	RC	33	9 (3.5)	254	MDR	159	AMGs+FLQs+LZD+CYC	6	139/225	35/225	15/225
							Pre-XDR	51					
							XDR	44					
Mase et al.[24]	2020	USA	RC	43.5	1 (7)	5	MDR	7	WHO-recommended regimen	5.5	12	N/R	1
							Pre-XDR	4					
							XDR	3					
Olayanju et al.[25]	2020	South Africa	PC	33	42 (51)	40	MDR	5	AMGs+FLQs+LZD+CFZ+TRD	6	52	N/R	N/R
							Pre-XDR	10					
							XDR	67					
				34	22 (55)	29	MDR	6	DLM+AMGs+FLQs+LZD+CFZ+TRD	6	27	N/R	N/R
							Pre-XDR	15					
							XDR	19					

Continue...▶

Table 1. Observational and experimental studies included in the meta-analysis. (Continued...)

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Salhotra et al.[26]	2020	India	PC	Range: 18-50	8 (1.3)	600	MDR	524	AMGs+FLQs+CFZ	6	513	N/R	73
							XDR	96					
Chesov et al.[27]	2020	Moldova	RC	37	17 (14.9)	58	MDR	114	AMGs+FLQs+CYC+PZA	6	63	31	10
Kang et al.[28]	2020	South Korea	RC	51.7	0	55	MDR	43	AMGs+FLQs+LZD+CYC	6	86	1	13
							Pre-XDR	47					
							XDR	17					
				47.7	1 (1.5)	47	MDR	8	DLM+AMGs+FLQs+LZD+CYC	6	58	3	3
							Pre-XDR	37					
							XDR	22					
Sarin et al.[29]	2019	India	PC	Range: 21-33	0	N/R	MDR/ Pre-XDR/ XDR	42	DLM+ FLQs+LZD+CFZ+IMP	6	25	N/R	10
Kempker et al.[30]	2019	USA	PC	37.3	2 (3)	8	MDR/XDR	64	FLQs+LZD+CFZ+CYC+IMP	5.5	42	1	0
Taune et al.[31]	2019	New Guinea	RC	39	1 (1.3)	33	MDR	55	AMGs+FLQs+LZD+CFZ+CYC+PZA	6	72	N/R	5
							Pre-XDR	10					
							XDR	12					
Ferlazzo et al.[32]	2018	Armenia, India, South Africa	RC	32.5	11 (39)	4	MDR	2	DLM+ FLQs+LZD+CFZ+IMP	6	22	N/R	1
							Pre-XDR	12					
							XDR	14					
Hewison et al.[33]	2018	Armenia, Georgia	RC	40.5	4 (4.8)	N/R	MDR	6	FLQs+LZD+CFZ+IMP	6	48	6	10
							Pre-XDR	36					
							XDR	40					
Ndjeka et al.[34]	2018	South Africa	PC	34	134 (67)	N/R	Pre-XDR	122	FLQs+LZD+CFZ	6	146	9	25
							XDR	78					
Zhao et al.[35]	2018	South Africa	RC	Range: 35-49	110 (68)	N/R	MDR	162	FLQs+PZA+ETH+hINH+ETM+TRD	6	111/146	7/119	11/145
Kim et al.[36]	2018	South Korea	RC	52	N/R	N/R	MDR/ Pre-XDR/ XDR	39	FLQs+LZD+CFZ	5.6	24	N/R	N/R

Continue...▶

Table 1. Observational and experimental studies included in the meta-analysis. (Continued...)

Author	Year	Country	Type of study	Mean/ median age	HIV +, n (%)	Previously treated for TB	TB disease	No. of patients receiving BDQ	Other drugs included in the regimen	Duration of treatment (months)	Outcomes		
											Treatment success	Treatment failure	Death
Achar et al.[37]	2017	South Africa, Tajikistan, Uzbekistan, Belarus	PC	Children/ adolescents	0	N/R	Pre-XDR/ XDR	23	FLQs+LZD+CFZ+IMP	6	23	0	0
Guglielmetti et al.[38]	2017	France	RC	38	2 (4.4)	34	MDR/ Pre-XDR/ XDR	45	AMGs+FLQs+LZD+CFZ+CYC+PZA+ETH+ETM	6	36	1	3
Borisov et al.[10]	2017	Multicenter	RC	35	94 (22.1)	334	MDR	233	AMGs+FLQs+LZD+CFZ+IMP	5.5	176/247	18/247	33/247
							XDR	195					
Conradie et al.[39]	2020	South Africa	CT	35	56 (51)	N/R	MDR	38	LZD+PMD	6	98	2	7
							XDR	71					
Tweed et al.[40]	2019	South Africa, Tanzania, Uganda	CT	34	25 (42)	N/R	RR	60	FLQs+PZA+PMD	6	58	N/R	0
Pym et al.[41]	2016	Multicenter	CT	32	8 (4)	177	MDR	124	AMGs+FLQs+ CYC+PZA+ETH	6	163	N/R	N/R
							Pre-XDR	44					
							XDR	37					
Diacon et al.[42]	2014	Multicenter	CT	32	5 (8)	N/R	MDR	66	AMGs+FLQs+ CYC+PZA+ETH	6	52	N/R	N/R

PC: prospective cohort; RC: retrospective cohort; CT: clinical trial; BDQ: bedaquiline; DLM: delamanid; FLQs: fluoroquinolones; LZD: linezolid; CFZ: clofazimine; CYC: cycloserine; AMGs: aminoglycosides; MEM/CLV: meropenem-clavulanate; TRD: terizidone; IMP: imipenem; ETH: ethionamide; hINH: high-dose isoniazid; ETM: ethambutol; PZA: pyrazinamide; PMD: pretomanid; MDR: multidrug-resistant; XDR: extensively drug-resistant; RR: rifampin-resistant; and N/R: not reported.

Table 2. Quality assessment of the observational studies included in the meta-analysis.

Author	1	2	3	4	5	6	7	8	9	10	11
Koirala et al.[11]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kwon et al.[16]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Shi et al.[17]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Gao et al.[18]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Barvaliya et al.[19]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kashongwe et al.[20]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Das et al.[21]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Lee et al.[22]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al.[23]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Mase et al.[24]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Olayanju et al.[25]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Salhotra et al.[26]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Chesov et al.[27]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kang et al.[28]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Sarin et al.[29]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kempker et al.[30]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Taune et al.[31]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ferlazzo et al.[32]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Hewison et al.[33]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Ndjeka et al.[34]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Zhao et al.[35]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Kim et al.[36]	Yes	Yes	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Achar et al.[37]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Guglielmetti et al.[38]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Borisov et al.[10]	N/A	N/A	Yes	No	No	Yes	Yes	Yes	Yes	Yes	Yes

1. Were the two groups similar and recruited from the same population?
2. Were the exposures measured similarly to assign people to both exposed and unexposed groups?
3. Was the exposure measured in a valid and reliable way?
4. Were confounding factors identified?
5. Were strategies to deal with confounding factors stated?
6. Were the groups/participants free of the outcome at the start of the study?
7. Were the outcomes measured in a valid and reliable way?
8. Was the follow-up time reported and long enough for outcomes to occur?
9. Was follow-up complete, and, if not, were the reasons for loss to follow-up described and explored?
10. Were strategies to address incomplete follow-up utilized?
11. Was appropriate statistical analysis used?

Table 3. Quality assessment of the experimental studies included in the meta-analysis.

Author	1	2	3	4	5	6	7	8	9	10	11	12	13
Conradie et al.[39]	No	N/A	N/A	No	No	No	No	Yes	Yes	N/A	Yes	Yes	No
Tweed et al.[40]	Yes	No	Yes	No	No	No	No	Yes	Yes	Yes	Yes	Yes	Yes
Pym et al.[41]	No	No	N/A	No	No	No	No	Yes	Yes	N/A	Yes	Yes	No
Diacon et al.[42]	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes

1. Was true randomization used for assignment of participants to treatment groups?
2. Was allocation to treatment groups concealed?
3. Were treatment groups similar at baseline?
4. Were participants blind to treatment assignment?
5. Were those delivering treatment blind to treatment assignment?
6. Were outcome assessors blind to treatment assignment?
7. Were treatment groups treated identically other than the intervention of interest?
8. Was follow-up complete, and, if not, were differences between groups in terms of their follow-up adequately described and analyzed?
9. Were participants analyzed in the groups to which they were randomized?
10. Were outcomes measured in the same way for treatment groups?
11. Were outcomes measured in a reliable way?
12. Was appropriate statistical analysis used?
13. Was the trial design appropriate and were any deviations from the standard randomized controlled trial design accounted for in the conduct and analysis of the trial?

Study	Statistics for each study			Weight (Random)	Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Relative weight	
Koirala et al.[11]	0.742	0.695	0.783	5.16	
Kwon et al.[16]	0.821	0.636	0.924	2.94	
Shi et al.[17]	0.921	0.876	0.950	4.43	
Gao et al.[18]	0.853	0.793	0.898	4.68	
Barvaliya et al.[19]	0.803	0.725	0.863	4.61	
Kashongwe et al.[20]	0.531	0.361	0.694	3.77	
Das et al.[21]	0.923	0.609	0.989	1.14	
Lee et al.[22]	0.568	0.453	0.675	4.54	
Kim et al.[23]	0.618	0.553	0.679	5.08	
Mase et al.[24]	0.857	0.573	0.964	1.79	
Olayanju et al.[25]	0.648	0.559	0.727	4.81	
Salhotra et al.[26]	0.827	0.796	0.855	5.20	
Chesov et al.[27]	0.553	0.461	0.641	4.82	
Kang et al.[28]	0.828	0.764	0.877	4.75	
Sarin et al.[29]	0.595	0.443	0.731	4.03	
Kempker et al.[30]	0.656	0.533	0.762	4.36	
Taune et al.[31]	0.935	0.853	0.973	3.11	
Ferlazzo et al.[32]	0.786	0.598	0.900	3.12	
Hewison et al.[33]	0.585	0.476	0.687	4.61	
Ndjeka et al.[34]	0.730	0.664	0.787	4.97	
Zhao et al.[35]	0.760	0.684	0.823	4.78	
Kim et al.[36]	0.615	0.456	0.753	3.93	
Achar et al.[37]	0.979	0.741	0.999	0.67	
Guglielmetti et al.[38]	0.800	0.658	0.893	3.65	
Borisov et al.[10]	0.713	0.653	0.766	5.06	
	0.747	0.698	0.790		

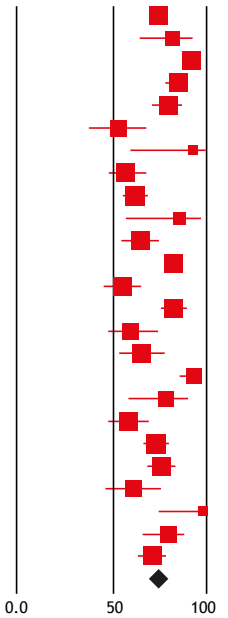

Figure 2. Treatment success rate in the observational studies included in the meta-analysis.

Study	Statistics for each study			Weight (Random)	Event rate and 95% CI
	Event rate	Lower limit	Upper limit	Relative weight	
Conradie et al.[39]	0.899	0.827	0.943	26.77	
Tweed et al.[40]	0.967	0.876	0.992	12.90	
Pym et al.[41]	0.795	0.734	0.845	32.81	
Diacon et al.[42]	0.788	0.673	0.870	27.52	
	0.861	0.768	0.921		

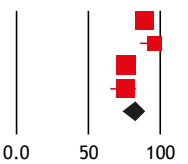

Figure 3. Treatment success rate in the experimental studies included in the meta-analysis.

Previous studies have shown that adding bedaquiline to regimens effectively reduces drug-resistant tuberculosis.[10,43] However, some studies have raised the issue of its potential toxicity, mainly when delamanid and other drugs prolonging the QT interval are prescribed in the regimen (e.g., fluoroquinolones and clofazimine).[10,43]

Two previous systematic reviews on bedaquiline, one published in 2016 and the other in 2018, included a small number of patients. In a systematic review of 2 randomized controlled trials (which were published as 3 articles) including 176 patients, no differences in culture conversion were found between bedaquiline and placebo.[44] Even though the point estimate showed a 33% improvement in the response rate with the use of bedaquiline vs. placebo, this finding was not statistically significant, because of the small sample sizes.[44]

Pontali et al. reported an 81.4% sputum culture conversion rate after 6 months of treatment and a 71.4% treatment success rate in a systematic review including 7 studies investigating 87 adults with drug-resistant tuberculosis treated with delamanid and bedaquiline.[45]

In a phase 2 trial conducted by Diacon et al., 160 patients were randomly assigned to receive either 400 mg of bedaquiline once daily for 2 weeks, followed by 200 mg three times a week for 22 weeks, or placebo, both in combination with a preferred background regimen.[42] The authors demonstrated that adding bedaquiline to a preferred background regimen for 24 weeks resulted in faster culture conversion and a significantly higher culture conversion rate at 120 weeks. The cure rate at 120 weeks was 58% in the bedaquiline group and 32% in the placebo group.[42]

In a cohort study conducted by Mbuagbaw et al. and involving 537 patients treated with bedaquiline, the use of bedaquiline in the treatment regimen for > 6 months was related to positive outcomes, with a culture conversion rate of 78% at 6 months and a treatment success rate of 65.8%.[46] In a retrospective cohort study of 102 patients, the long-term outcome and

Table 4. Adverse effects in the studies included in the meta-analysis.

Author	QTc prolongation	Liver disease/ Elevated liver enzyme	Renal failure/ Increased creatinine levels	Optic neuropathy/ Blurred vision	Ototoxicity/ Hearing loss	Hematological disorders (anemia, thrombocytopenia, eosinophilia)	Gastrointestinal symptoms (diarrhea, vomiting, nausea, abdominal pain)	Peripheral neuropathy	Electrolyte disturbance	Arthralgia	Psychiatric disorder	Dermatological symptoms
Kwon et al.[16]	17	NR	N/R	N/R	N/R	N/R	1	N/R	N/R	N/R	N/R	N/R
Shi et al.[17]	85	59	21	13	10	24	15	16	5	3	9	2
Gao et al.[18]	39	35	9	2	6	15	11	8	11	2	6	N/R
Barvaliya et al.[19]	11	6	N/R	5	4	N/R	33	4	N/R	9	4	18
Kashongwe et al.[20]	3	1	N/R	2	5	14	15	15	N/R	N/R	N/R	15
Das et al.[21]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Lee et al.[22]	23	N/R	1	N/R	N/R	N/R	4	N/R	N/R	N/R	N/R	N/R
Kim et al.[23]	7	28	N/R	N/R	N/R	N/R	32	N/R	N/R	34	N/R	8
Mase et al.[24]	6	N/R	N/R	N/R	2	2	4	7	4	N/R	3	3
Olayanju et al.[25]	12	36	N/R	8	59	43	30	30	N/R	20	9	N/R
Salhotra et al.[26]	14	13	4	N/R	8	22	35	26	7	N/R	15	1
Kempker et al.[30]	1	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Taune et al.[31]	1	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Ferlazzo et al.[32]	4	N/R	1	N/R	N/R	N/R	1	1	N/R	N/R	2	N/R
Hewison et al.[33]	12	27	5	1	9	3	34	21	N/R	N/R	N/R	6
Ndjeka et al.[34]	10	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Achar et al.[37]	0	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Guglielmetti et al.[38]	13	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Borisov et al.[10]	24/248	N/R	47/413	10/413	N/R	86/412	130/413	96/412	N/R	84/412	29/413	63/412
Conradie et al.[39]	0	17	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Tweed et al.[40]	0	4	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R	N/R
Efeito aleatório combinado	10.4 (6.2-17.0)	11.7 (6.5-20.0)	4.6 (2.3-8.9)	3.8 (2.4-6.1)	7.8 (2.3-23.0)	13.6 (7.1-24.7)	15.3 (7.5-24.1)	13.8 (9.4-24.0)	4.7 (1.3-15.2)	8.1 (4.3-14.6)	5.1 (3.3-7.9)	7.5 (3.3-16.0)
Heterogeneidade, I^2 (%)	92%	93%	85%	50%	96%	94%	94%	94%	89%	89%	68%	91%
Teste de Begg, p	0.46	0.21	0.13	0.54	0.90	0.71	0.90	0.72	0.65	0.00	0.82	0.22

QTc: corrected QT; and N/R: not reported.

Table 5. Pooled treatment success rates for subgroups of studies.

Subgroup	No. of studies	No. of patients	Treatment success rate (%) (95% CI)	Heterogeneity I^2 (%)	Begg's test value of p
Treatment regimen:					
Regimen containing BDQ	22	3,287	74.5 (67.6-80.3)	91	0.61
Regimen containing BDQ+DLM	7	292	73.9 (62.1-83.0)	72	0.03
Type of study:					
Observational study	25	3,536	74.7 (69.8-79.0)	86	0.18
Experimental study	4	440	86.1 (76.8-92)	75	0.08

BDQ: bedaquiline; and DLM: delamanid.

safety of prolonged MDR-TB treatment with bedaquiline (for > 190 days) was investigated.[38] Outcomes and adverse effects were not significantly different between short-course and prolonged bedaquiline treatment, and most patients on bedaquiline-containing regimens achieved successful outcomes.[38]

Bedaquiline at treatment initiation and as part of an all-oral regimen may preserve good overall treatment outcomes while improving time to culture conversion and minimizing adverse effects, such as hearing loss, associated with the injectable agents.[24]

We found that a proportion of patients had adverse events related to bedaquiline in the studies included in our meta-analysis: 15.3% reported gastrointestinal symptoms, 13.8% had evidence of peripheral neuropathy, and 13.6% reported hematological toxic effects. Although patients taking bedaquiline should be carefully monitored, the adverse effects were manageable in the investigated studies, and adverse events leading to the discontinuation of bedaquiline were uncommon.

Although our study provides updated evidence on bedaquiline efficacy, it has some limitations. It does not evaluate adherence to treatment regimens containing bedaquiline, an important outcome determinant. Other limitations include variability and different patient characteristics across studies.

In conclusion, culture conversion and treatment success rates were found to be high in patients with drug-resistant tuberculosis receiving bedaquiline-containing regimens. Bedaquiline use can be implemented successfully in tuberculosis programs if financial and procurement barriers can be addressed to ensure availability. An efficient monitoring and surveillance system is needed to collect data on patients receiving new drugs and regimens to ensure best practices for the care and treatment of patients with drug-resistant tuberculosis.

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AUTHOR CONTRIBUTIONS

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

CONFLICTS OF INTEREST

None declared.

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Pulmonary metastasis of osteosarcoma: multiple presentations in a single patient

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TO THE EDITOR,

Osteosarcomas are the most common primary bone tumors.[1] Approximately 20% of patients with osteosarcoma present metastatic disease at the time of diagnosis, with the lung being the main organ affected.[2] The early diagnosis of pulmonary metastasis may be critical for planning effective therapy.[3] For this reason, chest CT screening should be considered. Usually, pulmonary metastases appear as multiple rounded nodules of various sizes, predominating in the lower portions of the lungs and sparing the apices.[4] However, they may have an atypical presentation. Herein, we describe an unusual case in which multiple atypical lung metastases were detected during treatment in a young male with femoral osteosarcoma.

A 16-year-old male was admitted to an oncology referral service due to the presence of a tumor in the right distal femur. Right thigh radiography revealed a bone lesion with aggressive proximal periosteal reactions (forming a Codman triangle) and a large soft-tissue mass containing foci of ossification (Figure 1A). A biopsy was obtained, and the pathological diagnosis was osteosarcoma.

Staging chest CT revealed multiple peripherally located rounded nodules in both lungs, some with ground-glass opacities and one with subpleural excavation, suggestive of metastasis. Before neoadjuvant chemotherapy, the patient presented chest pain and dyspnea. Bilateral pneumothorax was evidenced on a chest radiograph and attributed to nodule cavitation. Thoracostomy with pleural drainage and right pleurodesis was performed. Neoadjuvant chemotherapy was administered after stabilization of the patient's clinical condition. However, he evolved with progressive pneumothorax, seen on daily X-rays, despite conservative treatment.

The cavitation of most of the pre-existing nodules and persistence of bilateral pneumothorax were observed on chest CT (Figure 1B). Surgical treatment was chosen, and left metastasectomy and pleurectomy were performed. Pathological analysis confirmed the metastatic nature of the nodules (Figure 1C).

After 3 months of neoadjuvant chemotherapy, the primary disease progressed. Surgical planning was postponed, and another chemotherapy regimen was initiated. During second-line chemotherapy, chest CT showed an alteration of the lung lesion pattern; nodular opacities with ground-glass halos, suggesting hemorrhagic metastasis, were observed (Figure 1D).

The patient's right lower limb was amputated, and an adjuvant chemotherapy cycle was restarted. Chest CT performed 2 months later showed increases in the number and size of the hemorrhagic metastatic nodules, with no lesion pattern modification. Therefore, palliative chemotherapy was initiated.

At the last follow-up, 13 months after the first examination, chest CT confirmed substantial disease progression, with multiple masses showing soft-tissue density and foci of calcification, measuring up to 7.0 cm, and moderate pleural effusion (Figure 1E). The patient died 7 days after this chest CT examination.

Osteosarcoma is a high-grade malignancy that occurs predominantly in the long-bone metaphyses of children and young adults, with a peak incidence in the second decade of life.[1] Microscopy shows the proliferation of spindle and epithelioid cells with marked nuclear pleomorphism, with features such as the presence of mitotic figures and osteoid matrix formation. In addition, non-neoplastic giant cells are seen in around 25% of cases.

Initial metastases of osteosarcoma are characteristically hematogenous. Microscopic metastases are present in almost all patients at the time of diagnosis, and lung metastases are clinically detectable in approximately 15–20% of patients.[2]

Surgical treatment may lead to the increased survival of patients diagnosed with osteosarcoma. In addition, survival rates increase significantly after chemotherapy. However, despite the development of new protocols and more effective treatments, some cases still show disease recurrence, most commonly in the lungs.[2]

Pulmonary metastases are characterized by multiple well-defined nodules in the lung parenchyma. However, unusual radiological features of these lesions are frequently encountered in patients with osteosarcoma. Examples of atypical findings include cavitation, calcification, atypical location in the lung, micronodular forms, hemorrhagic metastases, and tumor thrombi.[4,5]

The frequency of cavitation is much lower for metastatic nodules than for primary tumors. Cavitating lung metastases are associated most commonly with squamous cell carcinoma. Lung metastases of sarcoma can also cavitate, presumably due to chemotherapy-induced tumor necrosis or even neoplastic lesion behavior. Cavitation may also occur via a check-valve mechanism prompted by tumor infiltration of bronchial structures.[3,4]

Pneumothorax is a frequent complication in these cases and is usually the result of bronchopleural fistula

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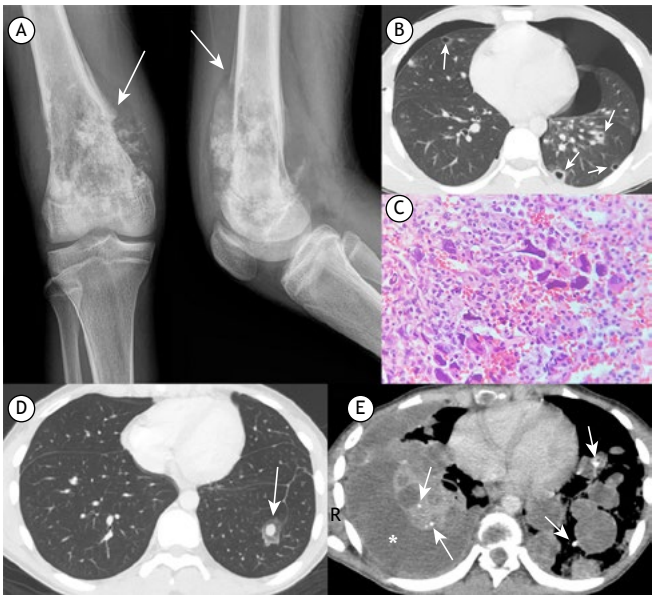

Figure 1. Frontal and lateral radiographs (A) of the right distal femur (taken in February 2019) showing a juxtacortical mass with a Codman triangle, periosteal reaction (white arrows), and calcification foci. The femoral metaphysis is involved and the tumor extends into the diaphysis. Chest CT image (B) obtained during neoadjuvant chemotherapy (in April 2019). Axial view showing multiple cavitated nodules, some of which are peripheral (white arrows). Bilateral pneumothorax can also be observed. Histological features (C) of a pulmonary nodule: a neoplasm composed of spindle cells and atypical epithelioid cells with an osteoid matrix surrounded by giant cells, similar to osteoclasts. Hematoxylin and eosin staining, original magnification ×40. Axial chest CT image (D) obtained during second-line chemotherapy (in October 2019) showing a nodular opacity in the left lower lobe with a ground-glass halo (white arrow), suggesting hemorrhagic metastases. Axial chest CT image (E) obtained with the mediastinal window during third-line chemotherapy (in March 2020) showing multiple bilateral masses with soft-tissue density. Note also the calcification foci (white arrows) and pleural effusion (asterisk).

formation due to tumor necrosis. For this reason, it is important to search for hidden lung metastases in patients diagnosed with osteosarcoma presenting with spontaneous pneumothorax.[5]

Hemorrhagic pulmonary metastases are lesions in which vessels have ruptured due to neovascular tissue fragility. They usually present as nodular opacities with ground-glass halos (the halo sign) or diffuse ill-defined margins. The halo sign is not specific, but the suspicion of hemorrhagic metastasis should be considered when it is present in patients with associated malignancies. Angiosarcoma and choriocarcinoma are the most representative causes of hemorrhagic pulmonary metastasis.[3,4]

Calcifications in primary nodules suggest a benign nature, generally corresponding to granulomas or hamartomas. Nevertheless, calcification or ossification may occur in metastatic nodules. Sarcomas and carcinomas, namely osteosarcomas, synoviosarcomas, chondrosarcomas, and mucinous and papillary adenocarcinomas, can produce calcified metastases. Lymph node involvement can also be seen with calcified metastases.[3,4]

Most cases of pulmonary metastasis present typical imaging features. Nonetheless, radiologists' knowledge of atypical presentations is essential for the differentiation of metastatic disease from synchronic primary lung cancer and benign lung conditions.

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Herd immunity threshold for SARS-CoV-2 and vaccination effectiveness in Brazil

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TO THE EDITOR,

Estimating the herd immunity threshold for COVID-19 in the midst of the pandemic is a challenge. This threshold, defined as the percentage of people to be vaccinated in order for improvements in disease indicators and pandemic control, is being modified as the virus mutates, leading to immune escape from vaccines and from immunity due to previous infection itself.[1]

In the history of human diseases caused by infectious agents, only smallpox has been eradicated. Smallpox can be transmitted by close contact and through droplets and respiratory secretions containing the infectious agent. Indirect contagion over longer distances, through aerosols, is much less common. The reproduction rate of the virus was equal to 5, meaning that each person with smallpox could infect another five people. The disease caused lesions to the patient's skin, making it easier to locate and isolate an infected person; furthermore, once sick or vaccinated, the possibility of reinfection was remote.[2] The eradication of smallpox took approximately 184 years, from the emergence of an effective vaccine to the complete disappearance of the disease.

The literature has shown that there are differences between the two diseases. The first is that many asymptomatic people infected with COVID-19 can continue to spread the virus and, therefore, it is more difficult to fight COVID-19 than smallpox. The second is that there are non-human reservoirs, and the third is that those who have had the disease can become infected again, and immunity against this new virus (SARS-CoV-2) is still not entirely understood.[3]

The objective of the control measures was not primarily to fight SARS-CoV-2 but to gain time to develop vaccines and, more recently, to vaccinate the entire population. However, control measures were to be adjusted according to the epidemic situation and evolution of the virus, which constantly undergoes mutations.[4]

In this sense, understanding the calculation of the herd immunity threshold is essential to establish new vaccination goals. This threshold is based on the basic reproduction rate (R_0) of the virus, assuming that the percentage of the vaccinated population is evenly distributed across all age groups and that vaccine efficacy is close to 100%.[5] The calculation of the reproduction rate of the virus that emerged in the city of Wuhan, China, yielded an R_0 close to 3. Therefore, the calculation of [1 - (1/Virus Reproduction Rate] * [1/Vaccine Efficacy] was considered. For SARS-CoV-2, using an R_0 value of 3 and vaccine efficacy equal to 100%, the calculation would be: [1 - (1/3)] * (1/1)], thus, [1 - (0.3)] * 1, *i.e.*, [0.70] * 1, which would result in a proportion of 70% of the population required to attain herd immunity.

However, no vaccine is 100% effective, and mutations in the virus can also make it more transmissible and modify its reproduction rate. In COVID-19, such increment in transmissibility occurred with the Alpha, Gamma, and, more recently, the Delta variant of SARS-CoV-2, the latter identified in mid-2021, showing a significant increase in its spread to a reproduction rate equal to seven ($R_0 = 7$).[6]

Brazil used different vaccines with distinct levels of efficacy. Considering the two main vaccines used so far, AstraZeneca/Fiocruz and CoronaVac/Butantan, the calculations need to be modified. A search evaluating the effectiveness of the two immunizers in 75,919,840 people vaccinated in the country after a full two-dose regimen of the AstraZeneca/Fiocruz vaccine found an overall effectiveness of 72.9% protection against infection, 88% against hospitalization, 89.1% against ICU admission, and 90.2% against death. People with the complete CoronaVac/Butantan vaccination regimen had a 52.7% lower risk of infection, 72.8% lower risk of hospitalization, 73.8% lower risk of going to the ICU, and 73.7% lower risk of death (Table 1).[7]

The calculations considering the different vaccine effectiveness levels and the impact of increasing the reproduction rate from 3 to 7 are shown in Table 1. It can be noted that it is probably impossible to reach a herd immunity threshold with the new variants of SARS-CoV-2 since they are more transmissible, and it would be necessary to vaccinate more than 95% of the population. Non-pharmaceutical interventions, such as physical distancing and the use of masks and antiseptic solutions, will continue to play an important role in keeping COVID-19 cases low regarding morbidity and mortality. The primary goal will be to reduce the number of hospitalizations and deaths due to the disease rather than break the path of viral transmission, although the latter would help reduce the spread of new variants.

With the emergence of new variants and the potential reduction of immunity against infections, new COVID-19 outbreaks appear.[8,9] The long-term perspective for the pandemic is that it will probably become an endemic disease, much like influenza. It is unlikely that the vaccine will completely stop the spread of SARS-CoV-2. Nonetheless, even without reaching the threshold of collective immunity, vaccination reduces hospitalizations and deaths due to COVID-19.[5]

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Table 1. Herd immunity threshold values for the AstraZeneca/Fiocruz and CoronaVac/Butantan vaccines considering the effectiveness of the two in Brazil and the impact of the increase in the virus reproduction rate (R_0) from 3 to 7.

	AstraZeneca/Fiocruz			CoronaVac/Butantan		
	Effectiveness (%)*	Threshold rate (%)		Effectiveness (%)*	Threshold rate (%)	
		R_0=3	R_0=7		R_0=3	R_0=7
Infection	72.9	91.4	117.5	52.7	127.0	163.0
Hospitalization	88.0	75.7	97.4	72.8	92.0	118.0
Death	90.2	73.9	95.0	73.7	90.0	116.0

* Cerqueira-Silva T. et al., 2021.

Currently, in Brazil, the prevalence of immunization coverage and absence of non-rigid pharmacological actions favor stationary permanence in scenarios of virus conflagration or coexistence. In these scenarios, viral circulation is reduced, but there is a frequent occurrence of local virus transmission, and outbreaks may occur mainly in the unvaccinated and immunosuppressed population.[4]

Both SARS-CoV-2 infection and COVID-19 vaccination induce an immune response that initially confers high levels of protection against symptomatic disease by COVID-19.[10] One of the present limitations is that there is not enough data to extend the findings related to infection-induced immunity to children or people with very mild or asymptomatic infection. In addition, the herd immunity threshold formula is used to predict the short- and long-term impacts of vaccination programs alone, to justify them economically, and to understand the nature of vaccine-induced immunity.

Therefore, the institution of a genomic surveillance program is essential to monitor mutations and the emergence of variants, especially those that evade the immune system. The revision of the herd immunity threshold with the expansion of complete vaccination coverage rates by age group, mainly in the most at-risk population, and studies that assess the duration of immunity, whether conferred by the disease or the vaccine, are essential for us to plan future vaccine booster campaigns.

AUTHOR CONTRIBUTIONS

ELNM, PCS, JPC, TC, and CMMS contributed to the conception and planning of the study, as well as the interpretation of data, writing and reviewing the preliminary and definitive versions, and the approval of the final version.

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Long-term survival following unilateral lung transplantation for end-stage silicosis relative to idiopathic pulmonary fibrosis

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TO THE EDITOR,

Silicosis is an occupational disease caused by exposure to free crystalline silicon dioxide that evolves as a progressive granulomatous inflammation, eventually leading to pulmonary fibrosis. Although cessation of exposure to silica improves the prognosis, it does not prevent disease progression, which ultimately leads to death. Lung transplantation (LTx) is the only therapeutic alternative for patients with end-stage silicosis, with a significant survival benefit when compared to conservative management. The procedure usually has a complicated intraoperative course due to bleeding and hemodynamic instability; therefore, only a restricted number of patients with end-stage silicosis worldwide have undergone transplantation.[1,2] Few studies have reported the intraoperative complications and long-term outcomes of LTx in these patients, and most of the data derives from studies in centers located in the United States.[2-9] However, little is known regarding the survival outcomes of the procedure in Latin America.

We conducted a retrospective study in a single quaternary center to evaluate the intraoperative and postoperative outcomes of patients with end-stage silicosis who underwent unilateral LTx between 1989 and April 2017. The outcomes of the end-stage silicosis group were compared to those of a group of patients with idiopathic pulmonary fibrosis (IPF), for whom intraoperative and postoperative LTx outcomes are well known in the literature. The IPF pairs were selected from a group that underwent LTx from 2012 to 2016 in order to best match for sex, age, and pre-transplant pulmonary function capacity. The diagnosis of silicosis and IPF were confirmed by pathological analysis of the explanted lung. End-stage silicosis was defined according to the International Society of Heart and Lung Transplantation guidelines.[10] Donor organ procurement and transplantation have been described elsewhere in detail.[1] After transplantation, all patients received a standard triple immunosuppressive regimen (cyclosporine, azathioprine, and prednisone) and antibiotic prophylaxis. Non-parametric tests were used to compare the two groups. The Mann-Whitney test was used for continuous variables, whereas the chi-squared ($\chi 2$) or Fisher's exact test were used for categorical variables. Cumulative survival probabilities after LTx were estimated using Kaplan-Meier curves, and differences in survival were tested with the log-rank test. A p-value lower than 0.05 was considered significant for all tests.

A total of 16 patients with end-stage silicosis and 16 IPF pairs were included in the study. The intraoperative complications and hospitalization course of both groups are shown in Table 1. The patients with silicosis were significantly younger than the IPF patients, a fact that is related to the natural history of each disease. Intraoperative bleeding, blood drainage from the chest tube, and the need for packed red blood cells were more than two times higher in the population with silicosis. None of the silicosis patients received any antiplatelet agent, and only one IPF patient was taking aspirin (100 mg daily) until the time of transplantation. Two IPF and seven silicosis patients received extracorporeal circulation intraoperatively, and none required extracorporeal membrane oxygenation (ECMO) at any time during hospital stay. However, the length of ICU and total hospital stay were not significantly different between groups.

The median time of follow-up was 4.1 years for the fibrosis group (IQR 1.9 – 5 years) and 4.7 years (IQR 2.1 – 5 years) for the silicosis group. One year following LTx, the survival rates were 81.3% for silicosis and 87.5% for fibrosis. The 3-year estimated survival rate was 68.3% for silicosis and 56.3% for fibrosis. The Kaplan-Meier curves for estimated survival revealed that silicosis was not associated with a significantly higher 5-year mortality rate when compared to fibrosis (50% for both groups, $p = 0.883$).

In this single-center study, we found that the long-term survival of patients with end-stage silicosis following unilateral LTx was not significantly different from that of the IPF patients. This observation is in accordance with more recent studies from other centers, particularly in the United States,[2-4,6] and adds to the current body of evidence contrasting with the findings of Giuseppe et al.[9] in which patients with silicosis following LTx had worse survival compared to IPF patients.

Intraoperative complications of LTx in silicosis are challenging not only due to the difficulty in dissecting the lungs, but also the significant amount of bleeding. The more complicated intraoperative course of silicosis could potentially worsen the outcomes of these patients, including increased length of stay (LOS) and decreased survival after LTx. In the present comparison, however, there was no significant difference in the LOS between patients with IPF and those with silicosis. More importantly, this study demonstrated that the 5-year survival rate

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Table 1. Clinical characteristics and intraoperative and postoperative parameters of end-stage silicosis and IPF patients submitted to LTx.

Parameter	Silicosis n = 16	IPF n = 16	p-value
Age, years	44 ± 10	61 ± 8	<0.001
Smoking history (pack-year)	7 (44)	13 (81)	0.066
Time of exposure to silica, years	9 [4-14]	-	-
FEV_1, % predicted	35 ± 17	50 ± 17	0.022
FVC, % predicted	42 ± 14	47 ± 13	0.341
sPAP, mmHg	50 ± 20	48 ± 12	0.491
Intraoperative bleeding*, mL	1709 [1322-2775]	300 [262-662]	<0.001
Blood drainage 1h to 24h (chest tube)**, mL	2022 [1572-2716]	510 [350-725]	<0.001
Total blood drainage (chest tube), mL	4757 [3917-6905]	1505 [991-2112]	0.001
Volume of intraoperative RBC, mL	1035 [431-1725]	500 [500-750]	0.014
Need for ECC, n (%)	7 (44)	2 (12)	0.113
Time of ECC, min	83 ± 22	143 ± 32	0.009
Ischemic duration, min	281 ± 67	247 ± 65	0.152
Length of chest tube stay, days	9 ± 3	4 ± 2	<0.001
Length of ICU stay, days	11 ± 6	7 ± 5	0.093
Length of hospitalization, days	25 ± 18	20 ± 7	0.289
Median time on waiting list, years	1.3 ± 0.4	1.5 ± 0.6	0.180

Note: Data was presented as No. (%), mean ± SD, or median [IQR]. IPF, idiopathic pulmonary fibrosis; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; sPAP, systolic pulmonary arterial pressure; RBC, red blood cell; ECC, extracorporeal circulation; ICU, intensive care unit. *The intraoperative blood loss was measured by the volume of blood aspirated from the surgical field, as well as by weighing the compresses moistened with blood from the surgical field. **Total content drained through the chest tube in the first 24 hours after surgery.

after LTx in silicosis did not differ from that of the IPF patients, despite the worse intraoperative course.

This study had several limitations, being a retrospective cohort performed at a single institution. Despite our attempt to best match the IPF patients with those with silicosis undergoing lung transplantation (especially for sex), the natural history of each disease limits such approach. Our control population may have been subjected to selection bias, as we attempted to match the characteristics to those of the silicosis group. Even though the silicosis population underwent transplantation at an earlier period (recruitment between 1989 and April 2017) than the fibrosis group (2012 to 2016), there were no significant differences between groups regarding survival. Lastly, we did not include any case of bilateral LTx since there are limited bilateral procedures for IPF or none for silicosis at our service.

In conclusion, our cohort of patients with end-stage silicosis undergoing LTx at a single center in Brazil demonstrated that, despite the worse intraoperative course, such complications did not yield a lower long-term survival rate compared to IPF patients.

AUTHOR CONTRIBUITIONS

FAP, SA, DZN, and GW: Conceptualization, Methodology, Investigation, Data curation, Writing - original draft. GM, SMC, BH, LASF, and JJC: Investigation, Data curation, Writing - review & editing.

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Tuberculosis in Brazil: the impact of the COVID-19 pandemic

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TO THE EDITOR,

The spread of Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV-2) continues to progress, causing damage in several countries of the world due to its rapid transmissibility and significant mortality rates,[1,2] despite government measures to contain its transmission, such as movement control, the closing of schools, bans on travel and public gatherings, the mandatory use of masks, and hand hygiene.[1,2,3,4,5,6] The coronavirus disease (COVID-19) has clinical manifestations that are similar to those found in other infections also transmitted through the airways, such as pulmonary tuberculosis (TB).[1,2,3,4,5,6] Although TB is a global health problem, it is a curable disease, with affordable treatment and prevention. Nonetheless, it remains one of the leading causes of death from a single infectious agent worldwide, a situation threatened by COVID-19.[1,2,3,4,5,6,7]

The elimination of COVID-19 has been made a priority in relation to other diseases that can be treated through public healthcare.[7,8] During the COVID-19 pandemic, a major impact on the provision of TB health services was observed in several countries, through measures of relocation of professionals and budgets, and the interruption of services.[3,4,5,6,7,8]. However, we do not know the true extent of this damage; an increase in the number of undiagnosed TB cases is expected worldwide, which may reveal poor treatment results.[3,4,5,6,7,8] The simultaneous presentation of TB and COVID-19 is a matter of concern since the patient may be at a greater risk of poor outcomes and death than patients with COVID-19 alone.[7,8]

In Brazil, TB is a public health problem and one of compulsory notification, and the current situation presents a high burden regarding TB and TB-HIV co-infection.[9,10] The objective of the present study was to compare data from the Unified Health System (SUS) on the number of pulmonary TB cases reported in the 5 Brazilian geographic regions (North, Northeast, Southeast, South, and Midwest) from 2017 to 2019 with the same periods of 2020, the latter representing the period of the pandemic, to verify the real impact of the pandemic on the number of TB cases in Brazil.

The analyzed data were extracted from the Brazilian public database - Ministry of Health (MH) - Primary Care Health Information System (SISAB) https://sisab.saude.gov.br/ - of the SUS, which contains the average number of consultations of pulmonary TB in the Brazilian territory. These data came from consultations in public primary healthcare services carried out by doctors and nurses, whose patients' disease was suggestively classified as pulmonary TB (confirmed and laboratory-unconfirmed cases). Data from the MH - SUS for the past 12 months are subject to changes and updates.

The differences in the average number of pulmonary TB consultations reported by the Brazilian public health system in all geographical regions, in 2017, 2018, and 2019, compared to the same period in 2020, are shown in Figure 1. In this descriptive analysis of data by region, there was a significant increase in the percentage of pulmonary TB consultations in all Brazilian regions during the COVID-19 pandemic. Such increase ranged from 27,492 (156.0%) consultations, on average, in the Southeast region to 1,523 (25.0%) consultations, on average, in the South region. Considering all the Brazilian regions, the total average of consultations went from 48,688 in the period from 2017 to 2019 to 108,269 in 2020, representing a 122.4% increase in average TB consultations during the pandemic period.

Given the relevance of TB, it became necessary to include the data extracted from the Brazilian public database - MH - Notifiable Diseases Information System - SINAN (http://portalsinan.saude.gov.br/tuberculosis) in this study, in which the annual average of confirmed cases of pulmonary TB notified in Brazilian territory was obtained. Figure 1 shows the difference in the annual average of confirmed cases of pulmonary TB reported by the Brazilian public health system in all geographical regions in 2017, 2018, and 2019 compared to the same period of 2020, which represented the period of the pandemic.

Being a seasonal disease, there was a reduction in reported confirmed cases of pulmonary TB in all Brazilian regions, except for the North, during the pandemic period. The Southeast (-8.2%), South (-8.9%), and Northeast (-10.9%) regions presented a percentage decrease above the national average (-7.9%). During the pandemic period, the average number of reported TB cases decreased by 6,501 cases compared to the period from 2017 to 2019. These data reveal the impact of the pandemic on the number of pulmonary TB cases in Brazil. Therefore, there is a concern that the COVID-19 pandemic will hamper TB elimination goals in all Brazilian regions.[9,10]

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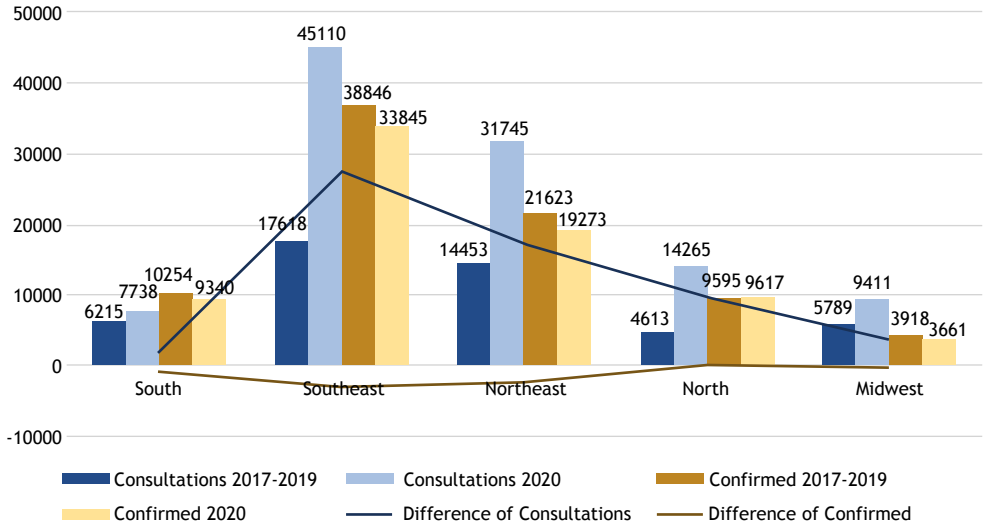

Figure 1. Difference between the annual average of pulmonary tuberculosis consultations and confirmed cases of pulmonary tuberculosis notified by the Brazilian public health system in all geographic regions in 2017, 2018, and 2019 in relation to the same period in 2020.

In 2020, 88,678 cases were confirmed for TB in Brazil, and 4,500 people died due to the disease in 2019.[10] According to the performed analyses, Brazil has experienced different levels of interruption of the health system, which has resulted in a reduction in the total number of notifications of pulmonary TB in the country (Figure 1) due to the measures adopted to contain the spread of SARS-CoV-2.[10] In the pandemic period, essential services for TB were restricted due to decreased resources and inputs, prioritizing the mitigation of COVID-19.[3,5,6] Data presented by the MH revealed an increment in the number of treatment dropouts and an increase in the number of deaths by TB.[10]

Overall, these findings are similar to those reported in other countries.[3,4,7,8] It is believed that the measures adopted for the care of COVID-19 influence the goals established by the WHO to reduce the global burden of TB.[3]

The increase in the number of consultations and the reduction of confirmed TB cases reported in the pandemic period evidenced herein are extremely worrying. Brazil, with its high burden due to TB, needs to guarantee the continuity of services in the control of *Mycobacterium tuberculosis* during the COVID-19 pandemic to achieve its TB elimination goals.

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Endobronchial histoplasmosis mimicking primary bronchogenic carcinoma during the COVID-19 pandemic

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TO THE EDITOR,

During the Coronavirus pandemic, the number of chest computed tomography (CT) scans increased, a fact that has benefited several patients on account of the incidental radiologic findings.[1] Chest CT scans play a crucial role in determining the severity of infection, particularly in hospitalized patients.[2] Naturally, with the increased use of CT scanning in the current scenario, higher rates of endobronchial lesion detection have also been expected.[3]

Endobronchial lesions often represent malignancy even in young adult patients, and carcinoid tumors are the most common.[4] Nevertheless, a large and heterogeneous group of possible etiologies have been reported, mimicking primary bronchogenic carcinoma.[5] Those include: lymphoma, broncholithiasis, metastatic disease, and fungal infections.[5] Although rare, a distinctive form of endobronchial granulomatous disease is that caused by *Histoplasma capsulatum.*

A 35-year-old non-smoking female patient presented with mild symptoms of cough and sore throat, diagnosed with COVID-19 based on PCR detection on initial nasopharyngeal/oropharyngeal swabs, and was admitted for a work-up. She had no comorbidities, and her physical examination was unremarkable. The patient underwent a chest CT, which was performed according to the institution's protocol to determine the severity of the infection. The CT did not reveal interstitial lung disease, although an 8-mm incidental pulmonary nodule was detected. This non-calcified, solid endobronchial nodule was situated in the anterior segmental bronchus of the left upper lobe, as shown in Figure 1A. The patient denied household or work exposure to tuberculosis (TB); however, she had had contact with bat guano during childhood for a limited period of time. This CT finding in the young woman led to a primary hypothesis of carcinoid tumor, as well as the findings upon bronchoscopy, as shown in Figure 1B. After complete resolution of COVID-19, we performed endobronchial biopsies with histopathological analysis and microbiological studies. The pathological findings revealed a non-caseous granuloma, and the results obtained by Grocott-Gomori methenamine silver (GMS) staining confirmed typical yeast forms of *Histoplasma capsulatum*, as shown in Figure 1C. The patient was then referred for standard follow-up with CT scans without antifungal treatment. After 6 months of follow-up, the patient had an uneventful evolution, and the imaging control showed a significant decrease in the endobronchial lesion, with no appearance of new lung lesions, as shown in Figure 1D.

Here, we report the case of an asymptomatic young female patient with an incidental radiologic finding during work-up for COVID-19. Although imaging suggested a solid endobronchial lesion mimicking either a benign or malignant pulmonary tumor, the bronchoscopy biopsies revealed endobronchial histoplasmosis infection.

Histoplasmosis is a fungal infection caused by a dimorphic fungus predominately found in soils enriched with bird and/or bat excreta and usually occurs by inhalation of the fungal organism. In endemic areas of pulmonary histoplasmosis, such as the United States, up to 500,000 new infections occur each year. This diagnosis is naturally listed as a differential diagnosis of endobronchial lesions, however not in Southeast Brazil.[6]

While the clinical features may vary, most people infected by *Histoplasma capsulatum* remain asymptomatic; however, approximately 10–40% can develop pulmonary or systemic disease.[3] In contrast, the direct endobronchial presentation is the least common. Only eleven cases of endobronchial histoplasmosis have been reported in the literature.[6] Despite improvements in imaging studies and serological procedures, accurate diagnosis remains challenging.

The radiologic findings of endobronchial histoplasmosis are not considered sufficient for diagnosis since they often mimic other granulomatous infections, such as tuberculosis, and neoplastic processes.[3] The diagnosis is confirmed by the presence of *H. capsulatum* in the tissue, obtained by endobronchial biopsy in most cases. The tissue sample must be stained using the GMS technique to reveal small, oval-shaped, single-budding, yeast-like organisms.[7]

A variety of tests, including the urine enzyme immunoassay for *Histoplasma* antigen, complement fixation, and culture, can help establish the diagnosis. However, the sensitivity of detection depends on clinical presentation and the host's status.[8] In the present case report, the patient was only tested for the *Histoplasma* antigen, with a negative result; other serum antigen tests were not available at our institution.

The treatment of histoplasmosis depends on the severity of the illness. While conservative management is adopted in immunocompetent asymptomatic patients, specific antifungal therapy should be offered in symptomatic

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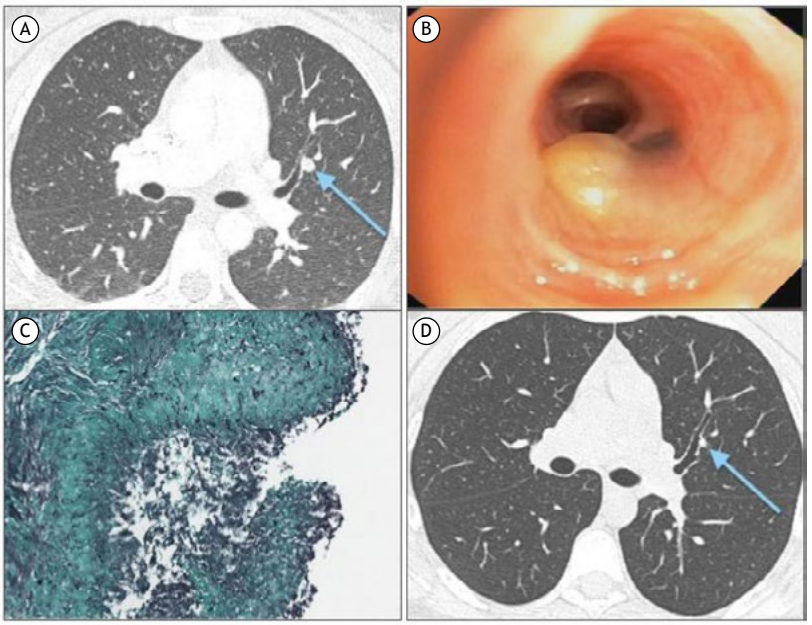

Figure 1. Radiological and histopathological findings of the endobronchial lesion. (A) Chest CT showing a non-calcified 8-mm endobronchial fungal lesion beside the anterior segmental bronchus of the left upper lobe (arrow). (B) Endobronchial nodular lesion seen by bronchoscopy mimicking a lung carcinoid tumor. (C) Histopathological analysis with Grocott staining showing bronchial wall fragments with respiratory epithelium and alveolar prolongation with chronic granulomatous inflammatory process with central caseous necrosis and small regular yeast-like structures (black stain), suggesting *Histoplasma* sp. (original magnification × 20). (D) Chest CT indicating 5-mm endobronchial histoplasmosis (arrow).

patients with diffuse infiltrative lesions.[9] The treatment of choice is oral itraconazole (200 mg/day) for six to twelve weeks.[10]

In conclusion, we believe endobronchial histoplasmosis should be considered part of the differential diagnosis of endobronchial lesions in young patients, even in non-endemic areas.

AUTHOR CONTRIBUTIONS

PDD: writing main content of text, editing, referencing. ANC and PRS: study conceptualization, editing, image selection. RMT: writing first draft of the case presentation, editing, study conceptualization, image selection.

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Traditional pipe smoking (*xanduca*) and respiratory function in the *Fulni-ô* indigenous people, Brazil: Project of Atherosclerosis among Indigenous Populations (PAI) study

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TO THE EDITOR:

Smoking is the leading cause of preventable death worldwide,[1] accounting for about 6% of the global burden of disease.[2] Since the publication of the first WHO report on the tobacco epidemic in 2008, much progress has been made in tackling the global smoking epidemic.[1] Even so, smoking is still responsible for about 8 million deaths annually[3] and an annual cost of US$ 1.4 trillion to the global economy.[1]

In specific groups, such as indigenous populations, little is known about the prevalence of smoking, whether traditional or commercial, and its consequences for the health of the respiratory system. Traditional pipe smoking differs from the commercial pipe smoking both in terms of chemical composition and the cosmology involved in the consumption of the substances.[4]

The aim of the present study was to describe the respiratory health in men and women from the *Fulni-ô* indigenous tribe, using pulmonary function parameters and their association with traditional pipe smoking in this community.

This was a cross-sectional study whose participants were inhabitants of the *Fulni-ô* indigenous village in the city of Águas Belas, in the state of Pernambuco, Brazil, in a transitional region between the *agreste* and the *sertão* of the state.[5] In the cosmology of the *Fulni-ô* indigenous people, the use of *xanduca*, a traditional pipe for smoking natural herbs from the Brazilian *caatinga* (e.g., *jurema*, *alecrim de caboclo*, *amecla*, among others) has a religious character that is associated with disease prevention.[6]

Inclusion criteria were men and women over 30 years of age. Exclusion criteria were individuals presenting with clinically manifest cardiac insufficiency, those with a history of an acute coronary event resulting in hospitalization, those with renal insufficiency on dialysis, those with a history of cardiac or peripheral artery surgical procedures, and those with a history of cerebrovascular disease requiring hospitalization.

This ancillary study included all the participants of the Project of Atherosclerosis among Indigenous Populations (PAI) recruited in the indigenous *Fulni-ô* village who agreed to undergo respiratory evaluation via spirometry. Individuals who used or had used commercial cigarettes, those who reported coughing at the time of data collection, and those who were diagnosed with another respiratory disease were excluded from the study. No *Fulni-ô* indigenous participant claimed to have never used tobacco in this study.

Sociodemographic, anthropometric, and clinical variables were analyzed: sex, age, educational level, height (cm), BMI, daily frequency of pipe smoking (times/day), duration of pipe smoking (years), smoking load (pipe-years), SpO_2, proportion of wood stove users, self-reported dyspnea, and risk factors for cardiovascular disease (arterial hypertension, diabetes, and dyslipidemia). Anthropometric measures were taken, and, following a period of rest, blood pressure (three measurements in both arms), heart rate, and oximetry were registered.

Smoking load was measured as the number of times the user filled the traditional pipe (*xanduca*) and was calculated as the number of times the pipe was used per day multiplied by the duration of pipe smoking, in years.

Pulmonary function was measured using a portable Micro Quark spirometer (Cosmed; Pavona di Albano, Italy), in conformity with the criteria established by the American Thoracic Society.[7] All participants received instructions on how to perform the test and tried up to six forced expiratory maneuvers, without coughing and without the use of bronchodilators. Participants were seated and used nose clips. The three best measures were considered for analysis. The spirometer was calibrated with a three-liter syringe before use every day.

The following respiratory parameters were collected: FVC, FEV_1, FEV_1/FVC ratio, PEF, and $FEF_{25-75\%}$. All variables were also evaluated as percentage of predicted values for the Brazilian population.[8] For the purpose of comparing lung function, subjects were divided into

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two groups (above and below median smoking load of 169.5 pipe-years). The t-test and the chi-square test were used to evaluate sex-related differences in the univariate analysis. Analyses were performed with the Stata statistical software package, version 10 (StataCorp LP, College Station, TX, USA). This study was approved by the Brazilian National Committee for Ethics in Research under the catalogue number 48235615.9.0000.5196.

We included a total of 116 participants from the *Fulni-ô* tribe, and 114 (98.3%) were active traditional pipe smokers. The mean age was 56.3 ± 11.0 years, and the mean BMI was 27.7 ± 4.5 kg/m^2, with no differences between genders. The mean daily frequency of pipe smoking was 6.2 ± 5.7 times/day, the duration of pipe smoking reached four decades (39.8 ± 15.1 years), and the mean smoking load was 261.3 ± 271.3 pipe-years. Importantly, 41% and 60% of the *Fulni-ô* men and women, respectively, started smoking before reaching 15 years of age. The use of wood stoves was reported by 11 individuals (9.5%; Table 1).

In the sample as a whole, 60 women (8.6%) and 8 men (17.4%) had FEV_1 below 80% of the predicted values. In contrast, 34 women (48.6%) and 20 men (43.5%) had FEV_1 values above 100% of the predicted values. Additionally, FEV_1 (in L) and FVC (in L) values were higher in the group with a smoking load below the median. Possible restrictive disorders were found in 5 (10.9%) and 7 (10.0%) of the men and women, respectively (Table 1).

Table 1. Epidemiological characterization, lung function parameters, and prevalence of respiratory disorders among *Fulni-ô* indigenous participants. Águas Belas, state of Pernambuco, Brazil.

Epidemiological characterization							
Parameter	Total		Women (n = 70)		Men (n = 46)		p*
	Mean	SD	Mean	SD	Mean	SD	
Age, years	56.3	11.1	56.3	11.9	56.3	9.9	0.99
BMI, kg/m^2	27.7	4.4	27.6	4.5	27.9	4.5	0.74
Height, cm	157.8	15.9	152.2	17.7	166.5	6.2	< 0.001
Daily frequency of pipe smoking, times/day	6.2	5.7	6.3	5.8	6.0	5.7	0.82
Duration of pipe smoking, years	39.8	15.1	40.8	15.4	38.4	14.7	0.42
Smoking load, pipe-years	261.3	271.4	265.3	264.9	255.3	284.8	0.85
SpO_2, %[a]	95.5	1.5	97.6	1.8	97.5	0.9	0.70
Educational level, years[b]	5.3	5.0	4.5	4.9	6.1	5.0	0.09
	n (%)		n (%)		n (%)		
Wood stove use	11 (9.5)		5 (7.1)		6 (13.0)		0.29
Dyspnea	6 (5.2)		4 (5.7)		2 (4.3)		0.74
Other cardiovascular risk factors	50 (43.1)		33 (47.1)		17 (36.9)		0.28
Lung function parameters according to median smoking load of 169.5 pipe-years							
Parameter	Above median (n = 58)		Below median (n = 58)				p*
	Mean	SD	Mean	SD			
FEV_1, L	2.54	0.66	2.82	0.72			-
FEV_1 , % predicted	97.12	15.87	98.35	15.03			0.04
FVC, L	3.16	0.85	3.50	0.90			-
FVC, % predicted	97.03	14.84	99.72	14.88			0.14
FEV_1/FVC, %	81.01	6.76	80.21	6.50			-
$FEF_{25-75\%}$, L/s	2.63	0.96	4.32	10.68			0.75
$FEF_{25-75\%}$, % predicted	104.78	34.86	102.38	33.48			0.05
PEF, L/s	5.38	2.01	5.78	1.94			-
PEF, % predicted	67.83	20.77	68.91	18.25			0.14
Prevalence of respiratory disorders, n (%)							
	Women (n = 70)				Men (n = 46)		
Obstructive respiratory disorder	Mild	Mild with reduced FVC	Mild with reduced FVC (> 0.7)	Mild (> 0.7)	Mild	Mild with reduced FVC	Mild with reduced FVC (> 0.7)	Mild (> 0.7)
	5 (7.14)	1 (1.42)	1 (1.42)	0 (0.0)	2 (4.34)	1 (2.17)	1 (2.17)	1 (2.17)
Possible restrictive disorder	7 (10.00)				5 (10.86)			

[a]Information available from 58 women and 40 men. [b]Information available from 66 women and 45 men. *The independent t-test and the chi-square test were used for continuous and categorical variables, respectively.

In this ancillary analysis of the PAI study, we show for the first time in the literature that smoking the traditional *xanduca* pipe has a high prevalence in the *Fulni-ô* indigenous community. There are few publications that deal with the deleterious effects associated with that use. In a study carried out in rural communities in Asia that use traditional hand-rolled cigarettes (*bidis*), a high prevalence of cardiorespiratory symptoms was observed among the population that were heavy smokers, who also showed lower ventilatory capacity and higher airflow obstruction than did those who were not.[9]

Although a higher prevalence of smoking among men has been described in urban environments,[1,3] the relationships between tradition and traditional pipe smoking in the *Fulni-ô* tribe seem to influence the elevated prevalence that we described in both sexes. The high prevalence of traditional pipe (*xanduca*) smoking among *Fulni-ô* indigenous people may, in part, be explained by the fact that traditional pipe smoking in indigenous communities is held not only as part of their traditions, but also as a practice that brings them closer to their deities through rituals that are unique to each people.[6,10]

The prolonged exposure to *xanduca* smoking described in our study indicates that *Fulni-ô* indigenous people have had the habit of smoking since childhood.[10] Little is known regarding the effects of xanduca smoke exposure in children, especially in the context of indigenous traditions.

Genetic factors that protect against damage caused by *xanduca* smoking might be present in the *Fulni-ô* community, which is the least urbanized indigenous community in the Northeast of Brazil. The pressure of natural selection of continuous exposure to intense *xanduca* smoking over many years might have molded favorable genetics in this population. Another factor worth mentioning concerns the fact that pipe users tend not to inhale the smoke, which means that they actively inhale less smoke than do cigarette smokers.[11]

In conclusion, we described the elevated prevalence of intense traditional pipe (*xanduca*) smoking in indigenous men and women in the Fulni-ô community, which often starts in childhood. Unfavorable pulmonary function parameters were predominant in men in comparison with women. In addition, FEV_1 (in L) and FVC (in L) values were higher in the group with a smoking load below the median.

AUTHOR CONTRIBUTIONS

VCP, DC, AAC, ACA, JM, DMFOA, RMPV, PVAMP, and JACL: conception and design of the research; data analysis and interpretation; and critical revision of the manuscript for intellectual content. VCP, ACA, and JM: data acquisition. VCP, ACA, DC, PVAMP, and CDFS: statistical analysis. VCP, ACA, AAC, JM, DMFOA, and CDFS: drafting and revision of the manuscript. All authors: approval of the final version.

CONFLICT OF INTEREST

None declared.

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A rare image of pancreatic-pleural fistula

Rita Costa[1], Josué Pinto[2], Pedro Fernandes[1]

A 49-year-old male with a history of chronic alcoholic pancreatitis presented to the emergency department with right-sided pleuritic chest pain. CT scans of the chest and abdomen after intravenous contrast administration showed a fistulous tract with fluid and gas extending from the pancreatic head into the right pleural space (Figure 1).

Empiric antibiotic therapy and fasting were implemented. Three days later, endoscopic retrograde cholangiopancreatography documented stenosis of the proximal portion of the main pancreatic duct and a fistula connecting the main pancreatic duct and the right pleural cavity (observed by contrast fluoroscopy showing a leak to the chest cavity). One single 5F pigtail drain was placed in the cephalopancreatic portion of the pancreatic duct. The patient was discharged three weeks later.

Pancreatic-pleural fistula is a rare complication of chronic pancreatitis, and right pleural effusions secondary to it are atypical. The sensitivity of CT to delineate the fistulous track is not very high, but in our case we got a rare and very enlightening image of a fistulous tract.[1]

AUTHOR CONTRIBUTIONS

RC and JP: drafting of the manuscript and approval of the final version. PF: revision of the manuscript and approval the final version.

CONFLICT OF INTEREST

None declared.

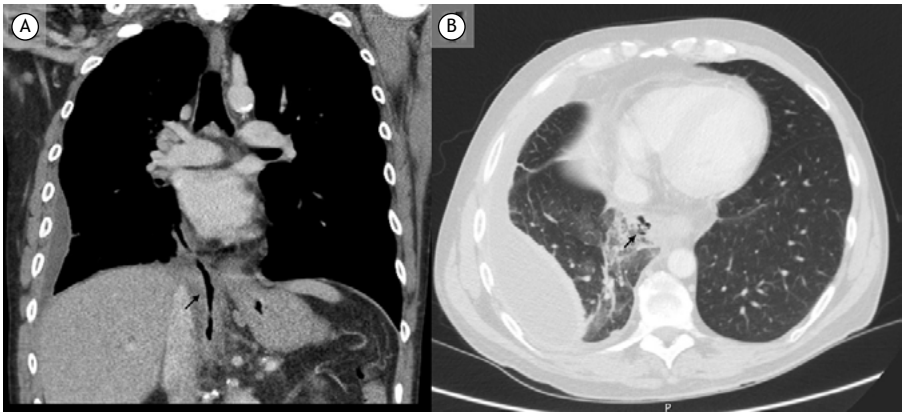

Figure 1. Coronal (in A) and axial (in B) CT images showing a fistulous tract (black arrows) with fluid and gas extending from the pancreatic head into the right pleural space and transposing the right hemidiaphragm.

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ELMO helmet for CPAP to treat COVID-19-related acute hypoxemic respiratory failure outside the ICU: aspects of/comments on its assembly and methodology

Mariano Mazza[1], Giuseppe Fiorentino[2], Antonio M. Esquinas[3]

We have read with great interest the study by Tomaz et al.,[1] which analyzes the clinical efficacy of a new model of a helmet-CPAP system, designated ELMOcpap, in COVID-19-related acute hypoxemic respiratory failure. We consider that that study published in the last issue of *Jornal Brasileiro de Pneumologia* represents a great advance regarding CPAP therapy, showing a new model of a helmet-CPAP device, and contributes to extend the use of such devices outside ICUs. However, we believe that there are some clinical and technical aspects that should be discussed.

First, Table 1[1] shows that all patients were affected by alkalosis (pH > 7.48) before starting therapy with the device, and the observed RR was not very high and not significantly different from that after its use (28.5 [24.5-34.0] vs. 26.5 [23.5-32.5] breaths/min; p = 0.866). We wonder if the authors considered the possibility of the presence of mixed alkalosis and if these data could be associated with successive helmet-CPAP setting adjustments. We think that this may also predispose patients to self-induced lung injury (P-SILI),[2] and we recommend that future studies about ELMOcpap should evaluate, by means of bench or clinical trials, data regarding V_T measurements, ELMOcpap settings, and P-SILI prevention.[3]

Second, according to Figure 1 in that study,[1] we observed that the authors have combined two humidification systems: an active humidifying jar system and a heat and moisture exchanger filter. We consider that this association could predispose to obstruction of the system by condensation, CPAP asynchrony, and, consequently, P-SILI,[2] particularly in such patients. Referring to the fact that "None of the research team members or hospital staff acquired COVID-19 during the study," it has not been stated in which way safety or diffusibility through the interface to prevent the spread of the virus was evaluated. Data about environmental air analysis would have been useful, so as to exclude that no one got infected only because the staff wore personal protective equipment and not because of interface security.

Additionally, an important aspect for a future design could be the measurement of internal helmet gas volume, the use of antiviral filters both on the inspiratory and expiratory ports, and the implementation of an anti-suffocation valve.

Lastly, we observed a great variability of total ELMOcpap therapy time, because the range of daily duration of the sessions was 60-1,230 min, and it is not clear whether defined criteria were established as a guideline, or whether the duration was dependent only on the patient; in addition, it is unclear whether other oxygen therapy options while ELMOcpap was not connected were applied. This is controversial if we consider the level of disease severity and gas exchange at admission showed in Table 2.[1] We also wonder if the authors designed the ELMOcpap device for continuous noninvasive support application outside the ICU as well, considering that they conducted the study with patients with moderate to severe ARDS, which is evident in Figure 3,[1] where we find values of $Pa_{O2}/FI_{O2} < 150$.

Further clinical trials are needed to evaluate some methodological and technical aspects of this new helmet-CPAP system to be used outside ICUs.

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Authors' reply

Betina Santos Tomaz[1], Gabriela Carvalho Gomes[2], Juliana Arcanjo Lino[2], David Guabiraba Abitbol de Menezes[2], Jorge Barbosa Soares[2], Vasco Furtado[3], Luiz Soares Júnior[1], Maria do Socorro Quintino Farias[4], Debora Lilian Nascimento Lima[4], Eanes Delgado Barros Pereira[1], Marcelo Alcantara Holanda[1,5]

We thank the authors for their comments and questions regarding our study entitled "ELMO, a new helmet interface for CPAP to treat COVID-19-related acute hypoxemic respiratory failure outside the ICU: a feasibility study."

Concerning the first point mentioned by the authors, we agree with the observation regarding the coexistence of metabolic alkalosis in at least 8 of the 10 patients whose arterial blood gas analysis at admission, before the use of ELMO, showed base excess values above 2.0 mEq/L. A possible cause would be the pharmacological therapy with corticosteroids routinely used in patients before their inclusion in the study. Therefore, metabolic alkalosis is not related to the sequential application of CPAP with the helmet.

The fact that some patients presented with hyperventilation in accordance with the respiratory alkalosis component is compatible with an increase in the respiratory drive, and, yes, that is possibly associated with an increase in transpulmonary pressure, a mechanism related to the occurrence of self-inflicted lung injury. In the absence of transpulmonary pressure measurement, we believe that V_T monitoring in devices such as the ELMO can identify those patients with a greater propensity to self-inflicted lung injury. The effects of the application of CPAP by helmet or another interface on V_T require investigation in clinical trials in the future, evaluating its relationship with the progression of lung injury or not. It is worth noting that, experimentally, the application of CPAP can attenuate the variation of transpulmonary pressure in ARDS.[1]

Concerning the second point, it is worth explaining the following: first, the heat and moisture exchanger filter used in the ELMO inspiratory branch serves only as a "damper" for the noise generated by the high flow of gases and not for its primary function (heat/humidity); second, the gas passage through the unheated jar was just a practical resource to offer the mixture of gases without raising their temperature. We even observed that this fact prevented condensation inside the helmet and, in volunteers, it was associated with a better sensation of comfort during the use of ELMOcpap due to the slightly cooler temperature around the head and face.[2] Because the CPAP mechanism has a continuous flow of gases, there is no occurrence of asynchrony, unlike helmets coupled to mechanical ventilators, and current trigger mechanisms are not designed for this interface.

The safety of the interface regarding the diffusibility of the virus was not the object of our study since it has already been reported in the literature[3]; the helmet interface has been considered safe and leakage is negligible when compared with face masks. The description of the absence of COVID-19 cases among researchers should not be seen as proof of this concept; however, we thought it best to report the data for recording purposes.

We agree with the idea of continuing to improve the design of the ELMO helmet on several fronts, including the improvement of anti-suffocation mechanisms, the coupling of filters in the gas inlet and outlet, the optimization of its internal volume to reduce the predisposition to CO_2 rebreathing, the monitoring of respiratory variables, such as RR, V_T, and FIO_2, as well as of intra-helmet pressure level, humidity, temperature, and others.

Given the innovation of the characteristics of that study with this type of device, our group considered that the total time of therapy would be the maximum tolerated by the patient, and, in agreement with the medical team, we alternated it with the only oxygen therapy then available (reservoir mask), because a high-flow nasal cannula was not available. The degree of comfort observed was great, and the large-scale use after the feasibility study revealed cases of continuous use of ELMOcpap for periods as long as 12-24 h (unpublished data), which is in line with other reports in the literature.

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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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