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HIGHLIGHT

Series on tuberculosis and other mycobacterial infections

Tele-ICU during the COVID-19 pandemic

Cystic fibrosis-related mortality in Brazil

omnaris®
ciclesonida

O único CTN* hipotônico.[1-5]

Alívio rápido e sustentado.[1-5]

1 hora
de início de ação[2]

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

1 ano
de alívio sustentado[5]

Indicado para crianças acima de 6 anos e adultos

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

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

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

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

COVIS PHARMA

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

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Tuberculosis Series 2021

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

This issue of the *Jornal Brasileiro de Pneumologia* (JBP) is dedicated to World Tuberculosis Day, which is celebrated every year on March 24. In 2015, tuberculosis surpassed HIV infection to become the leading cause of death from infectious disease worldwide. In 2019, 73,864 new tuberculosis cases were reported in Brazil (incidence of 35.0 cases/100,000 population). In 2018, 4,490 tuberculosis-related deaths were reported (2.2 deaths/100,000 population).[1] The lead article in the current issue of the JBP is the new consensus statement from the Brazilian Thoracic Association on the diagnosis of tuberculosis, based on the latest recommendations on the topic.[2]

Since the beginning of the COVID-19 pandemic, various cases of the tuberculosis-COVID-19 combination have been reported, increasing the already high potential for morbidity and mortality of each disease.[3-5] In this issue of the JBP, a review article[6] provides an overview of that combination, focusing on the differences between Brazil and Europe.

With regard to the epidemiology of tuberculosis in Brazil, the issue contains one ecological study[7] in which data on the prevalence and incidence of the disease, as well as on the associated mortality, were assessed for the various regions of the country. The authors of the study demonstrated that, although all of those indicators decreased slightly from 2006 to 2015, Brazil failed to reach the United Nations Millennium Development Goals target of reducing tuberculosis-related mortality by 50%. The authors suggested that regional differences were responsible for that failure and that this must be taken into account in the development of tuberculosis control measures in the country.

In this same issue, there are three articles on the diagnosis of tuberculosis: one regarding the quantification of adenosine deaminase to diagnose tuberculous pleural effusion in children[8]; and two related to the Xpert MTB/RIF test.[9,10] Pagano et al.[9] described the association between Xpert MTB/RIF cycle threshold (C_T) values and sputum smear microscopy findings in patients with pulmonary tuberculosis; a C_T cutoff value of 22.7 showed good predictive value for smear microscopy positivity, that being the first study in Brazil to assess the accuracy of C_T values as a measure of bacillary burden. Brito et al.[10] demonstrated that, in BAL fluid samples from patients under clinical suspicion of having pulmonary tuberculosis who have tested negative for AFB in sputum samples or those with scarce sputum production, the diagnostic performance of Xpert MTB/RIF is superior to that of smear microscopy.

This issue also contains a brief communication on tuberculosis treatment, in which Santos et al.[11] analyze and compare tuberculosis treatment outcomes between the homeless population and the general population in Brazil. Although there were differences among the Brazilian regions, all indicators were worse in the homeless population. The rates of loss to follow-up and mortality were, respectively, 2.9 and 2.5 times higher in the homeless population than in the general population. In addition, the rate of treatment success was approximately 50% lower in the former.

In another article included in this issue, Inoue et al.[12] describe the effects that advanced extrapulmonary solid cancer has on the progression of *Mycobacterium avium* complex lung disease. The authors retrospectively evaluated 286 patients and demonstrated that the median time to progression of *M. avium* complex lung disease was shorter in patients with coexisting advanced solid cancer. In addition, although indirectly related to *Mycobacterium tuberculosis* and nontuberculous mycobacteria, one letter to the editor reports a case of giant Rasmussen's aneurysm,[13] and one suggests a new pathophysiological theory for Lady Windermere syndrome.[14]

In summary, this tuberculosis series features several articles focusing on diverse aspects of the disease, highlighting the challenges faced in tuberculosis control, especially during the COVID-19 pandemic, and providing a comprehensive overview of some of the latest research in the field.

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Getting back on the road towards tuberculosis elimination: lessons learnt from the COVID-19 pandemic

Isabel Furtado[1], Ana Aguiar[2], Raquel Duarte[2,3,4,5]

Since early 2020, the world's attention has shifted to the COVID-19 pandemic, and the medical and scientific community has joined forces to fight it. However, although necessary, this diversion of attention has had an impact in all areas of health. The effect of COVID-19 on tuberculosis services is estimated to be global and dramatic. All over the world, we witnessed the reallocation of health care workers to fight the COVID-19 pandemic; the closure of many tuberculosis outpatient clinics and laboratories; the shortage of laboratory reagents for the diagnosis of tuberculosis and even the shortage of anti-tuberculosis drugs.[1] These shortages in resources may be due to the economic impact of the pandemic and stretched national budgets, which are likely to affect routine public health programmes.[2] In China, all of these changes led to a significant reduction in tuberculosis reports in comparison with the previous three years.[1] In a study including 37 tuberculosis centres worldwide, the Global Tuberculosis Network compared the first quarters of 2019 with those of 2020 and concluded that there were reductions in newly diagnosed cases of active tuberculosis and of latent tuberculosis, as well as in the number of visits of outpatients with active or latent tuberculosis.[3] The exact significance of this decrease has yet to be determined. Has there been a real decrease in the number of tuberculosis cases? Or is it a result of the disruption of and lack of access to tuberculosis services?[1]

Questions have been raised regarding tuberculosis/COVID-19 co-infection[4-6]: 1) Can COVID-19 increase the risk of developing active tuberculosis in patients previously exposed to *Mycobacterium tuberculosis*?; 2) Does COVID-19 increase the risk of tuberculosis mortality?; 3) Do immunosuppressants used in order to treat COVID-19 increase the risk of reactivation of tuberculosis?; 4) Are patients with post-tuberculosis sequelae at a higher risk of acquiring COVID-19?; 5) Does pulmonary fibrosis secondary to COVID-19 infection hinders the treatment of tuberculosis? As COVID-19 is a recent disease, scientific evidence remains scarce, and we will probably have to wait years before these questions are answered.

Silva et al.[7] offer us an excellent review of this subject, addressing most of the unanswered questions regarding tuberculosis/COVID-19 combination. Moreover, and perhaps more importantly, the authors reflect on how we can adapt and integrate existing programs to reduce the impact of COVID-19 and get back on track in the fight against tuberculosis.[7] They suggest that some of the tools that have been used for years in the fight against tuberculosis, namely masks, physical distancing and molecular diagnosis, are now helpful in the battle against COVID-19. However, new strategies set up to fight COVID-19 can also be adapted and targeted to fighting tuberculosis: the repurposing of newly created geospatial tracking systems to locate tuberculosis contacts, the use of virtual systems to ensure treatment compliance and the redirection of financial support from COVID-19 patients to tuberculosis patients, prioritising those living in poverty.[7]

It is possible to try to change our usual practice to minimise the impact that the COVID-19 pandemic has on tuberculosis. Worldwide, there is a significant number of good examples on how to maintain the standard of care in the fight against tuberculosis.[2,8-11] First, it is important to keep education on tuberculosis, both for the population and health professionals. Virtual conferences, seminars, workshops and community awareness must be encouraged.[2,8] With regard to the availability of services, for example, South Africa has set a community-based, neighbourhood-focused screening model, ensuring not only tuberculosis education but also sputum collection and tuberculosis screening.[12] With regard to treatment and patient support, various simple changes can be made: reducing the number of visits to clinics,[8,9] switching from injectable-based to oral regimens for drug-resistant tuberculosis,[9] providing an adequate supply of tuberculosis medication to patients for safe storage at home[2] and using virtual care and digital health technologies for adherence support, early initiation of treatment, remote monitoring of tuberculosis patients, counselling and follow-up.[2,8] Finally, with regard to infection control, the use of surgical masks must be encouraged for patients, visitors and health care staff,[8,10,11] and hand hygiene[8,10,11] and environmental disinfection with germicidal ultraviolet systems[10] can be implemented.

There is no doubt that the COVID-19 pandemic brought us a massive challenge at all levels and has weighed heavily on global mortality. However, the impact of COVID-19 is not limited to the disease itself, and we should not forget that its disruptive impact could kill millions of other people.

Tuberculosis remains a highly prevalent disease worldwide and, until April of 2020, had accounted for

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the highest number of deaths per day worldwide. Therefore, it is now important to identify the harms, redefine strategies and get back on the road towards tuberculosis elimination.

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Cystic fibrosis in Brazil: achievements in survival

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Cystic fibrosis (CF) is an autosomal recessive genetic disease that is chronic and progressive, being characterized by multisystem involvement.[1] CF is caused by mutations in a gene that is located on the long arm of chromosome 7 and that encodes the cystic fibrosis transmembrane conductance regulator (CFTR) protein, an epithelial cell chloride channel that allows the cotransport of sodium and chloride along with water across the cell membrane.[2] The estimated incidence of CF in Brazil is 1:7,576 live births; however, the incidence of CF differs across regions in Brazil, being highest in the southern and southeastern regions.[3] According to data from the Brazilian CF Patient Registry, a total of 5,517 patients were followed at referral centers in 2018.[4]

In recent decades, advances in the diagnosis and treatment of CF have significantly increased the life expectancy of CF patients. According to data from the Cystic Fibrosis Foundation Patient Registry, median survival is 46.2 years in the USA,[5] whereas, in Brazil, median survival is 43.8 years.[4] Newborn screening for CF is currently performed in all Brazilian states. Therefore, age at diagnosis has decreased, the median age at diagnosis of CF being 3.7 months in 2018.[4] Early initiation of treatment at a specialized referral center by a multidisciplinary team improves clinical outcomes, having a positive impact on patient prognosis.[6] According to data from the Brazilian CF Study Group, there are over 50 CF referral centers in 22 Brazilian states.[4] Treatment advances include control of respiratory infections, mucolytics, pancreatic enzyme replacement therapy, dietary supplementation, respiratory therapy, and physical exercise, all of which influence the survival of CF patients.[6] New drugs such as CFTR modulators are likely to increase the life expectancy of CF patients, allowing treatment of the molecular cause of CF. To date, four CFTR modulators have been developed for the treatment of patients with specific mutations.[7] However, these drugs remain unavailable for most CF patients in Brazil.

Although CF is a multisystem disease, lung disease is the primary cause of morbidity and mortality in CF patients. A vicious cycle of airway mucus accumulation, chronic inflammation, and recurrent infections leads to epithelial damage, tissue remodeling, and progressive lung function decline.[8] Patients with CF experience episodes of acute worsening of respiratory symptoms (pulmonary exacerbation) requiring oral antibiotics (for mild exacerbations) or hospitalization for intravenous antibiotic therapy in many cases.[9] Frequent exacerbations negatively influence prognosis and accelerate lung function decline, as well as being associated with increased morbidity and mortality in CF patients.[10] As the disease progresses and lung function declines, advanced-stage CF patients are referred for lung transplantation. However, the decision to pursue transplantation involves comparing the likelihood of survival with and without transplantation, as well as assessing the effect of wait-listing and transplantation on patient quality of life. In any case, lung disease is the most common cause of death in CF patients.[4,5,11] According to the Cystic Fibrosis Foundation,[5] there has been a steady decline in the mortality rate for patients with CF.[5] Although the median age at death has increased in recent years in Brazil (to 18.4 years),[4] it remains lower than those in the USA (32.4 years)[5] and Europe (29.0 years).[11]

In the current issue of the *Jornal Brasileiro de Pneumologia*, Santo et al.[12] describe causes of death and mortality data related to CF in Brazil on the basis of data from death certificates. For the 1999-2017 period, the overall CF-related number of deaths was 2,854, with CF being reported as the underlying cause of death in 83.5% of the death certificates. A continuous upward trend in the death rates was observed, with a significant annual percent change of 6.84% among males and 7.50% among females, the median age at death having increased from 7.5 years in 1999 to 56.5 years in 2017. According to the authors, the results are counterintuitive because the advances in CF diagnosis and treatment might result in an increase in the age at death but not in the mortality rates. However, the increasing mortality trend might be related to an increased number of patients being diagnosed with CF as a result of increased newborn screening for CF in Brazil. The most important finding in the study by Santo et al.[12] is the significant increase in the median age at death, probably due to advances in diagnosis and treatment.

In conclusion, advances in diagnosis and treatment, as well as improvements and expansion in multidisciplinary care centers, have changed the situation for CF patients in Brazil, resulting in a significant increase in life expectancy. Expanding the use of new drugs can result in improved mortality rates, life expectancy, and quality of life for CF patients in Brazil.

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Consolidation with bronchial dilation

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

A 72-year-old male former smoker presented with cough, chest pain, and dyspnea. Chest CT identified a consolidation with air bronchograms and bronchial dilation in the left upper lobe (Figure 1).

Consolidation, one of the most common chest CT findings, is characterized by the replacement of gas in the airspaces with fluid (i.e., transudate, exudate, or blood), cells, or other material (i.e., fat or protein). It can be hypodense (indicative of fat), which is generally characteristic of lipoid pneumonia, or hyperdense, as in pulmonary alveolar microlithiasis, parenchymal amyloidosis, talc pneumoconiosis, metastatic pulmonary calcification, and amiodarone-induced pulmonary toxicity.[1] However, most consolidations have soft-tissue density (similar to the densities of the heart and liver). This finding is highly nonspecific, being associated with various diseases; the differential diagnosis depends on the correlation of clinical and laboratory findings. The final diagnosis is possible only by anatomopathological evaluation in various cases. Imaging findings can help narrow the diagnostic possibilities. Initially, the determination of whether consolidation is the sole finding or whether associated patterns are present can aid in the differential diagnosis. In addition, the distribution of lesions (e.g., lobar, segmental, or predominating in the cortical or medullary regions) can be a useful parameter.

A characteristic, but rarely recognized tomographic finding is bronchial dilation in an area of consolidation. This pattern is very suggestive of pulmonary lymphoma (PL), especially mucosa-associated lymphoid tissue (MALT) PL. MALT underlying the respiratory tract epithelium is called bronchus-associated lymphoid tissue (BALT). Although the CT findings of PL are well described, the pattern of dilated air bronchograms inside areas of consolidation is not often recognized as a contributor to this diagnosis.[2] The main differential diagnosis is previously existing bronchiectasis intermingled with consolidation. The bronchial dilation seen in BALT lymphoma and that observed in bronchiectasis differ in many aspects. In BALT lymphoma, the bronchial wall is not destroyed and the dilation is reversible after the lymphoma has been treated. Lymphoma-associated bronchial dilation is always surrounded by a consolidation or mass (generally absent on CT scans in patients with bronchiectasis) and is not accompanied by sputum. However, bronchial dilation associated with bronchiectasis is irreversible due to bronchial wall destruction and is frequently associated with productive cough. Thus, the presence of bronchial dilation inside areas of consolidation appears to be a sufficiently specific CT finding to suggest the diagnosis of PL.[2] In our patient, the final diagnosis, made by lung biopsy, was BALT lymphoma.

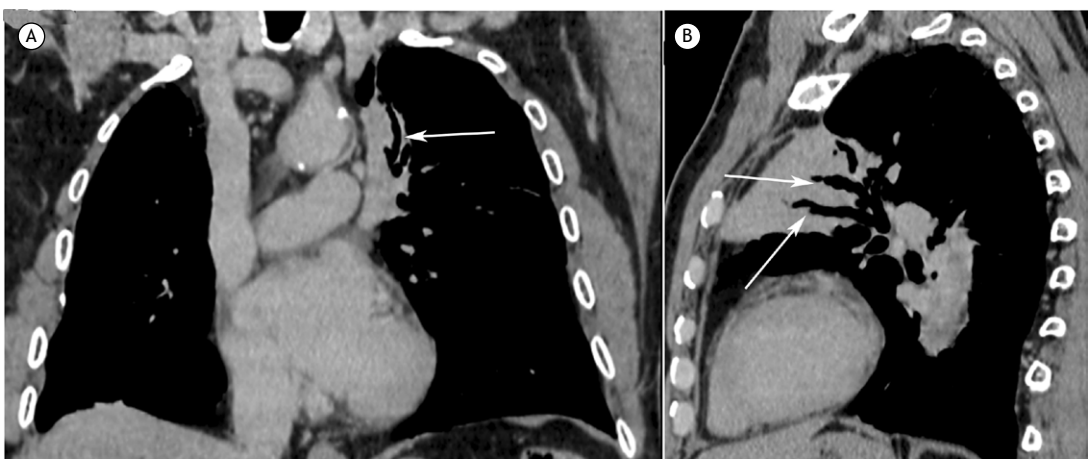

Figure 1. A 72-year-old man with biopsy-proven bronchus-associated lymphoid tissue lymphoma. Coronally (in A) and sagittally (in B) reconstructed CT images obtained with the mediastinal window setting showing an area of consolidation in the left upper lobe containing markedly dilated bronchi (arrows).

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Receiver operating characteristic analysis: an ally in the pandemic

Jezreel Pantaleón García[1,2], Juliana Carvalho Ferreira[1,3], Cecilia Maria Patino[1,4]

PRACTICAL SCENARIO

From a global public health perspective, a diagnostic test that accurately discriminates between positive and negative COVID-19 cases is critical to allocate human and material resources to manage the pandemic.[1] The ongoing COVID-19 pandemic has led to the expeditious development of multiple diagnostic tests to detect the SARS-CoV-2 infection. Thus, clinicians, researchers, and policy makers need to understand how to interpret the performance level of such diagnostic tests[1] to support the multilevel decision-making process. Here, we provide an overview of a commonly used tool to evaluate the accuracy of diagnostic or prognostic tests: the ROC curve.

ROC ANALYSIS

We use ROC analysis to graphically display, compare, and evaluate the accuracy of current and novel diagnostic tests. In order to do so, ROC curves integrate three related measures of accuracy: sensitivity (true positives), specificity (true negatives), and AUC.[2] These measures are calculated for any diagnostic test by comparing the test result (positive or negative) against a well-known gold standard that determines the true disease status in each case.

UNDERSTANDING ROC CURVES

ROC curves are created by plotting sensitivity (true positives) on the *y* axis against 1 − specificity (true negatives) on the *x* axis for every value found in a sample of subjects with and without the disease. It is expected that higher values would be more common among the subjects with the disease, and lower values would be more common among the subjects without the disease. In a perfect test, an obvious cutoff threshold can be identified that differentiates subjects with the disease from those without the disease, sensitivity and specificity being both 100%. Such a perfect differentiation is rarely the case for tests in real life, so ROC curves plot the trade-off between sensitivity and specificity for all possible cutoffs and the overall test accuracy. To express the diagnostic accuracy of a test numerically, we calculate the AUC, which estimates the probability of a random subject with the disease to have a higher value on the test than a subject without the disease. The probability ranges from 0% (AUC = 0) to 100% (AUC = 1).

USING ROC CURVES

Relative shapes of ROC curves within the plot are a quick approach to estimate and compare the accuracy between diagnostic tests (Figure 1). A perfect diagnostic test (AUC = 1.0) correctly identifies all positive and all negative results as diseased and non-diseased, respectively, and would reach the far top left. In contrast, a test that is inaccurate, or similar to flipping a coin, would result in a 45-degree line (AUC = 0.5). These two extremes (perfect test and uninformative test) are often used as references: ROC curves closer to a perfect diagnostic test have a higher AUC and are more accurate than are those closer to the random error line (AUC ~0.5).[2] Therefore, comparing multiple ROC curves may be an intuitive strategy to help us decide which the most accurate test for our clinical practice is. However, since there is always a trade-off between sensitivity and specificity, tests should not be evaluated by the AUC alone. In some cases, a test is more useful when it has high sensitivity (and, therefore, lower specificity), as when you cannot afford to miss the diagnosis. An example is when you are using a test to diagnose COVID-19. In that case, a test with lower

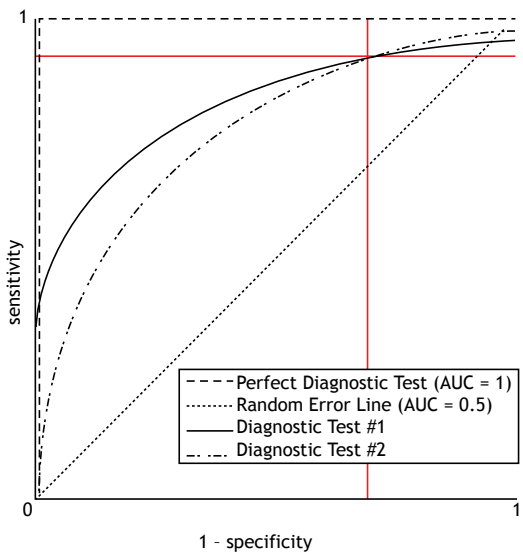

Figure 1. Comparative examples of ROC curves. ROC curve plots illustrating the accuracy performance of a perfect diagnostic test (AUC = 1), a random error line (AUC = 0.5) of an uninformative test, and two hypothetical diagnostic tests. Red lines depict a clinically relevant threshold of high sensitivity range in which the AUC of Diagnostic Test #2 outperforms Diagnostic Test #1.

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AUC that has a high sensitivity may be more useful in certain clinical scenarios than a test with slightly higher AUC with lower sensitivity (and greater specificity).

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Is this asthma, COPD, or both?

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BACKGROUND

Asthma and COPD are the commonest respiratory diseases followed by pulmonologists. Due to shared clinical features, discriminating between the two diseases can be challenging; moreover, there might be asthma-COPD overlap (ACO).[1] Symptomatic patients are often referred for pulmonary function tests (PFTs), because their physicians hope that such tests will provide clear-cut diagnostic information.

OVERVIEW

Patient "A" was a 61-year-old woman, former smoker (18 pack-years), who was referred for PFTs "to confirm asthma," because a previous spirometry had shown a large FEV_1 response (0.55 L) to bronchodilator. Repeated PFTs showed a moderate and proportional decrease in FEV_1 and FVC (FEV_1/FVC = 0.72) with a large post-bronchodilator volume response (ΔFVC = 0.81 L), leading to a commensurate increase in FEV_1, that is, pre- and post-bronchodilator FEV_1/FVC ratios were similar. Gas trapping was detected on body plethysmography (RV/TLC = 0.59), with preserved TLC; of note, DL_{CO}, carbon monoxide transfer coefficient (K_{CO}), and alveolar ventilation (V_A)/TLC ratio were all moderately reduced. These results combined were more consistent with COPD than asthma; in fact, a chest CT showed moderate-to-severe centrilobular emphysema and diffuse airway thickening. Patient "B" was a 73-year-old gentleman previously diagnosed with COPD, on the basis of a heavy smoking history and airflow limitation on remote spirometry. Repeated PFTs confirmed moderate airflow limitation (FEV_1/FVC = 0.58; FEV_1 = 64% of the predicted value). Following the use of inhaled bronchodilator, FEV_1 and mid-expiratory flows normalized. Lung volumes, DL_{CO}, K_{CO} and V_A/TLC ratio were within normal limits, as was a chest CT. Collectively, these data were deemed more consistent with asthma than COPD.

Table 1. Ten misconceptions regarding the value of pulmonary function tests in discriminating asthma from COPD.[a]

False statement	Comment
1. Normal baseline spirometry (i.e., with no previous use of a BD) excludes airway disease	Some patients with airway disease present with ΔFEV_1 > day-to-day variability seen in normal subjects (up to 12% and 200 mL) despite normal spirometry, suggesting increased bronchomotor tone
2. Normal spirometry excludes smoking-related lung disease	Smokers with imaging (airway disease and emphysema) and other functional ($\Downarrow DL_{CO}$ and/or $\Downarrow K_{CO}$) abnormalities may present with "preserved" spirometry
3. An isolated decrease in mid-expiratory flows ($\Downarrow FEF_{25-75\%}$) is not relevant from a symptomatic standpoint in subjects with suspected airway disease	$FEF_{25-75\%}$ < LLN (60% of predicted), particularly in a subject with preserved FVC (i.e., $\Downarrow FEF_{25-75\%}$/FVC ratio), increases the likelihood of dynamic gas trapping and exertional dyspnea in patients with airway disease
4. SVC does not add value to FVC	In the right clinical context, $\Downarrow FEV_1$/SVC ratio despite preserved FEV_1/FVC ratio may uncover airflow limitation both in asthma and COPD
5. A significant "flow" response to inhaled BD (e.g., $\Delta FEV_1 \geq$ 12% and ≥ 200 mL) signals asthma	A sizeable fraction of patients with COPD (~2/3) may present with a "flow" response at some point
6. Large ΔFEV_1 (e.g., ≥ 20% and ≥ 400 mL) indicates asthma	Such large changes in FEV_1 may occur in a patient with COPD showing a "volume" response, i.e., ΔFVC ≥ 12% and ≥ 200 mL leading to similar pre- and post-BD FEV_1/FVC ratios
7. A significant "volume" response to inhaled BD (e.g., ΔFVC ≥ 12% and ≥ 200 mL) signals COPD	A "volume" response may occur in patients with asthma showing gas trapping and extensive small airway disease
8. Lack of normalization of a baseline spirometry showing airflow limitation signals COPD	~1/3 of the patients with moderate-to-severe persistent asthma may present with "fixed" airflow limitation
9. A negative methacholine challenge test excludes asthma	A negative test only indicates the absence of "active" hyperresponsiveness at a given point in time
10. Normal DL_{CO} excludes COPD	COPD patients showing features of the chronic bronchitis phenotype may present with preserved DL_{CO}

BD: bronchodilator; K_{CO}: lung diffusing coefficient for carbon monoxide (DL_{CO}/alveolar volume); LLN: lower limit of normal; and SVC: slow vital capacity. [a]Δ indicates the changes promoted by a short-acting BD.

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The list of scenarios in which PFTs are ambiguous about the presence of asthma or COPD (Table 1) is considerably larger than is that describing the few "diagnostic" situations provided above. For instance, even if a large increase in post-bronchodilator FEV_1 (ΔFEV_1 ≥ 20% and ≥ 400 mL) is more commonly associated with asthma, this is not necessarily the case when the increase in FEV_1 is largely driven by volume recruitment (Patient "A"; Table 1, scenario 6). In practice, no cutoff value has provided excellent performance to differentiate asthma from COPD clearly.[1] The spirometric pattern designated Preserved Ratio Impaired Spirometry, also seen in Patient "A," has been described in both diseases.[2] Low DL_{CO} and K_{CO} speak against asthma (Patient "A"), but low DL_{CO} may occur in non-anemic patients with asthma if V_A is a low fraction of TLC.[3] Conversely, preserved (or increased) DL_{CO} is more consistent with asthma, but it may occur in COPD patients with a predominance of chronic bronchitis (Table 1, scenario 10).[4] Establishing the presence of ACO is even more challenging. Given the seven definitions of ACO,[5] spirometry-based criteria were the least reliable and stable over time.

CLINICAL MESSAGE

In various circumstances, PFTs alone are unable to definitively establish asthma and/or COPD (Table 1). Relating functional data with additional clinical information (pre-test likelihood of disease, potentially including eosinophil counts) is crucial to this endeavor. A cautious, noncommittal approach is recommended: even if the results do suggest one of the diseases, it is safer (and more honest) to state that "in the right clinical context," the results are "consistent with" asthma and/or COPD.

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Exercise-induced desaturation in subjects with non-cystic fibrosis bronchiectasis: laboratory-based tests versus field-based exercise tests

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ABSTRACT

Objective: To investigate the validity of field walking tests to identify exercise-induced hypoxemia and to compare cardiorespiratory responses and perceived effort between laboratory-based and field-based exercise tests in subjects with bronchiectasis. **Methods:** This was a cross-sectional study involving 72 non-oxygen-dependent participants (28 men; mean age = 48.3 ± 14.5 years; and mean FEV_1 = 54.1 ± 23.4% of the predicted value). The participants underwent cardiopulmonary exercise testing (CPET) on a treadmill and constant work-rate exercise testing (CWRET) on the same day (1 h apart). In another visit, they underwent incremental shuttle walk testing (ISWT) and endurance shuttle walk testing (ESWT; 1 h apart). Desaturation was defined as a reduction in SpO_2 ≥ 4% from rest to peak exercise. **Results:** CPET results were compared with ISWT results, as were CWRET results with ESWT results. There was no difference in the magnitude of desaturation between CPET and ISWT (–7.7 ± 6.3% vs. –6.6 ± 5.6%; p = 0.10) and between CWRET and ESWT (–6.8 ± 5.8% vs. –7.2 ± 6.3%; p = 0.50). The incremental tests showed an agreement in the magnitude of desaturation in the desaturation and no desaturation groups (42 and 14 participants, respectively; p < 0.01), as did the endurance tests (39 and 16 participants; p < 0.01). The magnitude of desaturation was similar among the participants who did or did not reach at least 85% of the maximum predicted HR. **Conclusions:** Field exercise tests showed good precision to detect desaturation. Field tests might be an alternative to laboratory tests when the clinical question is to investigate exercise-induced desaturation in subjects with bronchiectasis.

Keywords: Bronchiectasis; Oxygen; Hypoxia; Exercise test.

INTRODUCTION

Bronchiectasis is a chronic, progressive and debilitating disease characterized by chronic inflammation, recurrent exacerbations, and progressive loss of pulmonary function.[1] Impaired diffusion capacity and an underlying interstitial lung disease have been reported in bronchiectasis, also contributing to limited pulmonary gas exchange and oxygen desaturation during exertion.[2,3]

Exercise-induced desaturation is a common finding in chronic respiratory diseases,[4] and it has previously been demonstrated in patients with bronchiectasis.[5,6] An official systematic review of the European Respiratory Society and the American Thoracic Society[7] has highlighted the importance of quantifying oxygen desaturation in patients with chronic pulmonary diseases. This recommendation was based on the relationship between oxygen saturation and important outcomes, such as severity of the disease, prognosis, and muscle weakness.[7] In patients with bronchiectasis, poor gas exchange[8] and hypoxemia[9] are predictors of mortality. In this context, patients with exertional desaturation should be monitored more regularly than those without, in order to minimize possible negative consequences of repeated episodes of hypoxemia. Cardiopulmonary exercise testing (CPET) with pulmonary gas exchange analysis is the gold standard to assess the causes of exercise limitation,[10] but it is expensive and requires highly trained personnel. Therefore, CPET is not readily available in clinical practice, and it would not be the test of choice for detecting exertional desaturation.

In previous studies, mostly involving patients with COPD, field walking tests were found to be more sensitive in detecting the magnitude of desaturation than were cycle

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ergometer tests.[7] A similar finding was observed in subjects with bronchiectasis in whom the magnitude of desaturation was found to be higher during an incremental walk test, such as the incremental shuttle walk test (ISWT), than during an incremental cycle ergometer test, such as CPET.[6] This result is not completely surprising because walking and cycling are completely different activities. However, the degree of exercise-induced desaturation is quite similar between the ISWT and the endurance shuttle walk test (ESWT),[11] as well as between the ISWT and the six-minute walk test (6MWT) in subjects with COPD.[12] Recently, a study has suggested that field walking tests (6MWT, ISWT, and ESWT) can be used interchangeably for the evaluation of the level of exercise-induced desaturation in subjects with non-cystic fibrosis (NCF), because they lead to an equivalent oxygen desaturation.[13] To date, the magnitude of desaturation in similar modalities of exercise (based on walking) but in different contexts (laboratory or field) has yet to be investigated in subjects with bronchiectasis. Our hypothesis was that incremental tests—CPET on a treadmill or ISWT—and tests at a constant workload—constant work-rate exercise testing (CWRET) on a treadmill or ESWT)—would show similar desaturation results. The objective of this study was investigate the validity of the ISWT and ESWT as reliable tools in order to identify exercise-induced desaturation, comparing cardiorespiratory responses and perceived effort/fatigue between laboratory-based and field-based exercise tests in subjects with NCF bronchiectasis.

METHODS

This was a cross-sectional study involving patients with NCF bronchiectasis. The inclusion criteria were being ≥ 18 years of age, not depending on oxygen, being a nonsmoker, presenting with no other chronic lung or cardiovascular diseases, and being in a stable clinical condition (absence of changes in spirometry, dyspnea, cough, general condition, medications and doses, as well as in viscosity and color of secretions in the four weeks preceding entry into the study).[14] Patients who were unable to perform or understand how to perform the proposed tests were excluded, as were those who had decided to withdraw from the study. Bronchiectasis was diagnosed in accordance with followed the British Thoracic Society guideline for NCF bronchiectasis[14] and was confirmed by HRCT.

The study was conducted in two visits. At the first visit, spirometry was performed, BMI was calculated, and the perception of dyspnea was assessed by the modified Medical Research Council (mMRC) scale.[15] In addition, the participants were randomized to perform either CPET and CWRET or ISWT and ESWT. A bronchodilator (albuterol, 400 μg) was administered 15 minutes prior to the tests. At the second visit, seven days later, spirometry was performed again to evaluate clinical stability, and the participants performed the second set of tests . Desaturation was considered present if there was a reduction in SpO_2 ≥ 4% from rest to peak exercise.[4]

Spirometry was performed using Ultima CPX (MGC Diagnostics Corporation, Saint Paul, MN, USA). Acceptability and reproducibility criteria adopted for the technical procedures were those recommended by the Brazilian guidelines for lung function testing.[16] We collected data on FVC, FEV_1, and FEV_1/FVC ratio expressed in absolute values and as a percentage of the predicted value for the Brazilian population.[17]

The CPET was conducted on a treadmill (Millennium Classic; Inbramed/Inbrasport, Porto Alegre, RS, Brazil), using the protocol recommended by Balke and Ware,[18] including constant speed estimated on the basis of the physical fitness of the participant (pulmonary function and baseline dyspnea assessed by the mMRC scale). Increments of one percent in the inclination were imposed every minute. Considering the period of workload increment, the test should last 8-12 min. Measurements of HR (Polar Precision Performance; Polar Electro Inc., Bethpage, NY, USA) and SpO_2 (finger pulse oximeter model 9500; Nonin, Plymouth, MN, USA) were continuous during the test. Blood pressure (BP) was measured every 2 min of exercise. The Borg scale was used to rate the perception of dyspnea and leg fatigue[19] at rest and immediately after the end of the exercise.

The ISWT was performed in accordance with the original description[20] in a 10-m hallway. The test was stopped if the participant could not follow the rhythm delivered by the sound. The test was also stopped if the participant showed chest pain, intolerable dyspnea, leg cramps, staggering, diaphoresis, or a pale/ashen appearance.[7] Measurements of HR and SpO_2 were continuous during the test (using the same devices described for CPET) and recorded every minute. The BP and the Borg scale scores for the perception of dyspnea and leg fatigue[19] were obtained at rest and immediately after the end of the exercise. The ISWT was performed twice (30 min apart).[7] The best walk distance was expressed in absolute value and as a percentage of the predicted value.[20]

The CWRET was performed one hour after the CPET using the same maximum speed as that used for CPET and a maximum inclination of 75%. Electrocardiogram tracing, HR, and SpO_2 were continuously measured during the test. The BP was measured every 2 min of exercise. The Borg scale measured the perception of dyspnea and leg fatigue[19] at rest and immediately after the end of the exercise.

The ESWT was performed as recommended,[21] being performed one hour after the ISWT and using the same interruption criteria as in the ISWT. The ESWT speed was 85% of the peak oxygen uptake during the ISWT, as determined by the following regression equation: oxygen uptake = 4.19 + (0.025 × ISWT distance).[20,21] The HR and SpO_2 were continuously measured during the test. The BP and the Borg scales for the perception

of dyspnea and leg fatigue[19] were obtained at rest and immediately after the end of the exercise.

The present study was conducted in accordance with the principles of the Declaration of Helsinki, and the Research Ethics Committees of the *Nove de Julho* University (Reference no. 451538) and the São Paulo State University (Reference no. 0921/11) approved the study. All participants gave written informed consent.

Statistical analysis

We used the Shapiro-Wilk test to determine whether the data had normal or non-normal distribution. Data with parametric distribution were expressed as means and standard deviations, and those with nonparametric distribution (Borg and mMRC scale scores) were expressed as medians and interquartile ranges.

The baseline characteristics between the groups of the participants who did and did not desaturate were compared by the unpaired Student's t-test. Comparisons between CPET and ISWT, as well as between CWRET and ESWT were analyzed by the paired Student's t test for parametric data and by the Wilcoxon test for nonparametric data. The agreement regarding the level of desaturation between CPET and ISWT, as well as between CWRET and ESWT, were analyzed by the chi-square test and Cohen's kappa coefficient (< 0.00, no agreement; 0.00-0.20, slight agreement; 0.21-0.40, fair agreement; 0.41-0.60, moderate agreement; 0.61-0.80, substantial agreement; and 0.81-1.00, perfect agreement).[22] Accuracy, sensibility, specificity, and predictive values (and their respective 95% CIs) were also calculated. The unpaired Student's t-test was used in order to compare SpO_2 between the groups of participants who reached ≥ 85% and < 85% of the maximum predicted HR in the incremental and endurance tests. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using the SPSS Statistics software package, version 20.0 (IBM Corporation, Armonk, NY, USA). The post hoc power of the sample was calculated taking into account the chi-square test, because the basis of the present study was to investigate whether there was an association between desaturation (yes or no) and exercise tests (ISWT vs. CPET and ESWT vs. CWRET). The program G*Power, version 3.1 (Heinrich Heine University, Düsseldorf, Germany)[23] was used for this analysis.

RESULTS

A convenience sample of 92 individuals was recruited; 17 declined to participate. Therefore, 75 were included in the study. Of those, 3 were excluded (2 did not perform all tests, and 1 did not perform the tests correctly). A total of 72 individuals were therefore studied, 28 of whom were male. Most of the participants were normal-weight women with a restrictive and/or obstructive pattern on spirometry (Table 1). With regard to baseline characteristics, only pulmonary function test results differed between those who did or did not present with desaturation (Table 1).

A similar behavior in SpO_2 was observed, minute by minute, during the incremental and constant workload tests (Figure 1). Most subjects presented with desaturation in all tests (CPET: 74%; ISWT: 65%; CWRET: 64%; and ESWT: 68%). There was no difference in the levels of desaturation between the incremental and constant work-rate walk tests (Table 2). The agreement analysis between CPET and ISWT demonstrated that, of the 72 study participants, 42 presented with desaturation in both tests, and 14 presented with no desaturation in either tests (chi-square test = 17.287; $p < 0.01$). Comparing CWRET and ESWT, in the sample as a whole, 45 participants presented with desaturation in both tests, and 15 presented with no desaturation in either tests (chi-square test = 16.394; $p < 0.01$). Retrospective power analysis for both chi-square tests was 0.99. Table 3 summarizes the agreement analysis.

Distance, total exercise time, HR, systolic BP, and perception of dyspnea and leg fatigue were greater in CPET than in ISWT. Similarly, HR, systolic BP, and perception of dyspnea were greater in CWRET than in ESWT (Table 2). Regardless of the test, desaturation was similar among the participants who reached at least 85% of the maximum predicted HR or not (Table 2).

DISCUSSION

Field-based exercise tests with similar profiles to those of laboratory-based exercise tests induce similar oxygen desaturation in subjects with bronchiectasis. Cardiorespiratory responses and perception of effort were higher in laboratory-based tests than in field-based tests. Field tests are accurate for the detection of desaturation, demanding less effort from participants than do laboratory-based tests.

Oxygen desaturation cannot commonly be predicted from data obtained at rest. Therefore, exercise testing is important to determine patients who may present with desaturation during exertion.[24] Because CPET is not readily available in clinical practice, field walking tests can be an alternative for the assessment of exercise-induced desaturation, because they have low costs and are easy to perform.[7]

Exercise-induced desaturation has previously been demonstrated in individuals with bronchiectasis.[6] In that population, the level of desaturation is higher during ISWT than during CPET performed on a cycle ergometer.[6] In addition, 21% of patients who showed desaturation during ISWT showed no desaturation during CPET.[6] Similar results have been observed in subjects with COPD.[12,25,26] This finding might have occurred because the incremental CPET was performed on a cycle ergometer. However, an incremental walk test on a treadmill also led to a significantly lower PaO_2 than did an incremental cycle ergometer test in subjects with COPD.[27] Therefore, tests performed on a cycle ergometer may underestimate the real desaturation during exercise, making walk tests more sensitive for detecting desaturation.[7]

Table 1. Characteristics of the sample as a whole and of those who did and did not desaturate.[a]

Variable	Total sample	Group		p
		No desaturation	Desaturation	
	(N = 72)	(n = 14)	(n = 58)	
Age, years	48 ± 15	51 ± 16	48 ± 14	0.48
Male sex	28 (38.9)	3 (21.4)	25 (43.1)	0.11
Weight, kg	64.4 ± 14.4	64.2 ± 17.0	64.5 ± 13.8	0.96
Height, m	1.6 ± 0.1	1.6 ± 0.1	1.6 ± 0.1	0.53
BMI, kg/m^2	25.3 ± 5.5	25.5 ± 6.4	25.3 ± 5.3	0.89
mMRC score	2.0 [1.0-2.0]	2.0 [0.8-2.0]	2.0 [1.0-2.0]	0.55
FVC, L	2.3 ± 0.8	2.6 ± 0.8	2.3 ± 0.8	0.22
FVC, % predicted	68.7 ± 20.0	82.2 ± 22.5	65.5 ± 18.2	0.02
FEV_1, L	1.5 ± 0.6	1.9 ± 0.6	1.4 ± 0.6	0.01
FEV_1, % predicted	54.1 ± 23.4	74.1 ± 27.7	49.3 ± 19.6	< 0.01
FEV_1/FVC	0.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.01

mMRC: modified Medical Research Council dyspnea scale. [a]Values expressed as mean ± SD, n (%), or median [IQR].

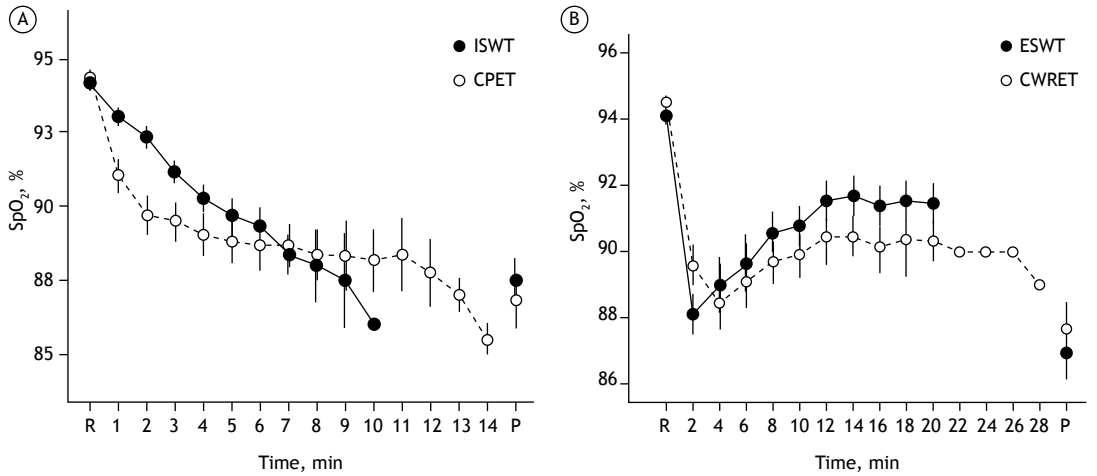

Figure 1. In A, comparison between the incremental shuttle walk test (ISWT) and cardiopulmonary exercise testing (CPET) regarding the variation of SpO_2 during the tests. In B, comparison between the endurance shuttle walk test (ESWT) and constant work-rate exercise testing (CWRET) regarding the variation of SpO_2 during the tests. The error bar (P) corresponds to the standard error.

In the present study, walk tests showed comparable levels of desaturation, even when using different approaches (incremental or endurance exercise tests). One previous study has demonstrated that the level of desaturation in subjects with bronchiectasis was similar during the 6MWT, ISWT, and ESWT (−6.8 ± 6.6; −6.1 ± 6.0; and −7.0 ± 5.4, respectively) and suggested that field walking tests can be used interchangeably for the evaluation of the level of exercise-induced desaturation in those subjects.[13] The same was found in patients with COPD when ISWT was compared with ESWT[11] and 6MWT.[26]

Incremental and endurance exercise tests induced more intense cardiovascular and ventilatory responses, as well as a higher perception of dyspnea, when performed on a treadmill rather than in a corridor/hallway. This is because there are important differences in the gait mechanics between these two forms of walking.[28-31] Treadmill walking requires greater effort and higher energy expenditure to maintain lateral balance control.[29,31,32] Furthermore, most patients are not familiar with that activity.[33] However, in our study, participants were allowed to support themselves using their hands on the treadmill. When subjects walk on a treadmill with hand support, there is a considerable reduction in the demand of walking and their responses change significantly. When hand support is allowed, body balance control increases, and energy consumption and the demand to maintain balance control decreases.[29,31,32] Because hand support was allowed in the present study, exercise time increased, and, consequently, more intense cardiopulmonary responses and higher perception of dyspnea were found in the tests performed on a treadmill.

Subjects that presented with desaturation had worse lung function parameters. This is not a surprising result because exertional desaturation has been associated with lower FEV_1 and worse prognosis.[33] We observed that the magnitude of desaturation was similar in the groups of participants who did and did not reach

Table 2. Performance and cardiorespiratory responses, as well as perception of dyspnea and leg fatigue, during the walk tests (N = 72).[a]

Variable	CPET	ISWT	p	CWRET	ESWT	p
SpO_2	86.8 ± 7.0	87.5 ± 6.0	0.23	86.8 ± 6.9	86.9 ± 7.2	0.17
ΔSpO_2	−7.7 ± 6.3	−6.6 ± 5.6	0.10	−6.8 ± 5.8	−7.2 ± 6.3	0.50
Distance, m	690.14 ± 265,8	455.4 ± 123.3	< 0.01	797.7 ± 490.4	756.4 ± 559.6	0.57
Speed, km/h	4.7 ± 1.0	5.3 ± 0.8	< 0.01	4.7 ± 1.0	5.1 ± 0.7	< 0.01
Slope, %	10.4 ± 4.0	N/A	N/A	7.9 ± 3.0	N/A	N/A
Distance, % of predicted	N/A	57.0 ± 15.2	N/A	N/A	N/A	N/A
Time, min	8.5 ± 2.5	7.11 ± 1.28	< 0.01	9.9 ± 5.8	8.9 ± 6.5	0.29
HR, bpm	148.9 ± 19.3	135.1 ± 20.4	< 0.01	144.7 ± 19.8	135.7 ± 20.3	< 0.01
HR, % of predicted	87.0 ± 9.0	78.9 ± 11.4	< 0.01	84.5 ± 9.9	79.3 ± 11.8	< 0.01
HR ≥ 85% of predicted	44 (61.1)	23 (31.9)	< 0.01	30 (41.7)	26 (36.1)	< 0.01
SpO_2 (HR ≥ 85% of predicted)	87.3 ± 5.8	86.8 ± 5.9	0.77	87.9 ± 5.5	85.6 ± 7.4	0.19
ΔSpO_2 (HR ≥ 85% of predicted)	−7.1 ± 5.0	−7.6 ± 5.8	0.74	−6.5 ± 4.8	−8.3 ± 6.1	0.23
HR < 85% of predicted	28 (38.9)	49 (60.1)	< 0.01	42 (58.3)	46 (63.9)	< 0.01
SpO_2 (HR < 85% of predicted)	86.1 ± 8.4	87.9 ± 6.1	0.33	87.5 ± 7.1	87.7 ± 7.0	0.91
ΔSpO_2 (HR < 85% of predicted)	−8.6 ± 8.0	−6.2 ± 5.5	0.17	−7.0 ± 6.4	−6.6 ± 6.4	0.73
SBP, mmHg	154.8 ± 17.7	136.3 ± 20.2	< 0.01	153.1 ± 16.3	138.1 ± 17.8	< 0.01
DBP, mmHg	79.9 ± 10.5	77.3 ± 9.5	0.48	79.4 ± 11.5	77.0 ± 10.2	0.05
Borg scale, dyspnea	5 [4–8]	4 [3-7]	< 0.01	5 [4-7]	4 [2–6]	< 0.01
Borg scale, leg fatigue	5 [3–7]	3 [2-6]	< 0.01	4 [2-7]	4 [2–6]	0.30

CPET: cardiopulmonary exercise testing; ISWT: incremental shuttle walk test; CWRET: constant work-rate exercise testing; ESWT: endurance shuttle walk test; ΔSpO_2: SpO_2 at rest minus SpO_2 at the peak of exercise; SBP: systolic blood pressure; DBP: diastolic blood pressure. [a]Values expressed as mean ± SD, n (%), or median [IQR].

Table 3. Accuracy, sensitivity, specificity, predictive values, and agreement between laboratory-based and field-based exercise tests.[a]

Variable	ISWT vs. CPET	ESWT vs. CWRET
Accuracy	77.8 (66.4-86.7)	83.3 (72.7-91.1)
Sensitivity	79.3 (66.0-89.0)	84.9 (72.4-93.3)
Specificity	73.7 (48.8-90.9)	79.0 (54.4-94.0)
PPV	89.4 (76.9-96.5)	84.9 (72.4-93.3)
NPV	56.0 (34.9-75.6)	65.2 (42.7-83.6)
Kappa	0.481 (0.265-0.649)	0.475 (0.234-0.678)

ISWT: incremental shuttle walk test; CPET: cardiopulmonary exercise testing; ESWT: endurance shuttle walk test; CWRET: constant work-rate exercise testing; PPV: positive predictive value; and NPV: negative predictive value. [a]Value (95% CI).

the maximum predicted HR (≥ 85% and < 85%, respectively) in the incremental and constant load walk tests. These findings suggest that the highest cardiac load occurred due to a better performance on the tests rather to a tachycardic response to hypoxemia. When healthy individuals who showed desaturation at the end of the ISWT were compared with those who showed no desaturation at the end of the test, no difference was found in cardiac stress between the groups (88.3 ± 9.3% vs. 87.6 ± 9.6% of maximum predicted HR).[34]

The present study has some limitations. Although we used a convenience sample, a post hoc power analysis indicated that our sample was sufficient to show associations between the tests being compared in relation to our main objective. Pulmonary function analysis was performed only by spirometry. We know that the evaluation of DLCO would increase sensitivity for detecting gas exchange abnormalities. However, the study was not aimed at investigating the determinants of exercise-induced desaturation. Although SpO_2 was recorded every minute, a more accurate comparison of the tests regarding the time to achieve desaturation was not possible in our study.

In conclusion, the magnitude of desaturation was similar between incremental walk tests (CPET and ISWT) and constant workload walk tests (CWRET and ESWT), demonstrating that field walking tests showed good precision to detect desaturation. Cardiorespiratory responses, perceived effort, and perception of fatigue were greater in laboratory-based than in field-based exercise tests. In this context, field walking tests might be an alternative to laboratory-based tests when the objective is to investigate exercise-induced desaturation in subjects with bronchiectasis.

AUTHOR CONTRIBUTIONS

CHYO: conception and design of the study; data acquisition, analysis, and interpretation; drafting of

the manuscript; and final approval of the version to be published. AJ: data analysis and interpretation; critical revision of the manuscript for important intellectual content; drafting of the manuscript; and final approval of the version to be published. AAC: conception and design of the study; data analysis; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. MIZF: data analysis; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. RAA and SZR: data analysis and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. RS: conception and design of the study; data analysis and interpretation; critical revision of the manuscript for important intellectual content; and final approval of the version to be published. SDC: conception and design of the study; data analysis and interpretation; drafting of the manuscript; critical revision of the manuscript for important intellectual content; and final approval of the version to be published.

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ORIGINAL ARTICLE

Cystic fibrosis-related mortality trends in Brazil for the 1999-2017 period: a multiple-cause-of-death study

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ABSTRACT

Objective: To describe causes of death and mortality data related to cystic fibrosis (CF) using a multiple-cause-of-death methodology. **Methods:** Annual mortality data for the 1999-2017 period were extracted from the Brazilian National Ministry of Health Mortality Database. All death certificates in which category E84 (CF) of the ICD-10, was listed as an underlying or associated cause of death were selected. Epidemiological and clinical data were described, and standardized mortality rates were calculated per year and for the 2000-2017 period. A joinpoint regression analysis was performed to detect changes in the mortality rates during the study period. **Results:** Overall, 2,854 CF-related deaths were identified during the study period, ranging from 68 in 1999 to 289 in 2017. CF was the underlying cause of death in 83.5% of the death certificates. A continuous upward trend in the death rates was observed, with a significant annual percent change of 6.84% (5.3-8.4%) among males and 7.50% (6.6-8.4%) among females. The median age at death increased from 7.5 years in 1999 to 56.5 years in 2017. Diseases of the respiratory system accounted for 77% of the associated causes in the death certificates that reported CF as the underlying cause of death. **Conclusions:** A significant and continuous increase in CF-related death rates was found in Brazil in the last years, as well as a concurrent increase in the median age at death.

Keywords: Cystic fibrosis/mortality; Cause of death; Death certificates; Brazil.

INTRODUCTION

Cystic fibrosis (CF) is a genetic disorder caused by mutations in the *cystic fibrosis transmembrane conductance regulator* (*CFTR*) gene, which encodes the CFTR protein, a chloride and bicarbonate channel localized in the apical plasma membrane of epithelial cells.[1] CF results in chronic respiratory infections and bronchiectasis, being the most common life-shortening genetic disease in the White population, with prevalences varying in different ethnic backgrounds and countries.[2] In Brazil, the prevalence of CF is estimated to be from 1:7,500 to 1:15,000 live births, depending on the region.[3]

Brazilian national mortality data originate from death certificates that are provided by doctors or those prepared through reports from witnesses and are documented in civil registry offices.[4] Demographic and medical data from death certificates are coded and processed by vital epidemiological surveillance services located in each of the federal states and the Federal District and sent to the Ministry of Health to be consolidated as data from the whole country.[5] Primary mortality statistics is traditionally presented according to the underlying cause.[6] However, in recent decades, there has been an increasing demand to considering all causes of death stated on death certificates, not only the underlying cause. Such data are called "multiple causes of death", and they provide information on the whole range of lethal processes that culminate in death, thereby offering new elements and perspectives for their prevention.[7]

The epidemiological knowledge on CF in Brazil has significantly been improving since the Brazilian CF Patient Registry started collecting data in 2011. This database currently comprises data from over 5,000 patients.[8] However, the estimated prevalence[3] of CF indicates that there might be a significant number of undiagnosed patients or disengaged patients from traditional CF health care centers. Therefore, the present study aimed to describe CF-related causes of death and mortality based on data from death certificates using the multiple-cause-of-death methodology.

METHODS

Annual mortality data were extracted from the Brazilian National Ministry of Health Mortality Database using the multiple-cause-of-death methodology.[9] For the 1999-2017 period, we selected all deaths related to CF (ICD-10 category E84),[10] listed as a cause of death on any line or in any part of the International Form of Medical Certificate of Cause of Death (the medical certification section of the death certificate).[6] Complications of the underlying cause (part I of the medical certification section) and contributing causes (part II of the medical certification section) were jointly designated as associated (non-underlying) causes of death.[7]

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The causes of death were automatically processed using the software *Seletor de Causa Básica* (Underlying Cause Selector) provided by the Brazilian Ministry of Health, which involves the use of algorithms and decision tables that incorporate the WHO mortality standards and the etiological relationships among the causes of death.[11] To reconstruct the morbid process leading to death, all causes of death listed in the medical certification section of the death certificate were considered, including those classified or considered as ill-defined or defined as modes of death by the WHO.[6]

Using mortality rates, proportions, and historical trends, we studied the distributions of the following variables: sex, age at death (divided into 5-year age brackets), year of death, underlying cause of death, associated (non-underlying) cause(s) of death, total contribution of each cause of death, mean number of causes of death listed per death certificate, and geographical distribution of deaths. Medical and demographic variables were processed using dBASE III Plus, version 1.1 and dBASE IV (Ashton-Tate Corporation, Torrance, CA, USA); Epi Info, version 6.04d (dbDOS™ PRO 6 DOS-based emulation); and Excel. We used a freeware multiple-cause tabulator software in order to present the associated causes and calculate the mean number of causes per death certificate.[12]

CF-related mortality rates (per 1,000,000 population) were calculated per year and for the entire period (2000-2017) based on the number of deaths reporting CF as an underlying or associated cause. In order to calculate the mean mortality rate, the overall number of deaths was divided by the sum of the respective annual population counts for the 18-year study period. Mid-year estimates of the Brazilian population were used (except for the year of 1999, which lacked an acceptable mid-year estimate of the annual population). We used the software Epidat, version 4.2 (*Dirección Xeral de Innovación e Xestión da Saúde Pública*, *Xunta de Galicia*, Spain) in order to standardize crude and mean mortality rates in accordance with the new WHO standard population.[13] Crude and standardized rates were calculated by 5-year age brackets.

For the presentation of the associated causes listed on the death certificates on which CF was mentioned as one of the causes of death, we prepared special lists showing the causes that are usually associated with CF, as well as those mentioned more frequently. Duplication/multiplication of causes of death was avoided when present in abbreviated lists. The number of causes depends on the range of the class in the ICD-10 (constituted by subcategories, categories, blocks, and chapters); therefore, if two or more causes mentioned in the medical certification section were included in the same class, only one cause was computed.

We used ANOVA in order to compare the mean numbers of causes mentioned on the death certificates and the Kruskal-Wallis H test to compare the median age at death between groups. We used the Joinpoint Regression Program, version 4.7.0.0 (National Cancer Institute, Bethesda, MD, USA) to evaluate changes in age-standardized rate trends. Assuming a Poisson distribution, joinpoint analysis chooses the best fitting point (or points) at which the rate significantly increases or decreases. To provide uniformity and synthesis, we allowed one joinpoint. Values of $p < 0.05$ were considered significant.

RESULTS

For the 1999-2017 period, the overall CF-related number of deaths was 2,854 in Brazil: 1,387 (48.6%) in males and 1,467 (51.4%) in females (Table 1). A mean number of 150 deaths occurred per year, ranging from 68 in 1999 to 289 in 2017. CF was reported to be the underlying cause of death in 2,384 death certificates (83.5%) and an associated (non-underlying) cause of death in 470 (16.5%). A large variation among the distribution of deaths in the Brazilian states, the Federal District, and regions was noticed; for instance, between 1999 and 2017, although only 6 deaths occurred in the state of Roraima (northern region), 696 deaths were reported in the state of São Paulo (southeastern region) for the same period. The median age at death was also significantly different according to the Brazilian regions (Table 1 and Figure 1).

Mortality rates for the 2000-2017 period are presented in Table 2 and Figure 2. There was an insignificant higher standardized mean death rate among males (0.8619 deaths per million population) when compared with that among females (0.8345 per million population) and an upward trend in the death rate for both genders (Figure 2). Among males, the standardized mortality rate increased from 0.54 (0.00-0.89) to 1.37 (0.50-1.86) per million population, whereas, among females, it increased from 0.48 (0.00-0.86) to 1.38 (0.50-1.86) per million population from 2000 to 2017. A significant annual percent change was identified among males and females—6.84% (5.3-8.4%) and 7.50% (6.6-8.4%), respectively. Accordingly, a constant, significant upward trend in the annual percent change was found in all of the age brackets studied, except for males in the 0- to 4-year age bracket.

Regarding the age at death, approximately 20%, 25%, 50%, and 25% of the patients died at under 1, 4, 22, and 65 years of age, respectively. However, mean and median ages at death significantly increased during the study period. The medians in 1999 and in 2017 were 10.5 years and 50.5 years in males, and 6.5 years and 61.5 years in females, respectively (Figure 3).

The major associated causes of death in which CF was identified as the underlying cause of death (n = 2,384) are presented in Table 3, in accordance with the ICD-10 structure. Diseases of the respiratory system accounted for 77.0% of the associated causes, followed by infectious diseases (in 31.0%), and ill-defined causes (in 24.5%). The crude mean number of causes of death per death certificate was 3.41 ± 1.16 in those 2,384 death certificates in which CF was the underlying cause of death. Transplant-related mortality was reported in only 3.3% of the cases (Table 3).

Table 1. Number of cystic fibrosis-related deaths, as well as median and interquartile range of ages at death related to cystic fibrosis according to the qualification of the cause of death, gender, Brazilian regions, and year of death. Brazil, 1999-2017.

Variable	Deaths, n	Median age, years	IQR
CF death qualification			
Underlying cause	2,384	23.5	7.5-65.5
Non-underlying cause	470	15.5	0.3-69.5
Gender			
Male	1,387	22.5	2.5-64.5
Female	1,467	24.5	5.5-69.5
Brazilian regions			
North	202	38.5	2.5-69.5
Northeast	562	19.5	2.5-58.5
Southeast	1,360	29.5	8.5-70.5
South	542	19.5	2.5-58.5
Central-west	188	10.0	0.5-54.5
Years			
1999	68	7.50	0.5-24.5
2000	88	8.50	0.5-29.5
2001	82	13.5	1.5-61.5
2002	86	7.50	0.5-18.5
2003	73	7.50	0.5-40.5
2004	92	13.5	2.0-26.5
2005	123	11.5	0.7-47.5
2006	124	19.5	4.0-55.0
2007	117	19.5	0.6-58.5
2008	109	18.5	0.8-65.5
2009	168	20.0	1.5-67.0
2010	156	35.0	8.5-70.5
2011	172	24.5	1.5-72.5
2012	173	22.5	0.8-62.5
2013	201	32.5	7.5-67.5
2014	224	31.5	12.5-71.5
2015	251	40.5	13.5-69.5
2016	258	43.0	13.5-72.5
2017	289	56.5	18.5-74.5

Source: Brazilian National Ministry of Health. Unified Health System Information Technology Department. IQR: interquartile range; and CF: cystic fibrosis.

DISCUSSION

The present study clearly demonstrates that CF-related mortality rates increased in Brazil from 1999 to 2017, and there was a significant increase in the age at death during the same period. These results are counterintuitive because the advances in CF diagnosis and treatment might result in an increase in the age at death, but not in the mortality rates. To our knowledge, this is the first study of CF-related mortality in Brazil using the multiple-cause-of-death methodology, and it suggests that the diagnosis of CF might be increasing in the country.

The finding that CF was identified as the underlying cause in most of the certificates (83.5%) stands for the severe fatality of this condition. A study of CF-related mortality in the United States between 1979 and 1991 evaluated 6,500 deaths and reported that CF was the underlying cause of death in 92.5% of the death certificates.[14] A similar finding was described in Italy, where 480 CF-related deaths were identified from 2003 to 2011, CF reported to being the underlying cause in 87.5% of the death certificates.[15] In the past, CF was associated with mortality in the early years of life, a scenario that is currently different due to intensive treatment.[1,2,16] Despite major treatment advances, CF remains associated with reduced survival, especially in developing countries.[16] Data from the Brazilian CF Patient Registry indicate that the median age of survival in the country is 43 years of life,[8] whereas the median age at death is 15.7 years (interquartile range: 10.5-22.2); however, there might be some bias in these data because they are mostly related to patients under treatment in specialized CF centers.

The present study identified a worrying upward continuous trend in adjusted mortality rates related to CF regardless of sex and age brackets from 2000 to 2017. Contrasting results of CF-related mortality

Figure 1. Medians and interquartile ranges of age at death related to cystic fibrosis according to the regions in Brazil, 1999-2007.

trends have been reported in other countries, such as Spain and Italy, as well as in the European Union. In Spain, for the 1981-2016 period, there was an overall slight decrease in the age-adjusted mortality rate.[17] In 27 countries of the European Union, a continuous downward trend in CF-related mortality rates was observed from 1996 to 2010, although there were differences by country and sex.[18] In Italy, for the 1970-2011 period, CF-related mortality rates decreased in newborns and in children, whereas they increased in adolescents and young adults until 1990, but then decreased; however, in patients older than 19 years of age, they started to increase in 1990.[15]

The increasing mortality trend shown in the present study is unlikely to be caused by a worsening of medical treatment of CF patients over time. It is probably due to a greater number of deaths being attributed to CF in more recent years. In addition, it might be related to improvements in the clinical diagnosis of CF and to the adoption of CF newborn screening (CF-NBS). Although there are data indicating that CF-NBS could decrease CF-related neonatal mortality,[16] it could also increase death reporting due to a well-established CF diagnosis. The implementation of CF-NBS started in 2000-2001 in some Brazilian states (Santa Catarina, Paraná, and Minas Gerais), but it was only started in São Paulo, the most populous Brazilian state, in 2010.[19] Data from the Brazilian Ministry of Health describe an increase in the number of newly diagnosed cases of CF—from 132 in 2014 to 167 in 2018—and an increase of nearly 50% in the number of CF cases in regular follow-up during the same period.[19] Theoretically, all Brazilian states have been performing CF-NBS since 2013, but there is evidence that there are inequalities among the regions/states.[20]

The finding that the median and the mean age at death increased significantly for the 1999-2017 period was anticipated, because of advances in CF

Table 2. Standardized mortality rates related to cystic fibrosis and joinpoint analysis according to sex and age brackets. Brazil, 2000-2017.

Sex	SMR per million population			APC (95% CI)
	2000	2017	Mean	
Male				
Age bracket, years				
0-4	1.92	2.31	2.47	1.30 (−0.9 to 3.6)
5-24	0.40	0.87	0.55	6.23* (3.6-8.9)
25-64	0.10	0.80	0.39	9.42* (6.2-12.7)
65 and +	2.16	5.93	3.35	9.20* (6.2-12.3)
Overall	0.54	1.37	0.86	6.84* (5.3-8.4)
Female				
Age bracket, years				
0-4	2.12	2.14	2.33	3.91* (1.3-6.6)
5-24	0.41	1.02	0.62	5.87* (3.4-8.4)
25-64	0.17	0.63	0.36	8.56* (6.0-11.2)
65 and +	0.73	6.52	2.90	10.94* (7.4-14.6)
Overall	0.48	1.38	0.83	7.50* (6.6-8.4)

Source: Brazilian National Ministry of Health, Unified Health System Information Technology Department. SMR: standardized mortality rate; and APC: annual percent change. *APC is significantly different from zero at alpha = 0.05.

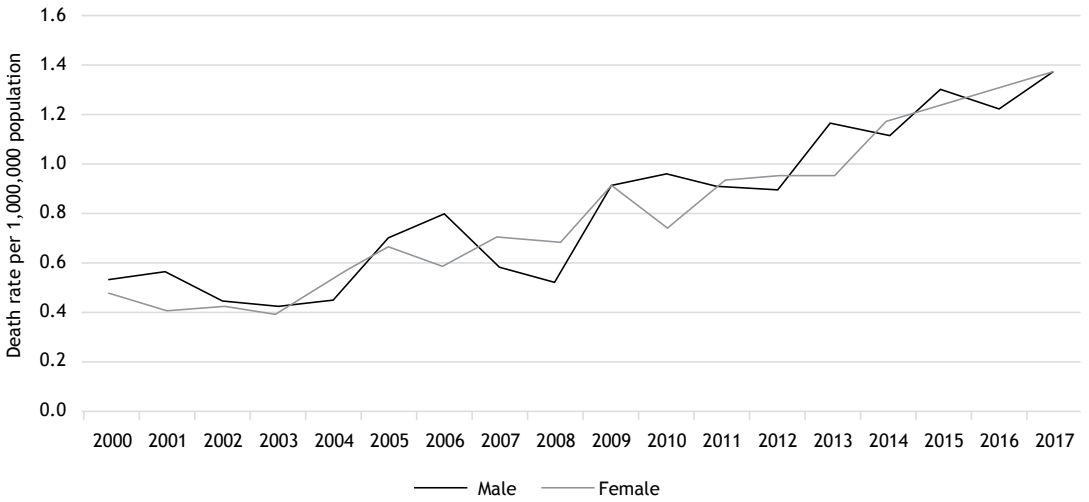

Figure 2. Age-standardized death rates related to cystic fibrosis according to sex. Brazil, 2000-2017.

treatment[1,16]; however, this is a paradoxical finding in the context of the upward trend in CF-related mortality rates, which cannot be attributed to the introduction of CFTR modulator therapies, because such medications are yet to be available for the majority of patients with CF in Brazil. Although the expansion of CF-NBS have significantly contributed to earlier CF diagnosis in Brazil,[8] our findings regarding the age at death are unlikely to be related to CF-NBS due to its recent implementation in most Brazilian states. Conversely, there is a clear contribution of CF-NBS to the number of newly diagnosed cases of CF.[8] The disturbing finding that 25% of the deaths were reported in the 0- to 4-year age bracket, conversely, might be related to earlier diagnosis by CF-NBS. One finding in the present study might alternatively indicate a distinct scenario for the increase in the number of CF-related death reports in older age brackets (> 25 years of age): the age at death was high in the northern region, but the number of CF patients was small,[8] probably due to the lack of consistent access to reliable CF diagnostic testing, leading to misreporting or misdiagnosis of the disease in some of the cases here reported.

The use of the multiple-cause-of-death methodology allowed the recovery of data of all associated causes of death, reported as comorbid conditions in the death certificates in which CF was the underlying cause. As expected, most of such associated conditions were respiratory diseases (77%), followed by infectious diseases (31%). Previous studies in the USA[14] and in Italy[15] selected only a subset of associated causes, chosen according to their prevalence and clinical relevance regarding CF. Some differences could be noticed between our results and theirs: the contribution of pneumonia (39.7%) in Brazil was greater than that verified in the USA (18.3%) and in Italy (19.8%);

Table 3. Associated (non-underlying) causes in death certificates (N = 2,384) in which cystic fibrosis was identified as the underlying cause. Brazil, 1999-2017.[a]

Associated causes of death (ICD-10 chapters and rubrics)	n	%
Certain infectious and parasitic diseases (A00-B99)	788	31.1
Intestinal infectious diseases (A00-A09)	22	0.9
Tuberculosis (A15-A19)	14	0.6
Septicemias (A40-A41)	749	31.4
Neoplasms (C00-D48)	23	1.0
Diseases of the blood and blood-forming organs and certain disorders involving (D50-D89)	63	2.6
Anemias (D50-D64)	26	1.1
Other diseases of the blood and blood-forming organs (D65-D89)	39	1.6
Endocrine, nutritional, and metabolic diseases (E00-E90)	359	15.1
Diabetes mellitus (E10-E14)	107	4.5
Malnutrition (E40-E46)	168	7.0
Mental and behavioral disorders (F01-F99)	24	1.0
Diseases of the nervous system (G00-G99)	34	1.4
Diseases of the circulatory system (I00-I99)	362	15.2
Hypertensive diseases (I10-I13)	74	3.1
Ischemic heart disease (I20-I25)	30	1.3
Pulmonary heart disease and diseases of pulmonary circulation (I26-I28)	93	3.9
Cardiomyopathy (I42)	9	0.4
Cardiac arrest (I46)	44	1.9
Cardiac arrhythmias (I47-I49)	26	1.1
Heart failure (I50)	83	3.5
Complications and ill-defined descriptions of heart disease (I51)	9	0.4
Diseases of the respiratory system (J00-J99)	1,836	77.0
Pneumonia (J12-J18)	947	39.7
Bronchitis (J40-J42)	3	0.1
Emphysema (J43)	20	0.8
Other chronic obstructive pulmonary disease (J44)	122	5.1
Asthma (J45-J46)	7	0.3
Bronchiectasis (J47)	59	2.5
Other respiratory diseases principally affecting the interstitium (J80-J84)	70	2.9
Respiratory failure, not elsewhere classified (NEC) (J96)	1,093	45.9
Other respiratory disorders (J98)	179	7.5
Diseases of the digestive system (K00-K93)	129	5.4
Paralytic ileus and intestinal obstruction without hernia (K56)	23	1.0
Diseases of liver (K70-K77)	49	2.1
Other disease of pancreas (K86)	21	0.9
Diseases of the skin and subcutaneous tissue (L00-L99)	3	0.1
Diseases of the musculoskeletal system and connective tissue (M00-M99)	20	0.8
Diseases of the genitourinary system (N00-N99)	150	6.3
Renal failure (N17-N19)	133	5.6
Pregnancy, childbirth, and the puerperium (O00-O99)	2	0.1
Certain conditions originating in the perinatal period (P00-P96)	84	3.5
Disorders related to short gestation and low birth weight NEC (P07)	28	1.2
Respiratory and cardiovascular disorders of perinatal period (P20-P29)	30	1.3
Bacterial sepsis of newborn (P36)	33	1.4
Other intestinal obstruction of newborn (P76)	11	0.5
Congenital malformations, deformations, and chromosomal abnormalities (Q00-Q99)	32	1.3
Symptoms, signs, and abnormal clinical and laboratory findings, NEC (R00-R99)	585	24.5
Hemorrhage from respiratory passages (R04)	33	1.4
Other symptoms and signs involving the circulatory and respiratory systems (R09)	215	9.0
Shock, not elsewhere classified (R57)	88	3.7
Cachexia (R64)	15	0.6
Failure of multiple organs (R688)	214	9.0
Injury, poisoning, and certain other consequences of external causes (S00-T98)	50	2.1
Foreign body in respiratory tract (T17)	16	0.7
Complications of procedures NEC (T81)	20	0.8
External causes of morbidity and mortality (V01-Y98)	92	3.9
Surgical operation with transplant of whole organ and other (Y83-Y84)	79	3.3
Factors influencing health status and contact with health services (Z00-Z99)	2	0.1

Source: Brazilian National Ministry of Health, Unified Health System Information Technology Department. ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision. [a]Duplication/multiplication of causes removed from ICD-10 chapters.

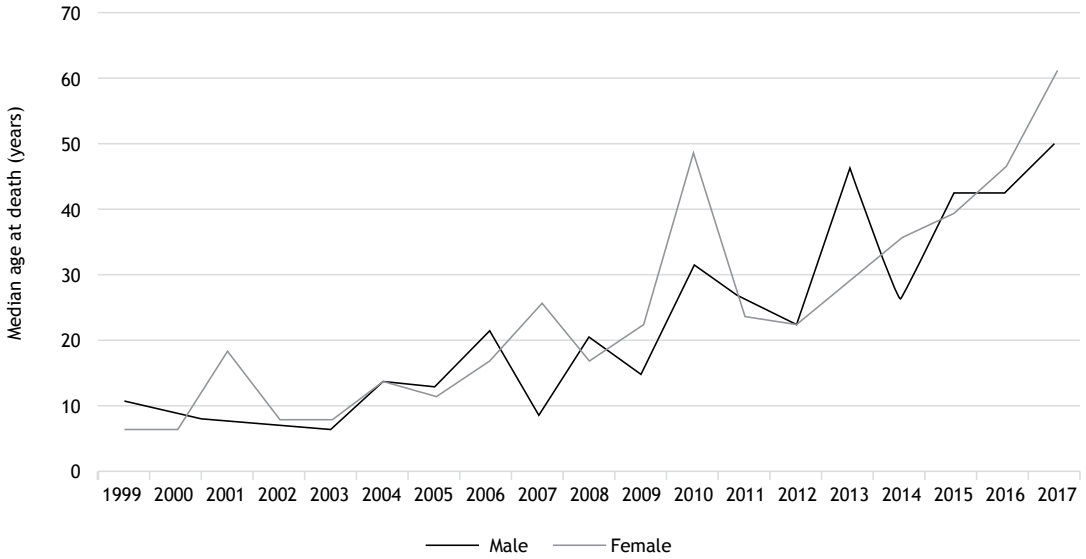

Figure 3. Trends in median age at death related to cystic fibrosis according to sex. Brazil, 1999-2017.

the same occurred in regard to the proportions of septicemia (31.4%) and malnutrition/cachexia (7.6%) in Brazil when compared with those in Italy (16.9% and 2.5%, respectively).[15,16] However, diabetes and renal failure were significant higher in Italy (16.5% and 12.9% respectively)[15] than they were in our study (4.5% and 5.6%, respectively).

Epidemiological knowledge of CF in Brazil has changed in the last decade due to the Brazilian CF Patient Registry. Comprising more than 5,000 CF patients from over 50 CF referral centers in 22 Brazilian states, the Registry displays, among other data, annual CF-related mortality: from 2009 to 2017, only 297 deaths were entered into the Registry, whereas we compiled 1,897 CF-related deaths for the same period. This difference can be explained by the difficulties of access of CF patients to specialized CF centers (where patients are entered into the Registry) and by inaccurate completion of the causes of death in death certificates. Both situations are likely to occur, because the estimated prevalence of CF indicates a much greater number of patients in Brazil.[3] Elbert et al.[21] compared CF-related mortality data obtained from the American CFF Registry and the Multiple Cause of Death File (based on death certificates for US residents) for the 2012-2014 period. A very good overlap was found between the two systems in the 1- to 60-year age bracket (87% of the records). For those older than 75 years of age, there were fewer than 5 CF-related deaths in the CFF Registry, whereas there were 42 in the Multiple Cause Of Death File. A similar picture was observed in those under 12 months of age.[21] We believe that some of the inconsistencies in our data could have the same explanation as that proposed by Elbert et al.[21]: among younger patients, difficulties to access to specialized CF centers or very premature death; among older patients, inaccuracies of death cause entries in death certificates.

The advantages and limitations of mortality studies using methodologies based on registries or death certificates have been discussed by Quintana-Gallego et al.,[18] who underscored that a coverage of nearly 100% of the population might be reached by means of death certificates. Population mortality statistics suffer from quantity and quality problems. For 2017, the Brazilian National Ministry of Health estimated a coverage of 96.3% in the whole country, ranging from 92.7% in the northern region to 100.0% in the southern region.[22] Regarding quality, a recent surveillance study on statistics using the multiple-cause-of-death methodology in Brazil revealed that the crude mean number of causes per death certificate increased from 2.81 to 3.02 (an increase of 7.5%) for the 2003-2015 period; the proportion of death certificates with only one cause of death decreased from 20.32% to 13.75%; and the proportion of death certificates with ill-defined causes of death as the underlying cause decreased from 12.95% to 5.59% (a decrease of 56.22%).[23] However, there are specific problems linked with CF. Although automatic processing of mortality data is used in Brazil, the inclusion of the causes of death is still a task performed by trained nosologists, who might make a mistake and introduce a wrong ICD-10 code. One of these risks happens with pulmonary fibrosis (ICD-10 four-character subcategory J84.1), which could be confounded with CF, or vice versa.[10] This is more likely to occur with older patients, because CF is usually expected to reduce life expectancy. In addition, because CF is a relatively rare cause of death, decision tables for automatic processing might not include the ICD-related mortality rules and dispositions involving all conditions and their natural history. Finally, it is of utmost importance that physicians correctly state all causes of death in the death certificates.

In conclusion, the present study depicted a significant and continuous increase in CF-related death rates in

Brazil in the last years, with a concurrent increase in the median age at death. We believe that these findings result from an increase in CF diagnosis in the country, and we hope that this upward trend in CF-related mortality rates will subside in the next few years, indicating that patients are receiving better health care.

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ORIGINAL ARTICLE

Implementation of Tele-ICU during the COVID-19 pandemic

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ABSTRACT

Objective: To describe the implementation of a Tele-ICU program during the COVID-19 pandemic, as well as to describe and analyze the results of the first four months of operation of the program. **Methods:** This was a descriptive observational study of the implementation of a Tele-ICU program, followed by a retrospective analysis of clinical data of patients with COVID-19 admitted to ICUs between April and July of 2020. **Results:** The Tele-ICU program was implemented over a four-week period and proved to be feasible during the pandemic. Participants were trained remotely, and the program had an evidence-based design, the objective being to standardize care for patients with COVID-19. More than 100,000 views were recorded on the free online platforms and the mobile application. During the study period, the cases of 326 patients with COVID-19 were evaluated through the program. The median age was 60 years (IQR, 49-68 years). There was a predominance of males (56%). There was also a high prevalence of hypertension (49.1%) and diabetes mellitus (38.4%). At ICU admission, 83.7% of patients were on invasive mechanical ventilation, with a median PaO_2/FiO_2 ratio < 150. It was possible to use lung-protective ventilation in 75% of the patients. Overall, in-hospital mortality was 68%, and ICU mortality was 65%. **Conclusions:** Our Tele-ICU program provided multidisciplinary training to health care professionals and clinical follow-up for hundreds of critically ill patients. This public health care network initiative was unprecedented and proved to be feasible during the COVID-19 pandemic, encouraging the creation of similar projects that combine evidence-based practices, training, and Tele-ICU.

Keywords: Telemedicine; Critical care; Coronavirus infections; Patient care management.

INTRODUCTION

Prior to the current pandemic, the aging of the population and the steady increase in respiratory diseases had already alerted us to the need to mobilize technological resources and meet a growing demand for medical professionals trained in intensive care.[1] COVID-19, caused by the new coronavirus (SARS-CoV-2), was first identified in late 2019,[2,3] and there have since been millions of cases worldwide[4] and thousands of deaths in Brazil, which ranks third among the countries most affected by the pandemic.[5] Respiratory failure results in 10-25% of hospitalized patients requiring invasive mechanical ventilation (IMV).[6] The overall rate of IMV use in ICUs in Brazil has increased, from 22% before the pandemic to 48% at present.[7] The challenge of providing patient care during the pandemic has led to a discussion about the allocation of material and human resources.[6]

Through the application of telecommunications technology to health, telemedicine provides remote care. The use of telemedicine is strategic because it enables the exchange of knowledge between teams, as well as the training and education of multidisciplinary teams. Telemedicine also allows the auditing and monitoring of the processes involved in patient care.[8] The application of telemedicine to the care of critically ill patients shortens ICU stays, thereby increasing the availability of beds, and reduces overall in-hospital mortality.[9-12] During the pandemic, telemedicine was put forward as an option for the entire chain of care, from triage[13] to the dissemination of information—to health care teams providing patient care and to the general population.[14] In the state of New York, the epicenter of the pandemic in the United States, an existing telemedicine service was expanded, allowing telemetry of adverse events and facilitating bed management, as well as informing decisions regarding the management of material and human resources.[15] Even specialties not directly related to COVID-19, such as orthopedics, have implemented telemedicine to allow patient treatment during the pandemic.[8] In Brazil, telemedicine was approved by the Brazilian National Ministry of Health in Article 3 of Law no. 13,979, which was enacted on February 6, 2020, on an extraordinary and temporary basis during the pandemic period.

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Severe cases of COVID-19 progress to ARDS, the treatment of which is based on the adoption of lung-protective ventilation (LPV) strategies.[16,17] Nevertheless, the use of LPV strategies by health care professionals is still limited,[18] possibly because of their lack of knowledge about these strategies, inappropriate training, or lack of confidence in their ability to manage mechanical ventilators.[19-21]

The Respiratory ICU of the *Instituto do Coração* (InCor, Heart Institute) of the *Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo* (HCFMUSP, University of São Paulo School of Medicine *Hospital das Clínicas*) serves as a referral center for the treatment of severe respiratory cases and mechanical ventilation to public health care facilities in the state of São Paulo. The ICU team, in partnership with the *Secretaria de Estado da Saúde de São Paulo* (SES-SP, São Paulo State Department of Health), developed a treatment and training protocol for public ICUs in the state of São Paulo for use during the pandemic. The protocol focuses on interventions that are feasible via telemedicine: care of patients with suspected or confirmed COVID-19 respiratory failure; and training of multidisciplinary ICU teams during the pandemic.

The primary objective of the present article was to describe the implementation of a Tele-ICU program during the COVID-19 pandemic. The secondary objective was to describe and analyze the results of the first four months of operation of this new Tele-ICU program.

METHODS

Study description

This study describes the implementation of a Tele-ICU program, followed by a retrospective analysis of the clinical data of patients with COVID-19 admitted to the participating ICUs between April and July of 2020. The study was approved by the HCFMUSP Research Ethics Committee (Protocol no. 4.222.334). The Tele-ICU program was developed with the support and participation of the SES-SP.

Description of the treatment protocol

Specialists (in pulmonology, infectious diseases, clinical emergencies, and anesthesiology) at the HCFMUSP gathered and, after a review of the literature and consensus meetings, developed a treatment protocol for patients with COVID-19 ARDS and respiratory failure. The protocol was validated by the São Paulo State Coronavirus Contingency Center and was adopted by the SES-SP as the standard of care for the entire public health care network in the state.

The treatment protocol (see supplementary material) emphasizes the best practices in intensive care with an emphasis on LPV, suggesting a V_T of 6 mL/kg of ideal body weight, monitoring of plateau pressure, monitoring of driving pressure, and use of rescue maneuvers for patients with refractory hypoxemia. The protocol also recommends appropriate hand hygiene and use of personal protective equipment; proper selection of laboratory and imaging tests; use of fluids, antibiotics, and corticosteroids; prophylaxis of thromboembolic events; and weaning from IMV.

Implementation of the Tele-ICU program

The SES-SP elected the InCor-HCFMUSP Respiratory ICU (Agreement no. 20/2018) as the coordinating center of this Tele-ICU program for public hospitals in the state of São Paulo (SES TeleUTI Agreement no. 1140/2020).

The selection of hospitals to be invited to adopt the Tele-ICU program was made by the SES-SP, under the guidance of the São Paulo State Coronavirus Contingency Center, and was based on the incidence of patients with COVID-19 in their catchment area, those at which the incidence was highest being selected. The Tele-ICU program was implemented in two phases. Phase I included 9 hospitals, and phase II included an additional 11 hospitals. The participating hospitals are described in greater detail in Table S1 (supplementary material).

The InCor Information Technology Department developed its own platform, designated "iConf", which uses the main web conferencing resources of a commercial system, although under an open-source license (see supplementary material). On the iConf platform, all Tele-ICU data are stored on a server at InCor and are not shared with or handled by third parties, in compliance with the General Personal Data Protection Law (Law no. 13,853, which was enacted in 2019).

At InCor, the Tele-ICU program has a physical space consisting of rooms with two telemedicine stations each; in addition, there is a multidisciplinary room for data analysis and program planning, as well as a room for technical administrative support. At Incor and in the ICUs that participated in the Tele-ICU program, the telemedicine stations were set up with dual high-resolution monitors, a camera, an echo-canceling microphone, and an audio playback device. During the web conferencing sessions between health care professionals, the interaction between the teams was displayed on one of the monitors, whereas test results, materials of educational interest, and even a whiteboard for free writing were displayed on the other monitor (Figure S2, supplementary material).

In the last week of March, the final model of care was tested, and the Tele-ICU program began to operate fully on April 1, 2020. Teleconsultations occurred daily at predetermined times. Each telemedicine session between ICUs was planned to last about one hour, approximately 10 min being allocated to discuss each patient. In those discussions, a specialist physician at InCor helped collect clinical data for the purpose of diagnosis, discussed the findings, and recommended treatment in accordance with the protocol. Data

were then collected on a form that was structured and designed specifically for this Tele-ICU program, in accordance with the guidelines established by the REDCap Consortium.[22] The form, which was shared by the two ICU teams, ensured confidentiality. The selection of patients for discussion was the prerogative of the ICU team at the hospital where the patient was being treated.

Training of health care professionals and dissemination of the treatment protocol

The ICU teams selected to receive the Tele-ICU program were provided training by an InCor multidisciplinary team specializing in intensive care. Given the impossibility of face-to-face practical training during the pandemic, strategies were sought for diversifying the dissemination of knowledge, including distance training courses through video classes, tutorials, use of official portals, and adaptation of the protocol to mobile applications.

For the purpose of its wider dissemination, the treatment protocol for patients with COVID-19 was made available via free online platforms on the websites of the HCFMUSP *Escola de Educação Permanente* (EEP, School of Continuing Education; https://incor.eephcfmusp.org.br/course/index.php?categoryid=2) and of the SES-SP (http://eadses.saude.sp.gov.br/). Case discussion sessions were permeated with theoretical concepts, clarification was encouraged, and additional activities could be scheduled by video conference. The total duration of use of the distance education material on the platform was 25 h.

As support material for the training sessions and to facilitate patient care, a mobile application was made available for free.[23] The application included ideal body weight calculators for LPV, tutorials on oxygen therapy supplementation and forms of noninvasive mechanical ventilation, tutorials on orotracheal intubation, and a dose calculator for medications for rapid-sequence orotracheal intubation, as well as for dilutions of sedatives, analgesics, neuromuscular blocking agents, and vasoactive drugs.

Continuous assessment of the Tele-ICU program

The monitoring of the implementation of the Tele-ICU program aimed to improve health care professional performance in providing care. Performance and training indicators were chosen: number of discussions per teleconsultation; number of patients followed; number of canceled teleconsultations; mean number of patient discussions per visit; and number of clinical data forms completed. The analysis was sent to the hospital managers and to the SES-SP. If the result was below the target value, an action plan was agreed upon with the hospital manager and was reassessed in the following weeks. The initial goal was for 70% of teleconsultations to occur on the scheduled day, with a suggested daily average of three cases per teleconsultation. Another goal was to have < 20% of records with missing data that would preclude evaluation. Hospitals were contacted on a weekly basis to adjust these goals.

Data collection

The following patient clinical data were collected: age; gender; height; actual body weight; BMI; comorbidities[24]; pre-ICU admission functional status assessed on the basis of the ability to perform basic activities of daily living[25]; admission severity assessed by the Simplified Acute Physiology Score 3 (SAPS 3)[26]; and the use of intensive care therapies, such as vasoactive drugs, IMV, and hemodialysis. In addition, data were collected on length of ICU stay, LPV settings, duration of LPV, length of hospital stay, ICU mortality, and overall in-hospital mortality.

Data on training tools were collected up to July 31, 2020, as were data on the number of views on the EEP-HCFMUSP platform, number of health care professionals registered on the SES-SP platform, and number of users who downloaded the mobile application. Discharge from the ICU and hospital discharge were monitored up to August 28, 2020 for all patients admitted up to July 31 of that year.

Statistical analysis

The Shapiro-Wilk test was used in order to assess the distribution of continuous variables. Because those variables had a nonparametric distribution, they were expressed as median and IQR. Categorical variables were expressed as absolute and relative frequency.

This study followed the 2016 Standards for Quality Improvement Reporting Excellence, the goal of which is to improve the quality of studies.[27] All analyses were performed using the R software (R Core Team, 2017).

RESULTS

Structuring of the Tele-ICU network for the care of patients with COVID-19 began in April of 2020. The cost for installing the equipment was approximately R$10,000 (approximately US$1,850 as per the exchange rate in November of 2020) per participating hospital. The monthly cost of operating the service, including teleconsultations and multidisciplinary training, was R$20,000 per participating hospital (approximately US$3,700).

Between April and July of 2020, a total of 105,486 views were recorded on the EEP-HCFMUSP free online platform, and 3,484 distance learning course registrations were made on the SES-SP platform. The mobile application was installed by more than 3,000 users up to July of that year.

During the study period, the cases of 454 patients were discussed. Among those patients, the COVID-19 diagnosis was confirmed by RT-PCR in 326 (74%) and was excluded in 113. For the remaining 15 patients, there was insufficient information for analysis. The patient inclusion flow chart is presented in Figure 1.

Table 1 shows the demographic, clinical, and biochemical data at ICU admission and on the first day of Tele-ICU discussion, for the 326 COVID-19 patients treated during the study period. Table 1 also shows data on IMV, rescue maneuvers for hypoxemia, and tracheostomy. Of those 326 patients, 273 (83.7%) required IMV. With regard to IMV settings on the first day of Tele-ICU discussion, we found that the median V_T per kg of predicted ideal body weight was 6.1 mL/kg (5.6-6.9 mL/kg), the median plateau pressure was 25 cmH_2O (21-28 cmH_2O), and the median driving pressure was 13 cmH_2O (11-15 cmH_2O).

During the study period, ICU mortality was 65% and overall in-hospital mortality was 68%. ICU mortality decreased from 73.2% in April to 58.7% in July, and overall in-hospital mortality decreased from 73.2% in April to 64.8% in July. Considering only the patients who underwent IMV, we found that ICU mortality and overall in-hospital mortality were 76% and 78%, respectively. ICU mortality decreased from 88% in April to 67% in July, whereas overall in-hospital mortality decreased from 88% in April to 71% in July. The median SAPS 3 was 55 (49-67) in April, 54 (46-65) in May, 53 (47-61) in June, and 53 (45-62) in July.

Figure 2 shows the rates of ICU mortality and overall in-hospital mortality over the months evaluated. Figure 3 shows the length of ICU stays and overall hospital stays during the same period.

DISCUSSION

In March of 2020, a Tele-ICU program was implemented at InCor-HCFMUSP to meet the high demand for specialized resources for treating patients with COVID-19. The provision of training facilitated standardization of care for patients with COVID-19, as did the rapid dissemination of the treatment and LPV protocols to health care professionals. Over the study period, severity at admission, as assessed by the SAPS 3, remained similar, whereas ICU mortality and overall in-hospital mortality decreased, suggesting that, in addition to factors such as increases in scientific information and in clinical experience in the management of COVID-19 during that period, factors related to the provision of training and to Tele-ICU support may have contributed to those decreases. Between April and July, length of ICU stay decreased by 1 day and length of hospital stay decreased by 5 days.

The Tele-ICU program found solutions to diversify the method of dissemination of the treatment protocol through video classes, discussion forums on the distance learning platform, classes offered during teleconsultations, and use of the mobile application. These measures may have improved health care professional adherence to the LPV strategy and the observed result, as was suggested in a study showing improved clinical outcomes, increased adoption of good practices, and even cost reduction after educational activities through Tele-ICU.[28]

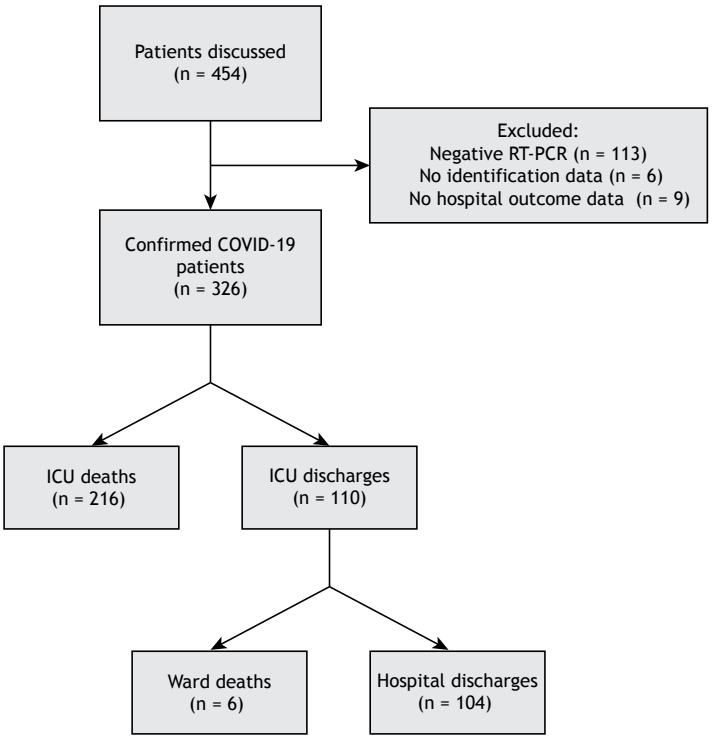

Figure 1. Flow chart of evaluation via the Tele-ICU program during the study period.

Table 1. Demographic, clinical, laboratory, and treatment characteristics, as well as data on the use of mechanical ventilation, at ICU admission and on the first day of Tele-ICU discussion, for the COVID-19 patients treated during the study period.[a]

Variable	N = 326
Age, years	60 [49-68]
Male gender	182 (56.0)
BMI, kg/m^2	27.7 [24.7-32.6]
Able to perform basic activities of daily living without assistance	265 (97.4)
SAPS 3	53 [47-64]
Comorbidities	
Hypertension	160 (49.1)
Diabetes	125 (38.4)
Obesity (BMI > 30 kg/m^2)	90 (27.6)
COPD	22 (6.7)
Heart disease	21 (6.4)
Dyslipidemia	11 (3.4)
Chronic kidney disease	12 (3.6)
None	32 (9.8)
Laboratory test results on the first day of Tele-ICU discussion	
Creatinine, mg/dL	1.1 [0.8-2.8]
pH	7.34 [7.26-7.42]
PO_2, mmHg	84 [69-115]
PCO_2, mmHg	48 [42-58]
Bicarbonate, mmol/L	26 [23-30]
Base excess, mmol/L	0.5 [−3.8 to 4.2]
IMV settings on the first day of Tele-ICU discussion	
Compliance, mL/cmH_2O	30 [25-37]
V_T, mL/kg of predicted ideal body weight	6.1 [5.6-6.9]
Plateau pressure, cmH_2O	25 [21-28]
Driving pressure, cmH_2O	13 [11-15]
PEEP, cmH_2O	12 [10-14]
FiO_2, %	60 [40-80]
PaO_2/FiO_2	148 [104-223]
Organ support therapies during the ICU stay	
Use of IMV	273 (83.7)
Duration of IMV, days	13 [8-20]
Hemodialysis	72 (22.1)
Vasopressors	170 (52.1)
Corticosteroids	211 (64.7)
Rescue maneuvers for respiratory failure	
Prone positioning	82 (30.0)
PEEP titration	120 (44.0)
Alveolar recruitment	19 (7.0)
Use of neuromuscular blockade	101 (37.0)
Tracheostomy	29 (10.6)

SAPS 3: Simplified Acute Physiology Score 3; and IMV: invasive mechanical ventilation. [a]Values expressed as median [IQR] or n (%).

In terms of demographic data, our results are comparable to those of cohort studies of critically ill patients with COVID-19.[29-32] Similar to what has been reported in other studies,[33,34] life support therapies, such as vasoactive drug therapy and renal replacement therapy, both of which are associated with increased overall in-hospital mortality, were widely used in our group of patients. Because the patients treated through our Tele-ICU program should preferably be on IMV, we found a higher rate of IMV use than that reported for ICUs at other public hospitals in Brazil (83.7% vs. 64.3%).[7] The median PaO_2/FiO_2 ratio for the patients treated through the program was low in general and was lower than that reported in a multicenter study conducted in Italy.[31]

The median PaO_2/FiO_2 ratio in our sample was consistent with moderate to severe ARDS.[35] The mortality rate of ARDS in Brazil ranges from 53%

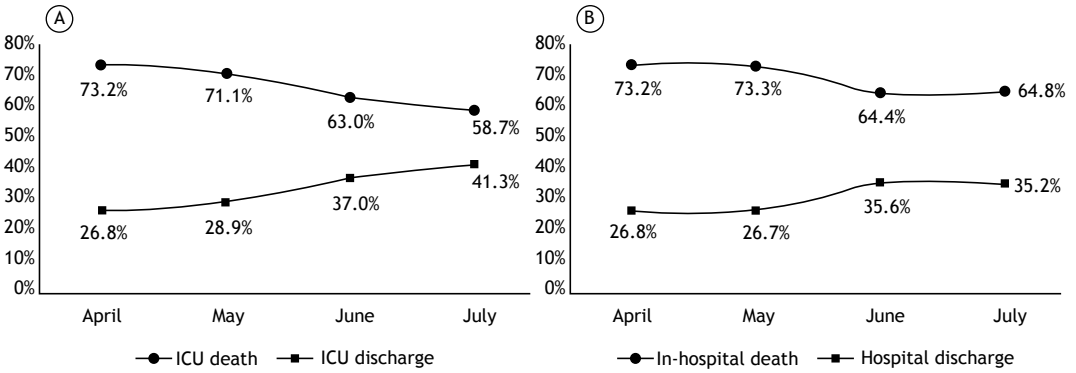

Figure 2. ICU mortality (in A) and overall in-hospital mortality (in B) during the study period.

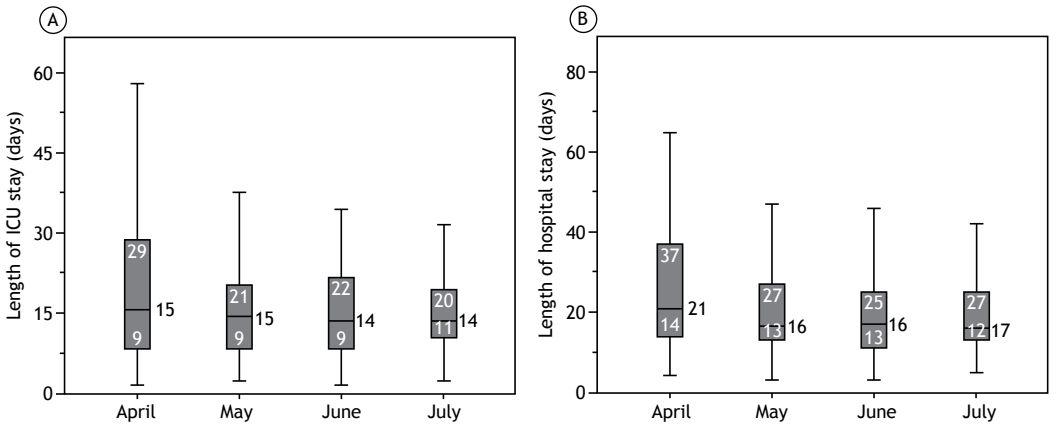

Figure 3. Length of ICU stay (in A) and length of hospital stay (in B) during the study period.

to 60%,[7] and a randomized clinical trial of patients with COVID-19 ARDS reported a 28-day mortality of up to 61.5%,[36] similar to that observed in the present study.

It is known that LPV reduces mortality, increases the number of IMV-free days,[17,37] and increases long-term survival.[38] Despite those benefits, it has been demonstrated that up to two thirds of patients do not receive LPV.[18] A study involving 45 ICUs in Brazil reported a 30% rate of ARDS and a higher median V_T than that delivered to the patients treated through our Tele-ICU program.[19] Adherence to the LPV protocol[39] was emphasized on a daily basis, and we succeeded in having 75% of the patients in our sample receive protective V_T (< 7 mL/kg of ideal body weight), protective plateau pressure, and protective driving pressure.[37,40] These protective settings were maintained during the first 3 days of monitoring (Table S2).

According to the database of the Brazilian ICU network, overall in-hospital mortality among COVID-19 patients on IMV in public ICUs was 69.3% up to November of 2020.[7] The sample of COVID-19 patients on IMV whose cases were discussed through our Tele-ICU program suffered from a selection bias on the part of the ICU team at the hospital of origin, who prioritized cases on the basis of severity and complexity. We found that overall in-hospital mortality was highest in the first two months of operation of the program, decreased in the third month, and remained stable in the fourth month.

One limitation of the present study is that not all cases of patients with COVID-19 admitted to ICUs were discussed through our Tele-ICU program; that is, we treated a subset of more severe cases selected by the physician at the hospital of origin. The exchange of information during teleconsultations was not always ideal, because patient medical records were sometimes unavailable and the data on the REDCap form could be incomplete. In addition, daily case discussions were sometimes ended because of complications at the hospital of origin or the overwhelming workload of health care professionals.

To our knowledge, this is the first Tele-ICU program to combine the provision of training/education with the provision of care in a statewide public health care network during the COVID-19 pandemic in Brazil. The effectiveness of the implementation of our Tele-ICU program is evidenced by the finding that the LPV protocol was actually used for cases of severe respiratory failure. With these data, we hope to encourage the creation of similar projects

that combine evidence-based practices, protocols, training, and teleconsultations.

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AUTHOR CONTRIBUTIONS

BRM, MVFG, MLG, MLAS, TFA, PGS, PC, and CRRC: conception and planning of the study, as well as interpretation of evidence; BRM, MVFG, MLG, MV, MLAS, TFA, MAG, APB, PGS, PC, and CRRC: drafting/revision of preliminary and final versions; and BRM, MVFG, MLG, MV, MLAS, TFA, MAG, APB, PGS, PC, and CRRC: approval of the final version.

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ORIGINAL ARTICLE

MRI-based differentiation between lymphoma and sarcoidosis in mediastinal lymph nodes

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ABSTRACT

Objective: Evaluation of enlarged mediastinal lymph nodes is crucial for patient management. Malignant lymphoma and sarcoidosis are often difficult to differentiate. Our objective was to determine the diagnostic accuracy of MRI for differentiating between sarcoidosis and malignant lymphoma. **Methods:** This was a retrospective study involving 47 patients who underwent chest MRI and were diagnosed with one of the diseases between 2017 and 2019. T1, T2, and diffusion-weighted signal intensity were measured. Apparent diffusion coefficients (ADCs) and T2 ratios were calculated. The diagnostic performance of MRI was determined by ROC analysis. **Results:** Mean T2 ratio was significantly lower in the sarcoidosis group than in the lymphoma group (p = 0.009). The T2-ratio cutoff value that best differentiated between lymphoma-related and sarcoidosis-related enlarged lymph nodes was 7.1, with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 58.3%, 95.6%, 76.5%, 93.3%, and 68.7%, respectively. The mean ADC was significantly lower in the lymphoma group than in the sarcoidosis group (p = 0.002). The ADC cutoff value that best differentiated between lymphoma-related and sarcoidosis-related enlarged lymph nodes was 1.205, with a sensitivity, specificity, positive predictive value, negative predictive value and accuracy of 87.5%, 82.6%, 85.1%, 84.0% and 86.3%, respectively. No significant differences were found between the two groups regarding T1 signal intensity, T2 signal intensity, and lymph node diameter. **Conclusions:** MRI parameters such as ADC, diffusion, and T2 ratio can be useful in the differentiation between sarcoidosis and lymphoma in the evaluation of enlarged lymph nodes.

Keywords: Diffusion magnetic resonance imaging; Lymphoma; Lymph nodes; Sarcoidosis.

INTRODUCTION

The evaluation of mediastinal lymph nodes is clinically essential for effective disease management and accurate prognosis.[1] Various infectious, inflammatory, and malignant conditions can cause mediastinal lymph node enlargement. Sarcoidosis is a benign systemic disorder of unknown etiology that frequently underlies thoracic diseases, chest abnormalities being seen in 85-95% of the patients who undergo chest X-ray.[2] In contrast, lymphoma is a malignant tumor of the lymphatic system that arises in lymphocytes. Interestingly, not only do these two conditions affect the lymph nodes, but the age at onset of both also overlaps. As such, the adenopathy caused by lymphoma can be confused with sarcoidosis upon initial detection even after imaging.[3]

When mediastinal lymph node enlargement occurs, histopathological analysis is the recommended means of obtaining a definitive diagnosis, providing a prognosis and determining which treatment course is best suited to manage the disease. However, interventional access to the mediastinum entails inherent risks for patients and sampling error. It also places a psychological burden on the patient during the period between the detection of the adenopathy by imaging methods and sampling results. Imaging techniques are very efficient in locating and evaluating enlarged mediastinal nodes.[4-6]

A readily available, primary technique for evaluating thoracic diseases is CT imaging. Despite being a well-established technique for pulmonary evaluation when used to assess lymph nodes, CT relies on morphological characteristics such as location, size, and distribution of lymph nodes. Cases of sarcoidosis with atypical findings and uncertain diagnosis can mimic other pathologies; the appearance of lymph nodes on CT scans can even resemble malignant disease.[7,8] Thus, the use of CT imaging is limited when it comes to distinguishing between

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malignant and benign enlarged lymph nodes.[7,9-12] PET-CT, a metabolic imaging technique, has promising yet controversial diagnostic potential for differentiation between granulomatous and malignant disease.[13,14] Although PET-CT is helpful for detecting malignant disease, it is more expensive, less accessible, and lacks specificity when compared with traditional CT.[15,16] In this scenario, MRI is a radiation-free, highly reproducible technique that is well-suited for lymph node assessment.[17] The lack of ionizing radiation makes it particularly appealing for evaluating young adults with symptoms that merely resemble malignancy. MRI sequences, such as diffusion-weighted imaging (DWI), can also provide quantitative metrics that facilitate effective lymph node characterization.[18-24]

The purpose of the present study was to determine the diagnostic accuracy of MRI for differentiating between sarcoidosis and lymphoma by quantitative evaluation of mediastinal lymph nodes in patients with either condition.

METHODS

Our institutional review board approved this study. Patient consent was waived due to the retrospective nature of the study. The authors have no conflicts of interest to declare.

Study population

This retrospective study included 47 consecutive adult patients from our institution who underwent chest MRI and were histopathologically diagnosed with either sarcoidosis or lymphoma over the course of two years (between January of 2017 and January of 2019). The diagnosis of sarcoidosis was based on the three major criteria recommended by the American Thoracic Society[25]: compatible clinical presentation, exclusion of alternative causes of granulomatous nodules, and histopathological evidence of non-necrotizing granulomatous inflammation. Patients whose MRI assessment was performed after treatment initiation were excluded from the analysis. Patients with recent thoracic interventions, radiation therapy initiated prior to MRI acquisition, or an active concomitant infectious disease were also excluded. Clinical data were obtained from the electronic medical records of the patients (Tasy EMR, Philips Clinical Informatics, Blumenau, Brazil).

MRI protocol

MRI was performed using a 1.5-T scanner (Magnetom AERA; Siemens Healthineers, Erlangen, Germany). A dedicated 8-element integrated matrix coil system covering the entire thorax was used for signal reception. A half-Fourier acquisition single-shot turbo spin-echo sequence was used. The following sequence parameters were used: repetition time (TR)/echo time (TE)/flip angle, infinite/92 ms/150°; parallel acquisition factor, 2; slice thickness, 5 mm; distance factor, 20%; and matrix size, 380 × 256 mm (transversally) and 400 × 320 mm (coronally). A volumetric interpolated breath-hold examination (VIBE) sequence was chosen for fast T1-weighted MRI. For the VIBE sequence, imaging parameters were as follows: TR/TE, 5.12 ms/2.51 ms; flip angle, 10°; partition thickness, 5 mm with no interslice gap; and matrix size, 256 × 116 mm, with a three-dimensional breath-hold imaging technique. A T2-weighted fat-saturated periodically rotated overlapping parallel lines with enhanced reconstruction sequence (BLADE; Siemens Healthineers) was also used, imaging parameters being as follows: TR/TE, 4,670 ms/113 ms; and partition thickness, 5 mm with no interslice gap. DWI was performed using a single-shot echo-planar technique, with a slice thickness of 6 mm under spectral attenuated inversion recovery and respiratory-triggered scanning. DWI parameters were as follows: TR/TE/flip angle, 3,000-4,500 ms/65 ms/90°; diffusion gradient encoding in three orthogonal directions; b = 0 and 800 s/mm^2; field of view, 350 mm; and matrix size, 128 × 128 mm. Imaging parameters are summarized in Table 1.

Image analysis

The MRI files were independently reviewed by two subspecialized chest radiologists who were blinded to patient clinical information and final diagnoses. When differences of opinion arose between the radiologists, a consensus was reached.

The largest lymph node from each patient was visually selected by the radiologist on the T2-weighted image. An elliptical two-dimensional region of interest was drawn around the chosen lymph node area on T2-weighted, T1-weighted, DWI, and apparent diffusion coefficient (ADC) map reconstructions. Necrotic regions were avoided. An elliptical region of interest was also placed around the adjacent latissimus dorsi muscle for T2-ratio determination. The T2 ratio was calculated by the signal intensity of the lymph node ($S_{T2\ lymph\ node}$) divided by the signal intensity of the latissimus dorsi muscle ($S_{T2\ skeletal\ muscle}$) on a T2-weighted image (i.e., T2 ratio = $S_{T2\ lymph\ node}/S_{T2\ skeletal\ muscle}$). Lymph node location, dimensions, and signal intensity (T1, T2, and diffusion-weighted signal intensity), as well as ADC, were recorded.

Statistical analysis

The data are presented as frequency and proportion, mean ± SD, or median [IQR]. The relationships between categorical variables were assessed using chi-square tests. To compare continuous variables, the Student's t-test or the unequal variance t-test was used. Sensitivity, specificity, positive predictive value, and negative predictive value of the MRI findings were calculated in relation to the corresponding histopathological diagnosis. Kappa coefficients were calculated to determine the inter-rater agreement using a 2 × 2 contingency table. A 95% CI was used. In all cases, the level of statistical significance was set at $p < 0.05$. All statistical analyses were performed using the IBM SPSS Statistics software package, version 22.0 (IBM Corporation, Armonk, NY, USA).

RESULTS

A total of 51 consecutive patients were initially included in the study. Three patients were excluded because they initiated treatment prior to undergoing MRI. One patient with a previous diagnosis of sarcoidosis was excluded because he eventually had a definitive diagnosis of tuberculosis. The remaining 47 patients with histopathology-based diagnoses of sarcoidosis or lymphoma were included in the study. A flow chart of the patient selection process is depicted in Figure 1. In our sample, 27 patients (57%) were men. The mean age of the patients was 51 ± 17 years. All of the patients were biopsied via mediastinoscopy. Of the 47 included patients, 23 (47%) had sarcoidosis and 24 (53%) had lymphoma. In the lymphoma group, 20 patients had non-Hodgkin's B-cell lymphoma and 4 had nodular sclerosing Hodgkin's lymphoma.

The mean diameters (including both short and long axis diameters) were 1.62 ± 0.60 cm in the sarcoidosis group and 2.78 ± 0.83 cm in the lymphoma group. In the sarcoidosis group, the largest lymph nodes were located in the subcarinal (n = 19) and right paratracheal (n = 4) spaces. In the lymphoma group, the largest lymph nodes were found in the subcarinal (n = 20), right hilar (n = 2), left paratracheal (n = 1), and left hilar (n = 1) spaces. Of the 23 patients with sarcoidosis, 20 had typical parenchymal CT findings of interstitial micronodules.[26] One patient exhibited pulmonary fibrosis, and 2 patients presented with no signs of pulmonary disease.

Table 1. Imaging parameters of the MRI protocol of the study.

Parameter	T1-weighted VIBE	T2-weighted fat-saturated PROPELLER	HASTE		DWI
Orientation	Transverse	Transverse	Transverse	Coronal	Transverse
TR (ms)/TE (ms)/FA (°)	5.12/2.51/10	4,670/113	infinite/92/150	infinite/92/150	3,000-4,500/65/90
FOV (mm)	Patient adapted	Patient adapted	Patient adapted	Patient adapted	350
Matrix (mm)	256 × 116	256 × 256	380 × 256	400 × 320	128 × 128
Slice thickness (mm)	5	5	5	5	6
Gating	No	Respiratory	No	No	Respiratory
Breath holding	Yes	No	Yes	Yes	No

VIBE: volumetric interpolated breath-hold examination (sequence); PROPELLER: periodically rotated overlapping parallel lines with enhanced reconstruction (sequence); HASTE: half-Fourier acquisition single-shot turbo spin-echo (sequence); DWI: diffusion-weighted imaging; TR: repetition time; TE: echo time; FA: flip angle; and FOV: field of view.

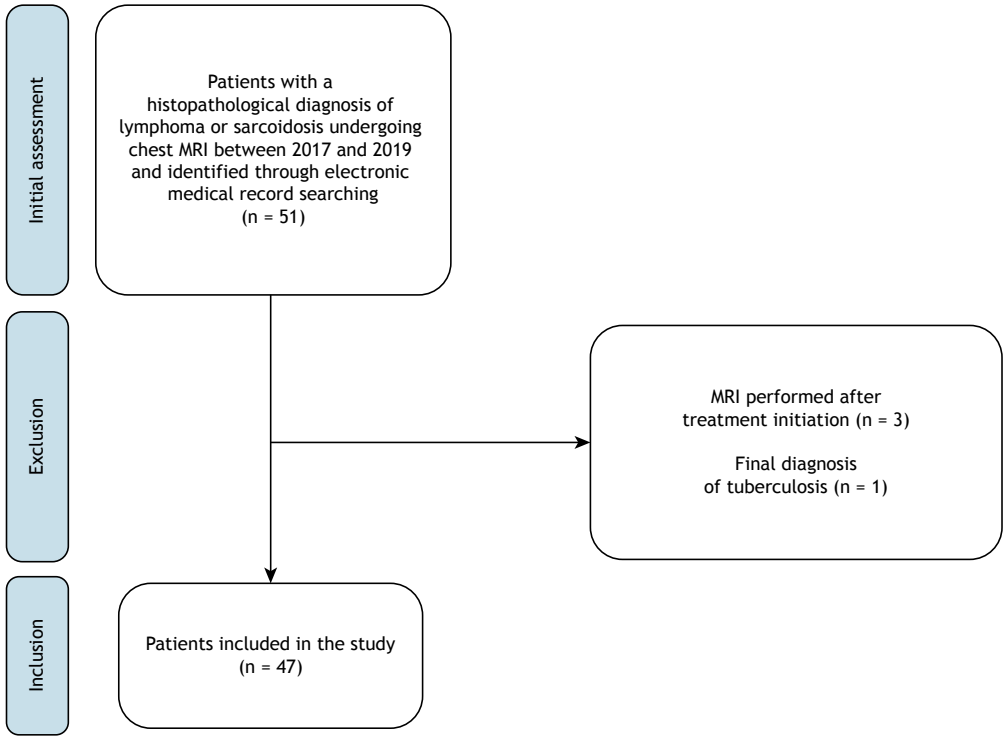

Figure 1. Flow chart of the patient selection process.

There were no significant differences between the two groups in terms of T1 signal intensity, T2 signal intensity, lymph node location, or lymph node size. The mean T2 ratio was significantly lower in the sarcoidosis group than in the lymphoma group (5.0 [3.7-5.3] and 8.3 [4.9-11.9], respectively; p = 0.009), as was the mean diffusion of the lymph nodes (22 [19-54] and 58 [24-96], respectively; p = 0.003). The mean ADC was significantly lower in the lymphoma group than in the sarcoidosis group (0.993 ± 0.508 × 10^{-3} mm^2/s vs. 1.668 ± 0.732 × 10^{-3} mm^2/s; p = 0.002). A ROC curve indicated that an ADC cutoff value of 1.205 × 10^{-3} mm^2/s was optimal for differentiating between lymph nodes affected by lymphoma and those affected by sarcoidosis. Using this cutoff value, sensitivity, specificity, positive predictive value, negative predictive value, and accuracy were 87.5%, 82.6%, 85.1%, 84.0%, and 86.3%, respectively. The T2 ratio cutoff value that best differentiated between lymphoma-affected and sarcoidosis-affected lymph nodes was 7.1, with a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy of 58.3%, 95.6%, 76.5%, 93.3%, and 68.7%, respectively. A kappa coefficient of 0.69 reflected substantial inter-rater agreement. A comprehensive comparison of the MRI findings between the sarcoidosis and lymphoma groups is shown in Table 2. Figures 2 and 3 exemplify our findings.

DISCUSSION

Given that pulmonary sarcoidosis can mimic several other pathologies, including malignant causes of adenopathy,[8] the differentiation between sarcoidosis and such pathologies is crucial for ensuring optimal patient outcomes. The importance of precise imaging-based diagnoses has motivated extensive research on more specific and sensitive means of determining the causes underlying lymph node enlargement. Mehrian & Ebrahimzadeh[12] used CT scans in order to identify variations in the site and morphology of thoracic lymph nodes that correlated differentially with sarcoidosis and lymphoma. Koo et al.[14] demonstrated that there was no significant difference between lymph nodes affected by sarcoidosis or malignant lymphoma using PET-CT, reinforcing the similarity between these pathologies and the difficulty of reaching a definitive diagnosis even with advanced imaging techniques. In the present study, MRI evaluation illuminated characteristics of enlarged mediastinal lymph nodes that have reliably and reproducibly distinguished between sarcoidosis and lymphoma.

Previous studies have also used MRI to differentiate between malignant and benign lymph node pathologies successfully using DWI- and ADC-based quantitative measurements.[18-24] Diffusion evinces the mobility of water molecules within tissues. Cellularity is a common pathological feature that is characteristic of neoplasms, restricting the movement of water molecules and thereby reducing their diffusion. However, lymph node enlargement caused by benign diseases (e.g., infection, congestive heart failure, and drug-induced lymphadenopathy) is more likely to increase diffusion. Due to the aforementioned characteristic of cellularity, MRI is not effective in differentiating subtypes of neoplasms. For example, Matoba et al.[27] found that the ADC values of lymph nodes affected by metastatic small cell carcinomas were not significantly different than those of lymph nodes affected by non-small cell carcinomas. Our results confirmed that ADC values of lymph nodes affected by malignant lymphoma were significantly lower than those of lymph nodes affected by sarcoidosis. Diffusion measurements also differed significantly, with lower values in the sarcoidosis group than in the malignant lymphoma group. The findings of the present study support the use of DWI and ADC mapping as an effective and accurate resource for distinguishing between mediastinal lymph nodes affected by either malignant or benign diseases.

Only patients who underwent MRI prior to initiating treatment were included in the present study, because the impact of treatment on DWI findings remains undetermined. Lymph node size and cellularity could change upon therapeutic intervention, as could tumor size and ADC values. One study[28] used DWI to evaluate lymph node eradication after chemoradiation therapy in patients with locally advanced rectal cancer, but no additional diagnostic benefit was conferred by adding DWI to the T2 imaging findings. In contrast, another study[29] found that DWI is more accurate

Table 2. Comparison of parameters between patients diagnosed with either sarcoidosis (n = 23) or lymphoma (n = 24).[a]

Parameter	Sarcoidosis	Lymphoma	p
Male	12 (52)	15 (62)	0.561
Age, years	49 ± 14	53 ± 18	0.406
Short axis diameter, cm	1.54 ± 0.48	1.69 ± 0.69	0.940
Long axis diameter, cm	2.73 ± 1.00	2.83 ± 0.65	0.474
T1	215 ± 96	159 ± 73	0.031
T2	190 [156-260]	126 [96-222]	0.123
DWI	22 [19-54]	58 [24-96]	0.003
ADC, × 10^{-3} mm^2/s	1.668 ± 0.732	0.993 ± 0.508	0.002
T2 ratio	5.0 [3.7-5.3]	8.3 [4.9-11.9]	0.009

DWI: diffusion-weighted imaging; and ADC: apparent diffusion coefficient. [a]Values expressed as n (%), mean ± SD, or median [IQR].

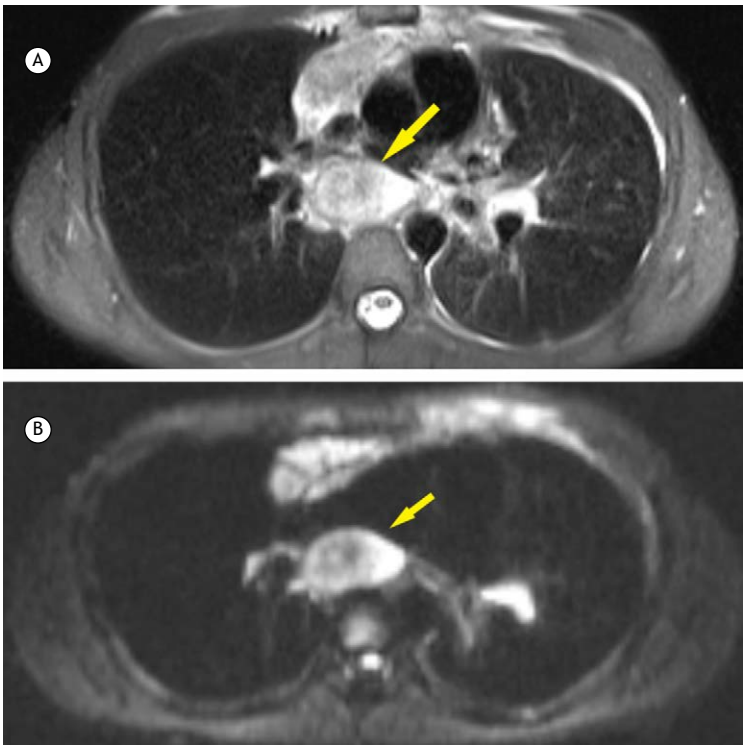

Figure 2. Transverse MRI scans of a 35-year-old man with sarcoidosis. In A, T2-weighted PROPELLER MRI of an enlarged mediastinal lymph node. In B, apparent diffusion coefficient (ADC) map reconstruction of the lymph node. PROPELLER: periodically rotated overlapping parallel lines with enhanced reconstruction. ADC = 1.74 × 10^{-3} mm^2/s.

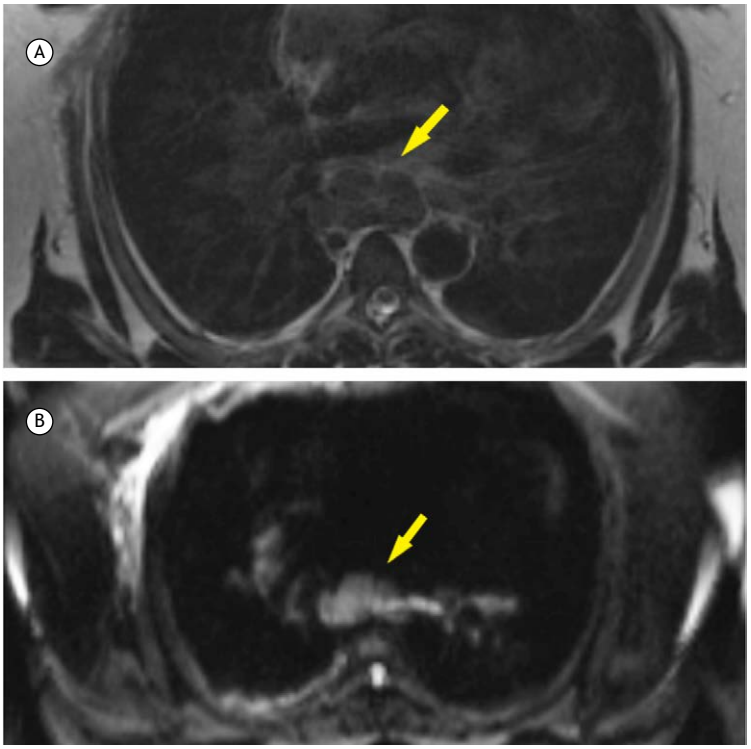

Figure 3. Transverse MRI scans of a 17-year-old man with Hodgkin lymphoma. In A, T2-weighted PROPELLER MRI of an enlarged mediastinal lymph node. In B, apparent diffusion coefficient (ADC) map reconstruction of the lymph node. PROPELLER: periodically rotated overlapping parallel lines with enhanced reconstruction. ADC = 0.9 × 10^{-3} mm^2/s.

than CT when assessing response to radiation therapy, chemotherapy, or both.

An important finding from this study is that the T2 ratio is lower in sarcoidosis-affected lymph nodes than in lymphoma-affected lymph nodes. The use of T2 ratio in our study is justified to avoid interindividual differences, such as those frequently caused by receiver-coil bias. The correlation between fibrotic and calcified contents in sarcoidosis-related lymph node enlargement is likely to be the cause of the lower T2 ratio found in our study, which aligns with the aforementioned literature. The T2 ratio was more specific but less accurate than ADC values in differentiating between mediastinal lymph nodes enlarged due to either lymphoma or sarcoidosis.

Chung et al.[30] described the dark lymph node sign, an MRI finding that is characteristic of lymph nodes affected by sarcoidosis. A possible correlation with fibrotic content may underlie the dark lymph node sign—a node with low internal intensity and hyperintensity along the peripheral rim on T2-weighted imaging. That study,[30] however, did not include patients with malignant diseases, such as lymphoma, which restricts their findings to granulomatous diseases. Moreover, they did not measure the signal intensity and based their findings on a largely qualitative evaluation of the imaging examination.

Our study has some limitations. The retrospective nature of the study carries inherent selection biases, and the data obtained from the electronic medical records of the patients could potentially be inaccurate, which could affect our results. Another limitation was the small number of patients with atypical findings of sarcoidosis on MRI imaging. Although no patients had active tuberculosis infection, the subjects were recruited from a population highly affected by the disease. Any selection bias in our research criteria could have prevented the inclusion of patients during the study period if the terms lymph nodes, sarcoidosis, or lymphoma were not cited in the medical reports. Although we controlled the MRI evaluation performed by the radiologists by using quantitative measurement parameters, another limitation is the inter-rater variability regarding the selection of the largest lymph node, lymph node measurements, and MRI signal quantification. Future studies should include cases of patients with enlarged mediastinal lymph nodes caused by other conditions (e.g., metastases, infectious diseases, and other inflammatory conditions). Quantitative evaluation of enlarged lymph nodes due to diseases other than sarcoidosis and lymphoma represents an important addition to the understanding of the behavior of lymphadenopathies within the context of different thoracic diseases.

In conclusion, MRI-based indications of diffusion and T2 ratio can facilitate the differentiation between sarcoidosis-related and lymphoma-related enlarged mediastinal lymph nodes. Although the T2 ratio was more specific but less accurate than ADC values, their combined ability to make such a crucial clinical distinction using MRI data represents an invaluable diagnostic advancement that is particularly relevant for young patients presenting with sarcoidosis or lymphoma, whose symptoms are highly similar.

AUTHOR CONTRIBUTIONS

FSS and BH: study conception and design, literature search, and acquisition and interpretation of data; GW: statistical analyses; FSS, GW, TMM, and THM: drafting of the manuscript; BH, EM, NV, THM, and TMM: critical revision of the manuscript for important intellectual content; BH: supervision, data integrity, and guarantor of the article.

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ORIGINAL ARTICLE

Tuberculosis in Brazil: one country, multiple realities

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ABSTRACT

Objective: To identify the determinants of tuberculosis-related variables in the various regions of Brazil and evaluate trends in those variables over the ten-year period preceding the end of the timeframe defined for the United Nations Millennium Development Goals (MDGs). **Methods:** This was an ecological analytical study in which we utilized eight national public databases to investigate the 716,971 new tuberculosis cases reported between 2006 and 2015. **Results:** Over the study period, there were slight reductions in the prevalence, incidence, and mortality associated with tuberculosis. Brazil did not reach the MDG for tuberculosis-related mortality. Among the performance indicators of tuberculosis control, there were improvements only in those related to treatment and treatment abandonment. In terms of the magnitude of tuberculosis, substantial regional differences were observed. The tuberculosis incidence rate was highest in the northern region, as were the annual mean temperature and relative air humidity. That region also had the second lowest human development index, primary health care (PHC) coverage, and number of hospitalizations for tuberculosis. The northeastern region had the highest PHC coverage, number of hospitalizations for primary care-sensitive conditions, and tuberculosis-related mortality rate. The southern region showed the smallest reductions in epidemiological indicators, together with the greatest increases in the frequency of treatment abandonment and retreatment. The central-west region showed the lowest overall magnitude of tuberculosis and better monitoring indicators. **Conclusions:** The situation related to tuberculosis differs among the five regions of Brazil. Those differences can make it difficult to control the disease in the country and could explain the fact that Brazil failed to reach the MDG for tuberculosis-related mortality. Tuberculosis control measures should be adapted to account for regional differences.

Keywords: Tuberculosis/epidemiology; Tuberculosis, pulmonary/epidemiology; Health status indicators; Social determinants of health; Healthcare disparities.

INTRODUCTION

In 1993, the World Health Organization (WHO) recognized tuberculosis as a global epidemic.[1,2] Despite notable progress, tuberculosis is still a public health problem that continues to be one of the most lethal transmissible diseases worldwide.[3] Brazil ranks 20th in the world in terms of the incidence of tuberculosis.[2] The WHO reported that Brazil is among the 22 countries where the burden of tuberculosis is high, and, therefore, there is a focus on reducing the incidence of tuberculosis in the country.[4] On the basis of those data, combating tuberculosis became one of the eight United Nations Millennium Development Goals (MDGs), the target being a 50% reduction in the incidence, prevalence, and mortality rates associated with the disease by 2015 (in relation to the rates reported for 1990).

Brazil covers approximately 50% of South America and is subdivided into five administrative/geographic regions (northern, northeastern, southeastern, southern and central-west regions). These five regions present different climatic patterns, socioeconomic features, political dynamics, and administrative structures.[5] Although the organization of health care services also differs substantially among the regions, the majority (71%) of the population depends on public health care services provided by the Brazilian Unified Health Care System. The primary health care (PHC) system is often the first point of contact for people who interact with the health care system.[6]

The care provided to patients suspected of having tuberculosis, to those with a confirmed diagnosis of tuberculosis, and to the contacts of tuberculosis patients

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influences the burden of the disease and the levels of its control, as well as the morbidity and mortality associated with the disease.[7] Therefore, the rates of treatment abandonment and retreatment, as well as other major indicators, are evaluated as a part of strategies to control tuberculosis, such strategies including sputum smear microscopy (for diagnosis and during treatment until confirmation of a clinical and bacteriological cure), directly observed therapy (DOT), and immediate sputum smear microscopy/culture in all cases of retreatment.

The decrease in the incidence of tuberculosis has been slow[3] and varies considerably among countries due to differences in the Human Development Index (HDI), sociocultural aspects, political structure, organization of health care services, and the implementation of national tuberculosis control programs (NTCPs).[8] Nevertheless, a multifactorial approach is important for strengthening the strategies to tackle the tuberculosis epidemic. Although epidemiological studies have assessed and reported results related to the dynamics of tuberculosis at the country level,[9] to date, there have been no studies using a multifactorial approach to address this issue over the long term.

The aim of this study was to add to the body of evidence in the literature on tuberculosis by collecting previously unpublished information from various national databases in Brazil. We combined many variables from different contexts into a single study to provide an expanded view of the many determinants of the tuberculosis burden in Brazil. In addition, we assessed the epidemiological trends over the ten-year period leading up to the deadline proposed by the WHO to achieve the MDGs, and we attempted to determine whether Brazil had met the proposed targets.

METHODS

This ecological study linked eight public domain databases to analyze the new tuberculosis cases registered in the Brazilian Case Registry Database between 2006 and 2015.[10] The data were collected from the databases of the Brazilian National Ministry of Health (NMH) *Departamento de Informática do Sistema Único de Saúde* (DATASUS, Information Technology Department of the Brazilian Unified Health Care System),[10] the Brazilian Institute of Geography and Statistics,[11] and the Brazilian National Meteorological Institute.[12]

The DATASUS databases used were those of the Brazilian Tuberculosis Case Registry Database,[10] the Support Room for Strategic Management,[1] the List of Health Indicators and Goals,[13] the National Immunization Program,[14] the National Registry of Health Care Facilities,[15] and the Hospital Information Service.[16] All variables, including detailed descriptions and the formulas used for calculations, together with relevant observations and sources of information, are displayed in Table 1. Analyses were performed in Microsoft Excel as well as with plots. There was no need for research ethics committee approval, because research using public domain information is not evaluated in the Brazilian National Research Ethics Committee system.

RESULTS

During the ten-year study period, 716,971 cases of tuberculosis were reported in Brazil (entries being classified as new cases, cases of recurrence, cases of retreatment after treatment abandonment, unclassified cases, transferred cases, or cases reported post-mortem). If only those classified as new cases are considered, the mean annual number of cases was 85,721. Table 2 shows various aspects of the tuberculosis epidemic in relation to the organization of health, social, economic, and environmental services in the five regions of the country. Figures 1 to 4, which analyze the trends of the epidemic, also clearly show that differences in dynamics among the regions have influenced those trends.

Brazil did not reach the MDG related to tuberculosis mortality. Substantial differences were observed among the regions, and regional differences should be taken into account when tuberculosis control measures are being planned. Over the study period, there was a slight reduction in the prevalence of tuberculosis in Brazil as a whole (from 46.1% in 2006 to 39.9% in 2015), the reduction being largest (from 48.1% to 37.4%) in the northeastern region and smallest (from 37.5% to 36.4%) in the southern region. The incidence of tuberculosis also decreased slightly in Brazil as a whole (from 38.6 cases/100,000 population in 2006 to 33.1 cases/100,000 population in 2015), the decrease being largest (from 45.8 to 38.8 cases/100,000 population) in the northern region and smallest (from 23.9 to 21.3 cases/100,000 population) in the central-west region. In addition, there was a slight reduction in the tuberculosis-related mortality rate in Brazil as a whole (from 2.5 deaths/100,000 population in 2006 to 2.2 deaths/100,000 population in 2015), the reduction being largest (from 3.1 to 2.6 deaths/100,000 population) in the northeastern region and smallest (from 1.5 to 1.4 deaths/100,000 population) in the central-west region (Figure 1).

In 2006, 2007, and 2008 (prior to the inclusion of ethambutol in the tuberculosis treatment regimen in Brazil), the nationwide tuberculosis-related mortality rates (deaths per 100,000 population) were 2.58, 2.57, and 2.57, respectively (mean, 2.573 ± 0.004). The nationwide tuberculosis-related mortality rate was 2.5 in 2009 (the first year of ethambutol use), after which there were slight reductions. In 2010, 2011, 2012, and 2013, the nationwide tuberculosis-related mortality rate (annual change) was 2.44 (−0.06%), 2.37 (−0.07%), 2.27 (−0.10%), and 2.29 (+0.02%), respectively. That rate was lowest in 2014 and 2015 (2.20 for both), corresponding to a reduction of 0.3% in relation to the 2009 rate (2.345). As illustrated in

Table 1. Description of variables and sources of information related to tuberculosis in Brazil.

Variable	Numerator	Denominator	Unit	Source
Magnitude of tuberculosis (2006-2015)				
TB prevalence	Current number of TB cases	Resident population in the same location and year	Cases/100,000 population	[1,11]
PTB prevalence	Current number of cases of PTB	Resident population in the same location and year	Cases/100,000 population	[10,11]
TB incidence	Total new cases of TB (all forms) in a given period, location, and year	Resident population in the same location and year	Cases/100,000 population	[1]
Smear-positive PTB incidence	Total new cases of smear-positive PTB in a given location and year	Resident population in the same location and year	Cases/100,000 population	[1]
TB-related mortality	Number of deaths due to TB in a given location and year	Resident population in the same location and year	Deaths/100,000 population	[1] for 2006-2014 [32] for 2015
Indicators of TB control (2006-2015)				
First SSM positive	Total number of first SSMs that were positive in a given location and year	Number of cases of PTB or PTB+EPTB in the same location and year	%	[11]
SSM in the 2nd month	Number of SSMs performed by the end of the 2nd month of treatment in a given location and year	Number of first SSMs that were positive in the same location and year	%	[11]
SSM in the 6th month	Number of SSMs performed by the end of the 6th month of treatment in a given location and year	Number of first SSMs that were positive in the same location and year	%	[11]
Patients in DOT	Number of TB cases in which DOT was used in a given location and year	Number of TB cases in the same location and year	%	[11]
Retreatment after relapse or treatment abandonment	Number of cases of relapse or treatment abandonment reported in a given location and year	Number of TB cases reported in the same location and year	%	[11]
Sputum culture in patients previously treated for TB	Number of previously treated cases of TB (relapse or readmission after treatment abandonment) submitted to sputum culture in a given location and year	Number of previously treated cases of TB in the same location and year	%	[11]
Treatment abandonment	Number of cases closed due to treatment abandonment in a given location and year	Number of cases closed in the same location and year	%	[11]
Health care indicators (2008-2015)				
BCG vaccine coverage	Number of BCG vaccinations in children < 1 year of age in a given location and year	Resident population < 1 year of age in the same location and year	%	[14]
Density of physicians	Number of physicians registered with the CNES in a given location and year	Resident population in the same location and year	Physicians/10,000 population	[15,11]
Density of nurses	Number of nurses registered with the CNES in a given location and year	Resident population in the same location and year	Nurses/10,000 population	[15,11]
Density of pharmacists	Number of pharmacists registered with the CNES in a given location and year	Resident population in the same location and year	Pharmacists/10,000 population	[15,11]
PHC coverage	Number of people seen by PHC teams × 3,000 in a given location and year	Resident population in the same location and year	%	[13]

Continued ▸

Variable	Numerator	Denominator	Unit	Source
Hospitalization for PCSCs	Number of hospitalizations for PCSCs in a given location and year	Total clinical hospitalizations in the same location and year	%	(13)
Socioeconomic indicators (2006-2015)				
Hospitalizations for TB	Total hospitalizations for TB in a given location and year	Number of TB cases in the same location and year	Hospitalizations/100 TB cases	(10,16)
Length of hospital stay	Days spent in the hospital for TB in a given location and year	Number of hospitalizations for TB in the same location and year	Mean number of days	(16)
Cost of hospitalization for TB	Amount spent on hospitalizations for TB in a given location and year	Number of days of hospitalization for TB in the same location and year	US$/day	(16)
In-hospital mortality	Number of deaths due to TB in a given location and year	Number of hospital admissions for TB in the same location and year	100	(16)
Summary (2008-2015)				
TB incidence rate	Total new cases of TB (all forms) in a given period, location, and year	Resident population in the same location and year	Cases/100,000 population	(1)
TB mortality rate	Number of deaths due to TB in a given location and year	Resident population in the same location and year	Cases/100,000 population	(1,41)
Density of physicians	Number of physicians registered with the CNES in a given location and year	Resident population in the same location and year	Physicians/10,000 population	(15,10)
Density of nurses	Number of nurses registered with the CNES in a given location and year	Resident population in the same location and year	Nurses/10,000 population	(15,10)
Density of pharmacists	Number of pharmacists registered with the CNES in a given location and year	Resident population in the same location and year	Pharmacists/10,000 population	(15,10)
PHC coverage	Number of people seen by PHC teams × 3,000 in a given location and year	Resident population in the same location and year	%	(13)
Hospitalizations for TB	Number of hospitalizations for treatment of TB in a given location and year	Number of TB cases in the same location and year	Admissions/100 TB cases	(10,15)
Cost of hospitalization for TB	Amount spent on hospitalizations for TB in a given location and year	Number of days of hospitalization for TB in the same location and year	US$/day	(11)
Demographic density	Population of the region	Area of the region in km^2	Population/km^2	(11)
HDI	Geometric mean of the income, education, and longevity indices		-	-
Temperature	-	-	˚C	(12)
Relative humidity	Actual vapor pressure	Saturation vapor pressure at the ambient temperature	%	(12)
Latitude	Distance from the Equator		Degree	-

TB: tuberculosis; PTB: pulmonary tuberculosis; SSM: sputum smear microscopy; EPTB: extrapulmonary tuberculosis; DOT: directly observed treatment; PHC: primary health care; PCSCs: primary care-sensitive conditions; CNES: *Cadastro Nacional de Estabelecimentos de Saúde* ([Brazilian] National Registry of Health Care Facilities); PHC: primary health care; HDI: Human Development Index.

Figure 1, there were also reductions in the incidence and prevalence of tuberculosis in the years after the inclusion of ethambutol. However, there were no significant changes between 2010 and 2014 in terms of the proportion of tuberculosis patients who abandoned treatment, although that proportion was lower in 2015 (Figure 2).

Table 2 shows the sociodemographic, climatic, and health care characteristics of the five regions of Brazil. The northern region of the country has the highest mean annual temperature (28°C) and highest mean annual relative humidity (81.5%), as well as having the second lowest mean HDI (0.701), lowest mean PHC coverage (59.5%), and lowest mean annual

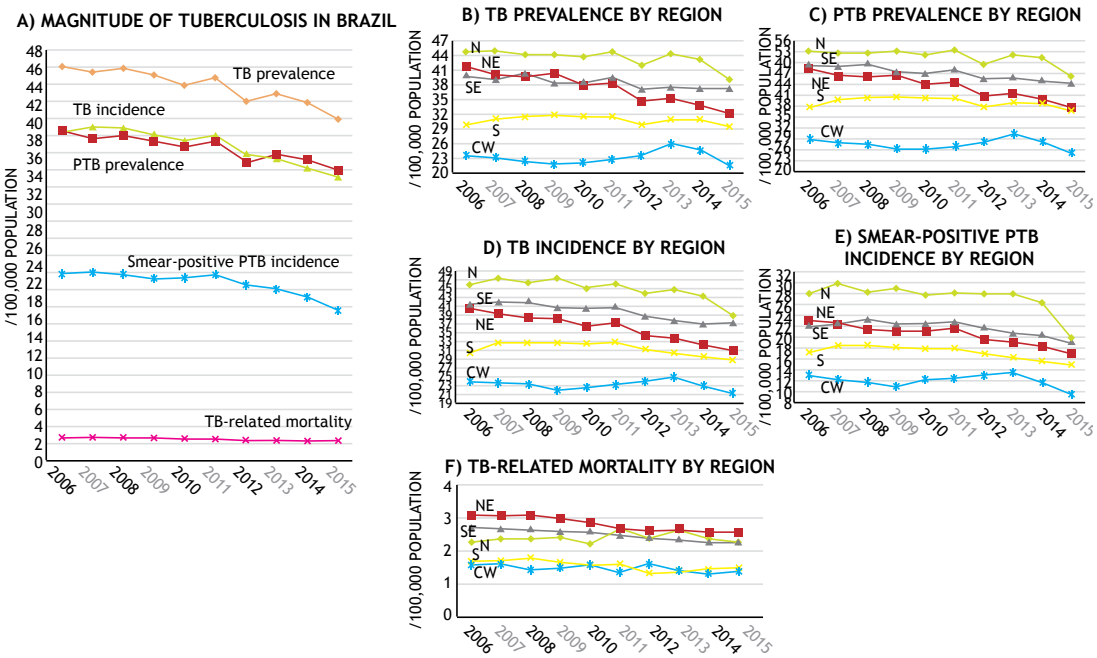

Figure 1. Magnitude of tuberculosis in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; PTB: pulmonary tuberculosis; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

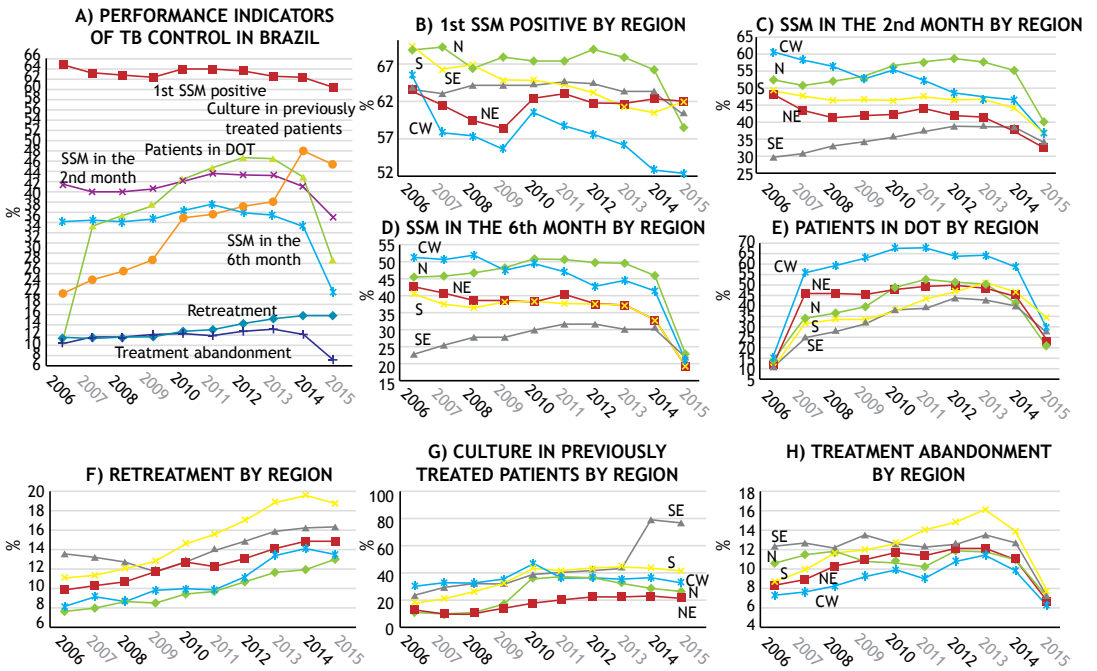

Figure 2. Performance indicators of tuberculosis control in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; SSM: sputum-smear microscopy; DOT: directly observed therapy; PTB: pulmonary tuberculosis; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west. [a]Among cases of PTB. [b]Among cases in which the 1st SSM was positive. [c]Among all cases of TB.

number of hospitalizations for tuberculosis (11.3). The northeastern region had the highest mean PHC coverage (75.2%), highest mean annual number of hospitalizations for tuberculosis (17.0), and highest mean tuberculosis-related mortality rate (2.9 deaths/100,000 population). The mean population density was highest (89.4 inhabitants/km^2) in the southeastern region. We found that the reductions in

Table 2. Demographic, socioeconomic, climatic, and health care characteristics of Brazil and its regions in relation to tuberculosis.[a]

Characteristics	Brazil as a whole	Region				
		Northern	Northeastern	Southeastern	Southern	Central-west
TB incidence (cases/100,000 population)	36.8 (33.2-39.0)	44.9 (38.9-47.5)	36.2 (31.0-40.7)	39.8 (37.1-42.1)	31.4 (28.8-32.9)	23.1 (21.3-24.9)
TB-related mortality (deaths/100,000 population)	2.4 (2.2-2.6)	2.4 (2.2-2.7)	2.9 (2.6-3.1)	2.5 (2.3-2.7)	1.6 (1.3-1.8)	1.5 (1.3-1.6)
Hospitalization for TB[b] (admissions/100 TB cases)	14.0 (12.8-15.4)	11.3 (10.1-12.6)	17.0 (13.9-20.2)	12.4 (10.9-13.6)	15.1 (13.3-17.5)	15.7 (13.9-17.8)
Cost/day of hospitalization for TB[b] (US$)	38.4 (26.0-49.3)	28.6 (16.0-40.6)	40.2 (28.0-48.9)	36.9 (25.6-49.6)	42.1 (27.4-52.7)	34.5 (19.6-42.0)
PHC coverage (%)	67.5 (64.8-73.0)	59.5 (56.1-68.2)	75.2 (72.7-80.3)	62.8 (59.7-68.2)	72.4 (69.1-78.4)	65.4 (62.5-68.7)
Density of health care workers[b]						
Physicians (staff/10,000 population)	15.3 (13.7-17.1)	8.0 (7.2-9.4)	10.0 (8.9-11.4)	19.8 (17.8-21.8)	16.5 (14.6-18.9)	15.7 (14.0-17.4)
Nurses (staff/10,000 population)	7.4 (5.3-9.8)	5.6 (4.2-7.5)	6.6 (4.8-8.6)	8.2 (5.8-11.0)	7.7 (5.6-10.5)	6.9 (4.8-9.2)
Pharmacists (staff/10,000 population)	1.5 (1.0-1.8)	1.3 (0.9-1.6)	1.2 (0.7-1.5)	1.4 (1.2-1.7)	2.1 (1.3-2.7)	1.7 (1.0-2.2)
Demographic density (inhabitants/km^2)	23.0 (22.0-24.0)	4.2 (3.9-4.5)	35.2 (33.8-36.4)	89.4 (85.8-92.7)	48.9 (47.0-50.7)	9.0 (8.3-9.6)
HDI[c]	0.744 (0.705-0.761)	0.701 (0.684-0.718)	0.685 (0.660-0.703)	0.773 (0.754-0.786)	0.779 (0.756-0.795)	0.769 (0.753-0.780)
Temperature (°C)	25.9 (14.3-34.2)	28.0 (21.7-33.6)	27.0 (19.8-34.2)	24.0 (16.4-29.7)	21.3 (14.3-24.9)	26.9 (20.1-31.0)
Relative air humidity (%)	74.5 (63.0-84.8)	81.5 (77.2-84.7)	72.6 (63.0-78.7)	73.5 (68.6-78.0)	79.0 (77.1-80.7)	69.7% (65.0-76.1)
Latitude, range of extremes	5,2188 ↔ −33,5861	5,2188 ↔ −13,3218	1,2015 ↔ −18,1367	14,3747 ↔ −25,0318	-22,5937 ↔ −33,5861	−7,7107 ↔ −23,8424

TB: tuberculosis; PHC: primary health care; and HDI: Human Development Index. [a]Values expressed as mean (range), except where otherwise indicated, and variables refer to the 2006-2015 period, except where otherwise indicated. [b]For the 2010-2015 period. [c]For the 2008-2015 period.

the indicators of incidence were smallest in the southern region. In that region, the reduction in tuberculosis incidence was 5.46 cases/100,000 population, whereas it was 23.86 cases/100,000 population (the highest value) in the northeastern region, and the reduction in the incidence of smear-positive pulmonary tuberculosis was 10.97 cases/100,000 population, whereas it was 28.60 cases/100,000 population (also the highest value) in the northeastern region. The southern region also showed the smallest decrease in the frequency of treatment abandonment/retreatment (from 8.7% to 7.8%), as shown in Figure 2. The incidence and mortality rates were lowest (23.1 cases/100,000 population and 1.5 deaths/100,000 population, respectively) in the central-west region.

In Brazil as a whole, the mean rates of DOT use and treatment abandonment were 36.7% and 11.4%, respectively, and similar rates were observed in all regions. In most years, the frequency of retreatment was highest in the southern region. Between 2006 and 2009, there was a temporary trend toward a decrease in the frequency of retreatment in the southeastern region, although there was no such trend in any of the other regions. All regions showed trends toward an increase in the proportion of patients in whom sputum culture was performed, that increase being greatest (mean, 214.2%) in the southeastern region, especially in 2014 and 2015 (Figure 2).

One of the main methods of preventing tuberculosis, coordinated by PHC, is immunization with the BCG vaccine, which showed a slight trend toward a decrease in the country but remained at values near 100.0%. The data collected showed a trend toward an improvement in the indicators related to health care workers (except pharmacists), PHC coverage, and hospitalization for primary care-sensitive conditions (PCSCs). Over the study period, PHC coverage, physician density, and nurse density increased by 12.7%, 24.8%, and 84.9%, respectively, while the number of hospitalizations decreased by 14.5% and pharmacist density decreased by 21.4% (Figure 3).

From 2006 to 2015, there was a trend toward an increase in the number of hospitalizations for tuberculosis treatment, although the in-hospital tuberculosis-related mortality rates remained stable. The mean length of hospital stay was 23.3 days, and there was a noticeable reduction in hospitalization costs from 2011 onward (Figure 4). The mean frequency of hospitalization for tuberculosis treatment was lowest in the northern region, as was the mean length of hospital stay and the mean total hospitalization cost. Of the patients with active tuberculosis, 14.0% were admitted to the hospital for treatment, generating a mean cost of US$38.40 per day (Figure 4).

DISCUSSION

To our knowledge, there have been no previous studies including all of the variables evaluated in the present study, stratifying the findings by region, and

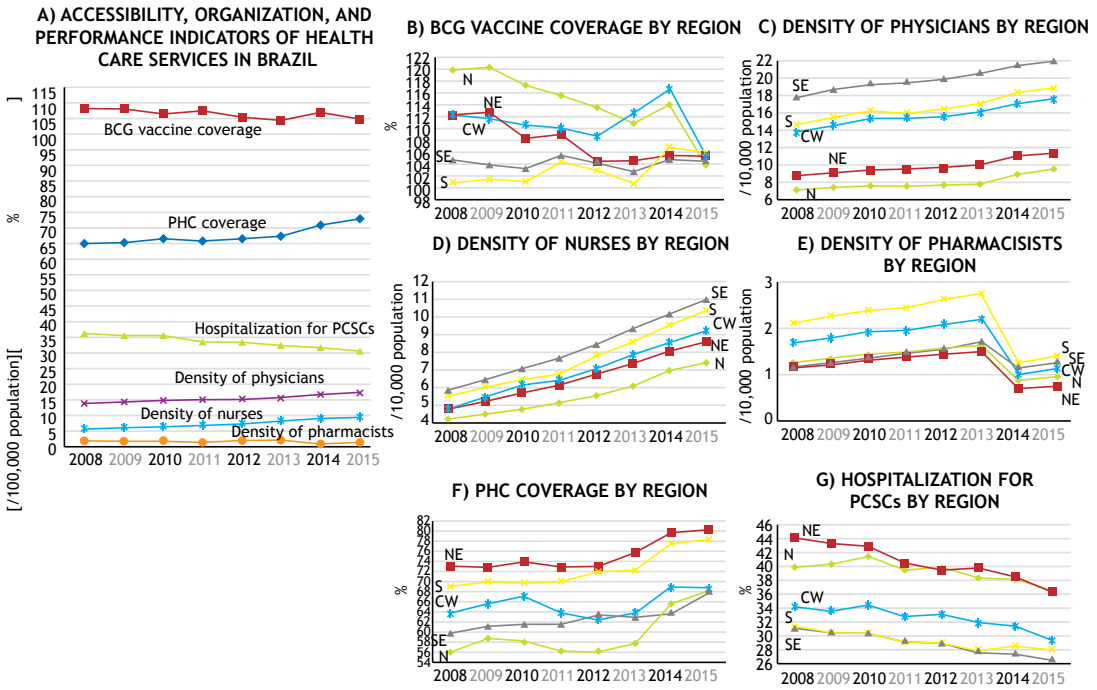

Figure 3. Accessibility, organization, and performance indicators of health care services in Brazil as a whole and by region, 2006-2015. PHC: primary health care; PCSCs: primary care-sensitive conditions; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

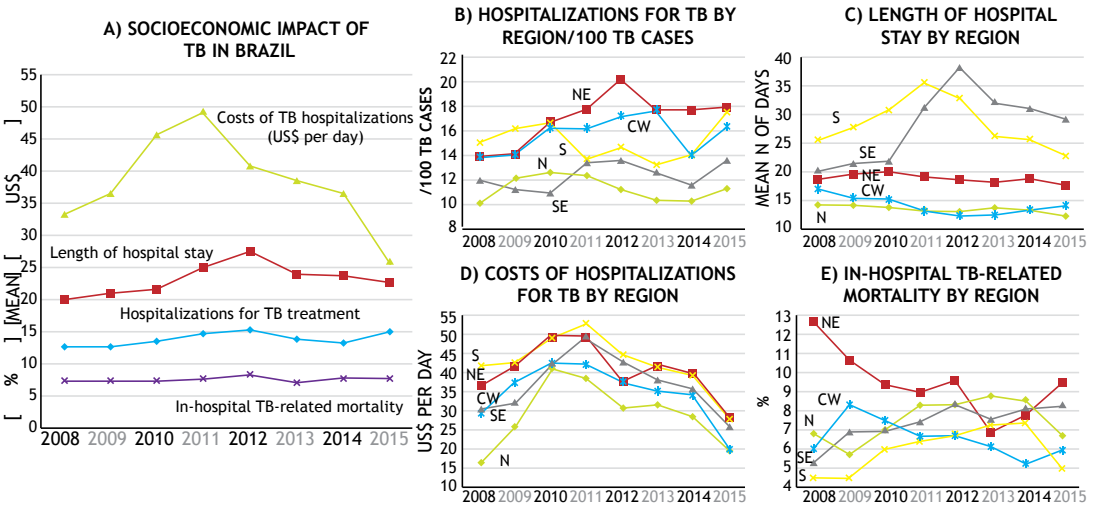

Figure 4. Socioeconomic impact of tuberculosis in Brazil as a whole and by region, 2006-2015. TB: tuberculosis; PHC: primary health care; PCSCs: primary care-sensitive conditions; N: northern; NE: northeastern; SE: southeastern; S: southern; and CW: central-west.

analyzing the long-term trends in Brazil. Although the WHO reported that all MDGs related to tuberculosis have been achieved,[4] our findings show that Brazil has failed to reach the mortality rate goal. The only region in the country that achieved the goal of reducing the tuberculosis-related mortality rate by 50.0% in relation to the 1990 rate, as proposed in the MDGs, was the southeastern region, where it was reduced from 4.6 to 2.3 deaths/100,000 population.

In addition to climatic and socioeconomic diversity, we observed substantial differences among the regions of Brazil, in terms of the magnitude of tuberculosis and general indicators of PHC performance, as well as in terms of the cost of tuberculosis, tuberculosis control, and specific indicators, such as the number of hospitalizations for tuberculosis. In 2015, Brazil was classified as having a high level of human development overall, ranking 79th in the worldwide ranking of countries by HDI,[17] although that level

was classified as low in the northern and northeastern regions. The HDI was highest for the southern and central-west regions, where the incidence of and mortality associated with tuberculosis were lowest. One study, analyzing data from 165 countries for the 2005-2011 period, identified a significant association between the HDI and tuberculosis-related morbidity.[18] Another study, using data from the 22 countries with the highest tuberculosis burden, detected a significant inverse correlation between HDI and the incidence of tuberculosis, showing that a one-point increase in the former cause the latter to decrease by 11.0% (95% CI: 2.03-19.06).[19]

Demographic heterogeneity may be another factor influencing the incidence of and mortality associated with tuberculosis in Brazil, where the population density is high in some regions and low in others. Tuberculosis transmission is associated with crowding, such as that seen in metropolitan areas in Brazil,[20] the region with the second highest tuberculosis incidence rate being the southeastern region, which is the most populous region of the country. A study conducted in 36 Turkish provinces (evaluating a collective total of 43,560,619 inhabitants) demonstrated a positive correlation between population density and the incidence of tuberculosis, the former being found to be an independent predictor of the latter.[8]

In the present study, we showed that the rates of treatment abandonment in Brazil have decreased since 2012. However, we also found that the annual retreatment rate in the country has increased, especially since 2009, reaching 15.9% in 2015, higher than the 12.0% reported for Morocco,[21] although the tuberculosis burden is higher in Brazil. In the southern region of Brazil, we observed a considerable increase in the treatment abandonment rate and a higher retreatment rate. A local study conducted in the state of Rio Grande do Sul (the fifth most populous state in the country) revealed major flaws in the Rio Grande do Sul State Tuberculosis Control Program.[22]

Although the use of DOT has increased in Brazil, by 2012 it was still below the 100.0% goal the WHO expected to be achieved worldwide by 2010.[23] In China, only 13.9% of the population was covered by the DOT strategy in 2012.[24] In Ethiopia, coverage was better, 70.0% of the population being covered by DOT in 2011.[25] The challenges for improving DOT coverage include financial and logistical barriers to health care access,[26] as well as the lengthy commitment required of human resources,[26,27] the need for a mixed public-private approach, and the need for professional awareness of the importance of DOT in all patients with tuberculosis (not only those who are smear-positive).[28]

The Brazilian NTCP recommends that tuberculosis control measures, including diagnosis and treatment monitoring, be decentralized.[29] However, expanding actions to address tuberculosis at PHC clinics and to decentralize control measures continues to be a challenge in Brazil,[30] where heterogeneous levels of organization, due to different regional administrative conditions, impede the decentralization process.[31] Therefore, the NTCP operates in different formats in many areas of the five regions and difficulties in achieving timely case management have been reported.[32]

Most of the Brazilian population depends on public health care services,[6] and the PHC system is the gateway to those services. Therefore, the level of PHC coverage of the population represents an important marker of access to health care services in the country. In 2015, the PHC coverage in Brazil was 73.0%, corresponding to an increase of 12.7% compared with that of 2006.

Among the five regions examined, the PHC coverage was lowest in the northern region, which also had the lowest concentrations of physicians and nurses, potentially delaying the diagnosis and evaluation of contacts of tuberculosis cases, thus favoring the maintenance of the transmission chain and probably accounting for our finding that the incidence rates were highest in that region. In addition, the combination of higher numbers of patients with smear-positive pulmonary tuberculosis, high treatment abandonment rates, and high retreatment rates also affects the rate of possible transmissions, which could explain the higher incidence and mortality rates in the region. Furthermore, other infectious diseases are endemic to the northern region, and the experience of clinicians with those other diseases could favor the local diagnosis of tuberculosis, which could have increased the tuberculosis incidence rate in the region.

Strategies aimed only at increasing PHC coverage and health professional awareness do not always produce actions consistent with the needs of the population, and the recommendations outlined in tuberculosis guidelines must therefore be followed.[33] We posit that higher PHC coverage does not necessarily lead to greater positive health impacts, given the regional differences in hospitalizations for PCSCs. Regions with extremely different PHC coverage exhibit similarly high rates of hospitalization for PCSCs. The northeastern region has good PHC coverage but presented the lowest expansion of the DOT strategy, a high number of hospitalizations for PCSCs, and higher rates of hospital admissions for and mortality due to tuberculosis. In view of these findings, the problem of tuberculosis in the northeastern region appears to be unique, not only in terms of the specific tuberculosis control measures required but also in terms of the quality and general effectiveness of health care services. A previous study demonstrated that the public health care system in the northeastern region is inefficient because of the low density of health care professionals and the low number of individuals who graduate with a health-related degree.[34]

Failure to diagnose and treat tuberculosis accurately and in a timely manner maintains the chain of transmission, thus increasing the number of hospitalizations, health expenditures, and even mortality

rates. In addition, tuberculosis affects the active work force and can therefore have a negative socioeconomic impact.[26,35] The rates of hospitalization for tuberculosis are 33.3% in China and 66.5% in Spain, substantially higher than the rate in Brazil, and hospitalizations account for a significant portion of the total costs associated with the disease.[36,37] In Brazil, hospital admissions for tuberculosis are avoided, being limited to special situations and patients with complications of the disease.[29] In contrast, hospitalization is a routine measure during the intensive phase of tuberculosis treatment in some countries in Eastern Europe and Central Asia.

The longer hospital stays observed in the southern and southeastern regions of Brazil could be explained by the lack of financial resources for infrastructure, the imbalance between the density of health care service providers and that of the population, and the migration of inhabitants from other regions.[34] The high population density can reduce the number of available beds, delaying the initiation of appropriate treatment in patients who require hospitalization, thus increasing the length of the hospital stay, hospitalization costs, and the risk of death. However, studies investigating hospitalization for other causes have also shown that hospitalization costs are higher in the southern region than in the northern region, likely because of the lower technological complexity of the hospitals in the latter.[38]

One influential factor in the estimates of the epidemiological aspects of tuberculosis is the pharmacological treatment used. In 1979, the basic treatment regimen recommended for new cases in Brazil was rifampin, isoniazid, and pyrazinamide for two months, followed by rifampin and isoniazid for four months. The inclusion of ethambutol was recommended for patients undergoing retreatment and for those with meningoencephalitis, the second phase of treatment being extended to seven months in the latter. Patients in whom those treatments failed were treated with a regimen of streptomycin, pyrazinamide, ethambutol, and ethionamide for three months, followed by ethambutol and ethionamide for nine months. In the 1980s and 1990s, there were occasional changes in the treatment employed in cases of treatment-resistant tuberculosis. Ethambutol was not added to the basic treatment regimen to be used in the treatment induction phase (for patients ≥ 10 years of age) until 2009, the same year in which the use of fixed-dose combination tablets was introduced.[39]

The results of the present study show that there have been slight reductions in the rates of incidence, prevalence, and mortality associated with tuberculosis in Brazil. Those reductions might be related, in part, to the introduction of ethambutol and of the fixed-dose combination tablets, which could have increased patient adherence to treatment by reducing the risk of forgetfulness.[40]

The Brazilian NMH should encourage tuberculosis researchers to assess factors related to the degree of decentralization and the causes of noncompliance with NTCP recommendations, as well as differences in the reasons for and frequency of hospitalizations for tuberculosis, together with the mean length of hospital stays, hospitalization costs, and in-hospital mortality, in order to obtain a better understanding of the regional differences in the country. We recommend a partnership between the NMH and universities or research groups investigating tuberculosis, in order to increase the validity of the studies. We anticipate that such studies will identify specific measures to improve tuberculosis control in Brazil.

Despite all being part of the same country, the five regions of Brazil present distinct tuberculosis scenarios. Regional differences may have contributed to difficulties in controlling the disease in the country and to the failure to reach the MDG for tuberculosis-related mortality. Such differences should be taken into consideration in order to adapt tuberculosis control measures to those distinct scenarios. Some variables influencing the dynamics of tuberculosis are intrinsic and difficult to circumvent, whereas others, such as the performance indicators of the activities proposed by the NTCP and implemented at PHC clinics, can and should be modified.

Investigations aimed at explaining operational differences in NTCPs may contribute to improving the tuberculosis situation nationwide, although the need to improve the performance of health care facilities in the clinical management of tuberculosis is already evident. In large countries such as Brazil, where there are contrasting socioeconomic, climatic, and health care conditions, there is also a need for a stratified analysis of similar variables to determine compliance with tuberculosis control measures and action plans.

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AUTHOR CONTRIBUTIONS

AOC: collection/analysis/interpretation of data, drafting of the manuscript, and approval of the final version; ACM: study conception/design, analysis/interpretation of data, drafting/revision of the manuscript, and approval of the final version; LON: data collection, interpretation of climatic data, and approval of the final version; KAR: interpretation of data, drafting of the manuscript, and approval of the final version; PC: analysis/interpretation of data and drafting/revision of the manuscript, and approval of the final version.

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Performance of the quantification of adenosine deaminase and determination of the lactate dehydrogenase/adenosine deaminase ratio for the diagnosis of pleural tuberculosis in children and adolescents

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ABSTRACT

Objective: To evaluate the accuracy of determining the adenosine deaminase (ADA) level, the 2'-deoxyadenosine/ADA ratio, and the LDH/ADA ratio in pleural fluid for the diagnosis of pleural tuberculosis (PT) in children and adolescents. **Methods:** This was a retrospective cross-sectional study conducted at a tertiary hospital in a high-tuberculosis-incidence area, between 2001 and 2018. All patients with ADA in pleural fluid and a confirmed diagnosis of PT (cPT) or parapneumonic effusion (PPE) were included. **Results:** The cPT and PPE groups comprised 25 and 68 individuals, respectively. At a cutoff of 40 U/L, ADA measurement showed the following: sensitivity, 88%; specificity, 31%; positive predictive value (PPV), 32%; negative predictive value (NPV), 88%; and overall accuracy, 46%. The best cutoffs were an ADA level of 125 U/L, a 2'-deoxyadenosine/ADA ratio of 0.5, and an LDH/ADA ratio of 8.3, with AUC of 0.67, 0.75, and 0.82, respectively. The sensitivity, specificity, PPV, NPV, and overall accuracy of the 125 U/L ADA cutoff were 84%, 65%, 47%, 92%, and 70%, respectively, compared with 79%, 79%, 59%, 91%, and 79%, respectively, for the 8.3 LDH/ADA ratio cutoff. Changing the LDH/ADA ratio cutoff to 3.0 increased the specificity to 98%. **Conclusions:** The ADA level and the 2'-deoxyadenosine/ADA ratio are not good biomarkers for the diagnosis of PT in pediatric patients. Determination of the LDH/ADA ratio provides the best overall accuracy for the diagnosis of PT in such patients.

Keywords: Adenosine deaminase; Pleural effusion; Tuberculosis, pleural/diagnosis; Child; Adolescent.

INTRODUCTION

Tuberculosis is a disease caused by infection with *Mycobacterium tuberculosis*.[1] Despite the success of pharmacotherapy over the past seven decades, tuberculosis is the leading cause of death from infectious disease worldwide.[2] Brazil is on the list of the 30 countries with the highest tuberculosis burdens.[1] In 2017, the incidence of tuberculosis in the city of Porto Alegre, capital of the southern Brazilian state of Rio Grande do Sul, was 90 cases per 100,000 population.[3]

Severe manifestations of tuberculosis are more common in the pediatric age group. Extrapulmonary tuberculosis occurs in approximately 20% of childhood cases of tuberculosis.[1] Studies conducted in low- and middle-income countries have found pleural tuberculosis (PT) to be the most common type of extrapulmonary tuberculosis among children and adolescents.[4-6]

A definitive diagnosis of PT is made via the identification of *M. tuberculosis* bacilli in sputum, pleural fluid, or pleural biopsy specimens.[7] It is difficult to diagnose tuberculosis in pediatric patients, and the use of diagnostic strategies that were developed for adults can result in many pediatric cases being missed.[8] The analysis of gastric aspirate and sputum samples reportedly has a low diagnostic yield[9]: 40-50% and 20-30%, respectively. Therefore, the diagnosis of PT in pediatric patients is usually based on a history of contact with an adult with pulmonary tuberculosis, together with clinical findings suggestive of the diagnosis, a positive reaction on a tuberculin skin test (TST), and pleural fluid analysis (showing unilateral exudative pleural effusion [PE] with a predominance of lymphocytes, as well as high protein content). Children with PT typically present with a low number of bacilli. Therefore, microscopy of pleural fluid samples rarely identifies AFB, and cultures are often negative. Although pleural biopsy offers a better sensitivity profile, it is invasive and not feasible in some settings.[9,10] Consequently, the quantification of pleural fluid biomarkers has become an attractive alternative to pleural biopsy.[11]

The analysis of adenosine deaminase (ADA) in pleural fluid, using a cutoff of 40 U/L, has been shown to

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have high sensitivity and specificity (89-99% and 88-99%, respectively) for the diagnosis of PT in adults. In children and adolescents, the differential diagnosis of elevated ADA activity is usually between PT and empyema, because other causes are rare in that population. The few studies involving pediatric patients have shown that the measurement of ADA is not very accurate in such patients.[12,13] In addition, measuring the activity of the ADA isoenzymes ADA1 and ADA2 could be valuable in cases of suspected false-negative or false-positive results.[10] Local anecdotal observations have suggested that the level of LDH in pleural fluid is generally lower in PT than in other types of inflammatory PE in which ADA is elevated, and that the assessment of this relationship has diagnostic utility.[14]

The aim of this study was to evaluate the determination of the ADA level, ADA isoenzyme levels, and the LDH/ADA ratio in pleural fluid as parameters to discriminate between tuberculous PE and parapneumonic effusion (PPE) in children and adolescents. We hypothesized that the determination of ADA isoenzyme levels and the LDH/ADA ratio would have greater accuracy for the diagnosis of PT than would the quantification of ADA.

METHODS

This was a retrospective cross-sectional study of all individuals ≤ 18 years of age for whom ADA levels were measured in pleural fluid samples at the Porto Alegre *Hospital de Clínicas*, a tertiary university hospital in the city of Porto Alegre, Brazil, between January of 2001 and June of 2018. Eligible participants were identified by reviewing the electronic medical records.

The study population consisted of two subgroups: patients with a confirmed diagnosis of PT; and patients diagnosed with PPE. Individuals with transudative effusion, as defined by Light's criteria,[15] were excluded, as were those with malignant PE, rheumatologic diseases, probable tuberculous PE, or PE of unknown etiology.

The etiology of PE was defined as follows:

- Confirmed PT (cPT)—*M. tuberculosis* identified by culture, PCR, or smear microscopy (Ziehl-Neelsen staining) of pleural fluid, pleural biopsy, sputum, BAL fluid, or gastric lavage fluid samples; or pleural biopsy sample showing a granuloma, with or without necrosis, and a clinical picture suggestive of PT
- Probable PT—clinical diagnosis of tuberculosis and good clinical response to treatment with antituberculosis drugs
- PPE—exudative PE associated with an infection in the pulmonary parenchyma related to any pathogen except *M. tuberculosis*, as well as the absence of an alternative cause identified over the clinical course
- Empyema—purulent PE, as evidenced by the macroscopic presence of pus, or a positive gram stain result or culture result in pleural fluid
- PE of unknown etiology—no clinical or pathological diagnosis determined from the medical record
- Malignant PE—positive pleural fluid cytology, positive pleural tissue histology, or confirmed malignancy at another site with radiological evidence of metastatic thoracic involvement

During the study period, LDH was analyzed by photometry; ADA was determined by the colorimetric method described by Giusti and Galanti[16]; and ADA isoenzyme activity was quantified by calculating the 2'-deoxyadenosine/ADA ratio.[17] Laboratory personnel were not blinded to patient clinical data, because the tests were ordered according to the treatment routine. In this context, it is mandatory for the attending physician to state why a specific examination is important for the investigation of the case.

The following clinical and biochemical data were retrieved from electronic medical records: in pleural fluid samples—pH, total protein, glucose, LDH, total leukocyte count with differential cytology, malignant cell screening result, ADA, 2'-deoxyadenosine/ADA ratio, LDH/ADA ratio, PCR result for *M. tuberculosis*, smear microscopy result, and the result of culture for aerobic bacteria and *M. tuberculosis*; in pleural biopsy samples—histopathological examination finding and results of smear microscopy/culture for *M. tuberculosis*; and other—TST result, as well as smear microscopy, culture (for *M. tuberculosis*), and PCR (for *M. tuberculosis*) results in gastric lavage fluid, sputum, and BAL fluid samples.

Statistical analyses were performed with the IBM SPSS Statistics software package, version 23.0 (IBM Corporation, Armonk, NY, USA). Categorical variables are expressed as absolute and relative frequencies. Continuous variables are expressed as median and interquartile range if their distribution was non-normal, and continuous variables with symmetric distribution, as mean and standard deviation or 95% confidence interval if their distribution was normal. The Kolmogorov-Smirnov test was used in order to determine whether the variables were normally distributed. The chi-square test was applied in order to compare categorical variables, and the Mann-Whitney test was used in order to detect significant differences between medians, whereas independent two-sample t-test was used in order to detect significant differences between means.

The performance of the determination of the ADA level, the LDH/ADA ratio, and the 2'-deoxyadenosine/ADA ratio in differentiating cPT from PPE was assessed by constructing ROC curves. We used the MedCalc statistical package, version 19.2.6 (MedCalc, Mariakerke, Belgium) to estimate the sample size. For an alpha level of 0.05, with a power of 90%, three times as many negative cases as positive cases, and a target AUC of 0.8 for the LDH/ADA ratio, significantly different from the null hypothesis value (0.5), the required sample sizes in the positive (cPT) group and the negative (PPE) group were 12 and 36, respectively. The best cutoff points were determined by calculating the Youden index. The

following test characteristics were calculated: overall accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). In the analysis of the accuracy of determining the 2′-deoxyadenosine/ADA and LDH/ADA ratios, we excluded patients for whom there were missing data.

The correlation between ADA level and age was determined by Spearman's correlation coefficient (r), which was classified as weak (r ≤ 0.3), moderate (r = 0.4-0.6), or strong (r > 0.6). Values of p ≤ 0.05 were considered statistically significant.

This study was approved by the Research Ethics Committee of the Porto Alegre *Hospital de Clínicas* (Reference no. 19814619.8.0000.5327). Because of the retrospective nature of the study, the requirement for written informed consent was waived.

RESULTS

We identified 131 patients for whom data regarding ADA levels were available. Of those 131 patients, 38 (29%) were excluded for the following reasons: having PE of unknown etiology (n = 18); having probable PT (n = 10); having malignant PE (n = 2); and having transudative PE (n = 7). One case (from the PPE group) was excluded due to an abnormally high ADA level (771 U/L), which was considered a laboratory error. Therefore, we reviewed data for a total of 93 patients (25 with cPT and 68 with PPE). Of the 25 patients in the cPT group, 1 (4.0%) was HIV-infected, as were 2 (2.9%) of the 68 patients in the PPE group. Other significant comorbidities among the patients in the PPE group were neoplastic disease (n = 5), sickle cell disease (n = 3), Down syndrome (n = 2), cystic fibrosis (n = 1), Fanconi anemia (n = 1), mitochondrial disease (n = 1), and congenital disorder of glycosylation (n = 1). The criteria for a clinical diagnosis of tuberculosis included fever (observed in all of the patients), cough (in 78%), chest pain (in 82%), dyspnea (in 43%), night sweats (in 8%), weight loss (in 17%), and hemoptysis (in none). Table 1 shows the main characteristics of each group. The methods used in order to confirm the diagnosis of PT are shown in Table 2. The PE was classified as empyema in 9 (13.2%) of the patients in the PPE group. The pleural fluid was cultured in 66 (97.1%) of the PPE group patients, and bacterial growth was detected in only 9 (13.6%), as follows: *Streptococcus pneumoniae* (n = 4); *Staphylococcus aureus* (n = 2); *Haemophilus* sp. (n = 1); *Stenotrophomonas maltophilia* (n = 1); and *Enterobacter* sp. (n = 1).

When we applied the most widely used ADA cutoff (40 U/L), we found the following in relation to its ability to diagnose PT: sensitivity of 88% (95% CI: 69-98); specificity of 31% (95% CI: 20-43); PPV of 32% (95% CI: 27-37); NPV of 88% (95% CI: 70-96); and overall accuracy of 46% (95% CI: 36-57). Because empyema is known to result in elevated ADA levels, which could worsen the diagnostic performance of their measurement, the analysis was repeated after the exclusion of cases of purulent PE. At the 40 U/L cutoff, the sensitivity, specificity, PPV, NPV, and overall accuracy were 88% (95% CI: 69-98), 36% (95% CI: 24-49), 37% (95% CI: 31-42), 88% (95% CI: 70-96), and 51% (95% CI: 40-62), respectively.

As shown in Figure 1, the ROC curve analysis of the determination of the ADA level, 2′-deoxyadenosine/ADA ratio, and LDH/ADA ratio showed that the best cutoffs, respectively, were as follows: 125 U/L (AUC = 0.67; 95% CI: 0.57-0.77; p = 0.003), 0.5 (AUC = 0.75; 95% CI: 0.62-0.85; p = 0.0001), and 8.3 (AUC = 0.82; 95% CI: 0.73-0.90; p < 0.0001). The characteristics of the tests at their best cutoffs are displayed in Table 3. After purulent PE had been excluded from the analysis, the best ADA cutoff (125 U/L) showed a slightly better diagnostic performance,

Table 1. Characteristics of the patients and of the pleural fluid samples.

Variable	PPE (n = 68)	cPT (n = 25)	p
Male patients, n (%)	44 (64.8)	12 (48.0)	0.22*
Patient age (years); median (IQR)	5.4 (2.4-13.9)	13.4 (7.4-14.7)	0.02†
TST induration ≥ 10 mm, n (%)[a]	1 (8.3)	11 (73.3)	<0.001*
pH, median (IQR)[b]	7.30 (7.11-7.42)	7.34 (7.26-7.38)	0.72†
Glucose (mg/dL), mean ± SD[c]	68.2 ± 47.6	68.9 ± 26.2	0.93‡
Proteins (g/dL), mean ± SD[d]	4.3 ± 1.3	5.3 ± 0.8	< 0.01‡
≥ 50% mononuclear cells, n (%)[e]	2 (13.3)	11 (78.6)	< 0.01*
LDH, median (IQR)[f]	883.5 (407.8-6097.3)	679.5 (484.8-1193.8)	0.29‡
ADA (U/L), mean ± SD	117.6 ± 107.5	159.7 ± 66.3	0.03‡
LDH/ADA ratio, median (IQR)	22.8 (10.4-43.5)	4.9 (2.7-8.3)	< 0.01†
2′-deoxyadenosine/ADA ratio, mean ± SD[g]	0.51 ± 0.18	0.35 ± 0.08	< 0.01‡

PPE: parapneumonic effusion; cPT: confirmed pleural tuberculosis; TST: tuberculin skin test; and ADA: adenosine deaminase. [a]Data available for only 23 of the PPE group patients and only 15 of the cPT group patients. [b]Data available for only 46 of the PPE group patients and only 16 of the cPT group patients. [c]Data available for only 61 of the PPE group patients and only 24 of the cPT group patients. [d]Data available for only 63 of the PPE group patients and only 24 of the cPT group patients. [e]Data available for only 15 of the PPE group patients and only 14 of the cPT group patients. [f]Data available for only 62 of the PPE group patients and only 24 of the cPT group patients. [g]Data available for only 40 of the PPE group patients and only 22 of the cPT group patients. *Chi-square test. †Mann-Whitney test. ‡t-test.

Table 2. Laboratory methods used in order to confirm the diagnosis of tuberculous pleural effusion (n = 25).

Method	Sample type	n (%)
Smear microscopy	Gastric lavage fluid	1 (4.0)
Culture	Pleural fluid	10 (40.0)
Culture	Gastric lavage fluid	2 (8.0)
Culture	BAL fluid	1 (4.0)
Culture	Pleural biopsy	6 (24.0)
PCR	Pleural fluid	2 (8.0)
PCR	BAL fluid	1 (4.0)
Histopathology	Pleural biopsy	5 (20.0)

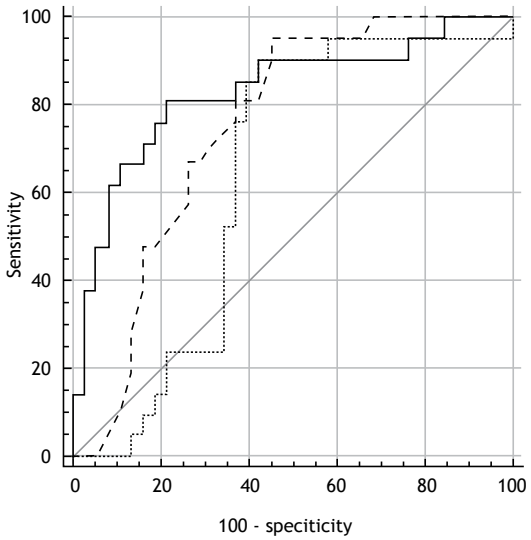

Figure 1. ROC curve analysis of the determination of the adenosine deaminase level (dotted line), the 2'-deoxyadenosine/adenosine deaminase ratio (dashed line), and the LDH/adenosine deaminase ratio (solid line) in pleural fluid samples.

with an AUC of 0.73, a sensitivity of 84%, and a specificity of 73%, whereas the performance of the best 2'-deoxyadenosine/ADA ratio cutoff (0.5) and the best LDH/ADA ratio cutoff (8.3) did not improve, with AUCs of 0.72 and 0.81, respectively.

Because biomarker-based, non-sputum diagnostic tuberculosis tests should have high specificity (≥ 98%), with no minimum target sensitivity,[18] we performed an additional analysis of determination of the LDH/ADA ratio at a cutoff of 3.0, which was found to have a sensitivity of 33% (95% CI: 16-55), a specificity of 98% (95% CI: 91-100), a PPV of 89% (95% CI: 51-98), an NPV of 79% (95% CI: 74-84), and an overall accuracy of 80% (95% CI: 70-88). In contrast, a change in the cutoff did not improve the specificity of ADA measurement. Finally, we found an inverse correlation between age and the level of ADA in pleural fluid ($r = -0.24$; $p = 0.02$).

DISCUSSION

The main results of this study suggest that determination of the ADA level and of the 2'-deoxyadenosine/ADA ratio in pleural fluid samples are not sufficiently accurate to be useful in the diagnosis of PT in children and adolescents. However, determination of the LDH/ADA ratio was found to have good accuracy for discriminating between tuberculous PE and PPE, especially when the cutoff was adjusted to favor specificity.

It is well established that measuring ADA in pleural fluid (with a cutoff of 40 U/L) performs well in the detection of PT in adults, with sensitivity and specificity values above 86%, as well as predictive values above 88%.[1,9,19] However, many studies in adults have included patients with transudative PE, and have not excluded patients with a probable diagnosis of tuberculosis.[19] That could explain the fact that, in our study sample, ADA measurement performed poorly, even after the cutoff was adjusted to 125 U/L, according to the Youden index. Another potential explanation for that fact is that we excluded patients with malignant PE, given that ADA levels are known to be considerably lower in patients with malignant PE than in those with tuberculous PE.[20,21]

Wu et al.[13] suggested that the quantification of ADA in pleural fluid is not an accurate method for the diagnosis of PT in pediatric patients. However, their study sample included patients with a probable diagnosis of tuberculosis. In addition, the authors did not provide data on the sensitivity, specificity, PPV, or NPV of the test.[13] In contrast, Mishra et al.[12] demonstrated that the accuracy of ADA quantification in pleural fluid is greater in patients with confirmed PT than in those with probable PT (85% vs. 75%), although their confirmed PT group comprised only 8 individuals.

Researchers and clinicians have emphasized the need for additional tests for the diagnosis of tuberculosis, especially for patients in whom the disease can be difficult to diagnose (such as children). The WHO recommends that new diagnostic tests for tuberculosis in pediatric patients have a minimum specificity of 98%, as well as recommending target sensitivity and specificity values of 90% and 70%, respectively, for screening tests.[22] In the present study, determination of the LDH/ADA ratio was the test that produced the best results, being particularly useful for excluding a diagnosis of PT, for which it was found to have an NPV of 91% and a sensitivity of 79% when a cutoff of 8.3 was used, as well as a specificity of 98% when a cutoff of 3.0 was used. In agreement with our findings, two retrospective studies showed that LDH/ADA ratios

Table 3. Characteristics of the tests and their best cutoffs, as determined by calculating the Youden index.

Parameter tested	Cutoff	AUC (95% CI)	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	Accuracy % (95% CI)
ADA (U/L)	> 125	0.67 (0.57-0.77)	84 (64-95)	65 (52-76)	47 (38-56)	92 (82-97)	70 (60-79)
2′-deoxyadenosine/ ADA ratio	≤ 0.5	0.75 (0.62-0.85)	95 (77-100)	50 (34-66)	51 (43-59)	95 (74-99)	66 (53-78)
LDH/ADA ratio	≤ 8.3	0.82 (0.73-0.90)	79 (58-93)	79 (67-88)	59 (46-71)	91 (82-96)	79 (69-87)

PPV: positive predictive value; NPV: negative predictive value; and ADA: adenosine deaminase.

were significantly lower in adults with PT than in those with PE of other etiologies.[14,23]

Other authors have reported an inverse correlation between age and the ADA level in pleural fluid.[20,24] On the basis of those data, it has been hypothesized that a higher cutoff would be needed in order to improve the diagnostic accuracy of ADA in pediatric patients. Similarly, in our study sample, we found that the ADA level in pleural fluid decreased significantly in parallel with increasing age. However, the correlation was weak, which indicates that this variation is not large enough to influence the interpretation of the test or to explain the fact that the phenomenon was observed only when the highest cutoff was used.

Our study has some limitations. The retrospective nature of the study and the small sample size resulted in wide confidence intervals. Although tuberculosis is quite prevalent in the region in which our study was conducted, PT is less common. According to the official epidemiological surveillance system for the city of Porto Alegre,[25] there were 352 cases of PT in subjects < 19 years of age in the city between 2001 and 2018. Only 24 (6.8%) of those cases were laboratory-confirmed. It should be borne in mind that our sample was restricted to individuals for whom ADA values were available and in whom the diagnosis of PT had been confirmed by extensive microbiological testing. Therefore, some patients who were classified as having PT in the surveillance system could not be included in our study. We understand the intrinsic limitation imposed by the retrospective nature of the study. However, given that PT requiring hospitalization is an uncommon event in pediatric patients, a prospective design would have entailed a very long follow-up period and still might not have resulted in an adequate number of patients for the analysis of accuracy. In addition, because our study encompassed a period of 17 years, there may be concern about the variability of the diagnostic methods used. In fact, there was no variation in the method of ADA assessment, which was the main outcome measure of the study. As for the analysis of LDH, there was variability in the equipment used (a Roche Cobas analyzer was replaced by a Siemens Advia analyzer, the latter being used for four years), although not in the method of analysis (ultraviolet spectrophotometry). Therefore, there was no difference in the interpretation of the results. Another limitation is that only a small number of patients underwent TST and cytological analysis of the pleural fluid. Consequently, it was not possible to study the accuracy of ADA measurement in a subgroup of patients with positive TST results and lymphocyte-predominant pleural fluid. In addition, we did not have a representative sample of HIV-infected patients.

Our study also has some strengths, such as the careful selection of the cPT group, in which we included only patients in whom the diagnosis had been confirmed by extensive microbiological testing of a variety of biological samples (sputum, gastric lavage fluid, pleural fluid, BAL fluid, and pleural biopsy).[18] In addition, we emphasize the original aspect of the study with regard to diagnostic methods not previously employed in pediatrics, such as the analysis of the LDH/ADA and 2′-deoxyadenosine/ADA ratios.

We are aware that our results do not represent the final word on this subject. Instead, we think that its importance lies in the fact that it raises new questions regarding the interpretation of ADA levels in the diagnosis of PT in pediatric patients, especially because there have been few studies on this subject in such patients. We believe that our findings will encourage the development of prospective studies, with larger patient samples, aimed at assessing the reproducibility of our findings in other populations.

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AUTHOR CONTRIBUTIONS

JLV: data curation; investigation; validation; visualization; drafting and revision of the preliminary and final versions; and approval of the final version. LF: data curation; formal analysis; investigation; validation; visualization; drafting and revision of the preliminary and final versions; and approval of the final version. ICSF: data curation; investigation; sourcing; validation; visualization; drafting and revision of the preliminary and final versions; and approval of the final version. VCBGC: conceptualization; data curation; formal analysis; investigation; methodology; project administration; sourcing; supervision; validation; visualization; drafting and revision of the preliminary and final versions; and approval of the final version.

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Effect of coexisting advanced extrapulmonary solid cancer on progression of *Mycobacterium avium* complex lung disease

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ABSTRACT

Objective: Although *Mycobacterium avium* complex (MAC) lung disease has been shown to be associated with lung cancer and hematologic malignancies, there have been few studies of its relationships with other types of cancer. The aim of this study was to assess the effect that coexisting advanced extrapulmonary solid tumors have on the progression of MAC lung disease. **Methods:** This was a retrospective study of patients diagnosed with MAC lung disease, on the basis of the American Thoracic Society (ATS) criteria, between October of 2005 and March of 2019. The patients were divided into three groups: those with advanced-stage cancer (A-SC group); those with early-stage cancer (E-SC group); and those without cancer (control group). Progression of MAC lung disease was defined as exacerbation seen on imaging. Patient characteristics and the time to progression were compared among the three groups. **Results:** A total of 286 patients met the ATS diagnostic criteria for MAC lung disease, and 128 of those were excluded. Of the remaining 158 patients, 20 (7.0%) were in the A-SC group, 36 (12.6%) were in the E-SC group, and 102 (35.7%) were in the control group. The median time to progression in the A-SC, E-SC, and control groups was 432, 3,595, and 2,829 days, respectively ($p < 0.01$). A proportional hazards model showed that the significant predictors of MAC lung disease progression were advanced-stage cancer (hazard ratio [HR] = 6.096; 95% CI: 2.688-13.826; $p < 0.01$), cavitary lesions (HR = 2.750; 95% CI: 1.306-5.791; $p < 0.01$), and a high Nodule-Infiltration-Cavity-Ectasis score (HR = 1.046; 95% CI: 1.004-1.091; $p = 0.033$). **Conclusions:** A coexisting advanced extrapulmonary solid tumor could hasten the progression of MAC lung disease.

Keywords: Nontuberculous mycobacteria; Mycobacterium avium complex; Neoplasms; Radiography.

INTRODUCTION

The prevalence of lung disease caused by nontuberculous mycobacteria (NTM) is increasing worldwide,[1-4] and *Mycobacterium avium* complex (MAC) lung disease is the most common type.[5-8] However, advances in treatment have improved the prognosis of patients with malignant tumors.[9,10] Although NTM lung disease has been associated with lung cancer and hematologic malignancies,[11-15] there have been few studies of its relationships with other cancers. Therefore, we decided to investigate the relationships that MAC lung disease has with malignancies other than lung cancer and hematologic malignancies. The specific objective of this study was to assess the effect that a coexisting advanced extrapulmonary solid tumor has on the progression of MAC lung disease.

METHODS

This was a retrospective study of patients who underwent AFB testing between October of 2005 and March of 2019 at Yokohama City University Hospital and Yokohama City University Medical Center. We selected patients meeting the American Thoracic Society (ATS) diagnostic criteria for NTM lung disease.[16] We further selected only those with MAC lung disease (caused by infection with *M. avium* or *M. intracellulare*), with or without cancer. The patients who had been diagnosed with cancer after being diagnosed with MAC lung disease were excluded, as were those with lung cancer or hematologic malignancies. The patients with a pre-existing diagnosis of an extrapulmonary solid malignant tumor were divided into two groups: those with advanced-stage cancer and those with early-stage cancer. The advanced-stage cancer group included those having no indication for curative treatment, including surgery and radiation therapy. The early-stage cancer group consisted of those who could be treated curatively. Separate from the advanced-stage cancer group and the early-stage cancer group, we evaluated a control group of patients with MAC lung disease who had no history of cancer or complications. Specifically, patients with chronic respiratory diseases, autoimmune diseases, or diseases that can affect the immune system were excluded.

The groups were compared in terms of baseline patient characteristics such as age; gender; smoking status;

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number of lung segments involved; the *Mycobacterium* species involved; symptoms; AFB smear status; cavitary disease; the Nodule-Infiltration-Cavity-Ectasis (NICE) score[17]; and the history of chemotherapy (defined as having receiving cytotoxic chemotherapy before the diagnosis of MAC lung disease). To assess disease progression, each lung was divided into three segments (upper lobe, middle lobe, and lower lobe for the right lung; and superior segment, lingular segment, and lower lobe for the left lung), and the lesion sites were counted. The lesions counted were recorded as the number of lung segments involved. Lesions were defined as nodules, cavities, or bronchiectasis with multiple small nodules and were assessed by chest CT.

The NICE scoring system was used as another method of image evaluation.[17] The system is used in order to score the extent and contents of NTM lung disease on chest X-rays. In brief, the left and right lungs were each divided into three zones, for a total of six zones. The left and right lungs were divided into the part above the carina, the part between the carina and the lower pulmonary vein, and the part below the lower pulmonary vein. In each zone, each of the four items (N, nodule; I, infiltration; C, cavity; E, ectasis) was assigned a score of 0 if there were no abnormal findings, 1 if there was involvement of < 25% of the zone, 2 if there was involvement of 25-50% of the zone, 3 if there was involvement of 50-75% of the zone, or 4 if there was involvement of > 75% of the zone. Therefore, the maximum score was 96 points (4 points for each of four items in each of six zones).

The main outcome measure was the progression of MAC lung disease, defined as progressively increasing nodules, infiltration, cavities, or bronchiectasis on follow-up chest X-rays,[18,19] as judged by two pulmonologists. Factors that could be predictors of that outcome were identified and analyzed.

The study was approved by the institutional review boards of Yokohama City University Graduate School of Medicine (Reference no. B171200032) and Yokohama City University Medical Center (Reference no. B190300054). The requirement for written informed consent was waived because of the retrospective nature of this study.

Statistical analysis

The times to progression in the advanced-stage cancer, early-stage cancer, and control groups were compared by using Kaplan-Meier curves. A time-to-event model was chosen on the basis of previous studies.[20,21] Multivariate analysis was performed to assess the effect that a coexisting advanced extrapulmonary solid tumor had on the progression of MAC lung disease. Variables were extracted through stepwise regression analysis, and a proportional hazards model was used for the extracted variables. The stepwise regression analysis included the following variables: advanced-stage cancer, early-stage cancer, age, gender, smoking status; number of lung segments involved; the *Mycobacterium* species involved; symptoms; AFB smear status; cavitary disease; NICE score; and history of chemotherapy. By using the proportional hazards model for those variables, with progression of MAC lung disease as the outcome, we were able to identify and analyze the factors that could be predictors of that progression.

Data are presented as mean ± standard deviation or as median (range) values. All statistical analyses were performed with the JMP statistical software package, version 15 (SAS Institute Inc., Cary, NC, USA). Continuous variables were compared with the t-test or the Mann-Whitney U test. Comparisons were made with Pearson's chi-square test or Fisher's exact test for nominal variables. Values of $p < 0.05$ were considered statistically significant, and all tests were two-tailed. Predictors of the progression of MAC lung disease were determined by stepwise regression analysis based on the Akaike information criterion and a proportional hazards model. Kaplan-Meier curves were used in order to compare the time to progression of MAC lung disease by group. A log-rank test was used in order to compare the time to progression of MAC lung disease among the groups.

RESULTS

Figure 1 shows the patient selection process. A total of 286 patients met the ATS criteria, of whom 83 were diagnosed with cancer prior to being diagnosed with MAC lung disease. Of the 83 eligible patients with cancer, 27 had lung cancer or a hematologic malignancy and were therefore excluded. Thus, we included 56 patients with a pre-existing diagnosis of an extrapulmonary solid malignant tumor. Of those 56 patients, 20 were assigned to the advanced-stage cancer group, and 36 were assigned to the early-stage cancer group. A total of 197 patients had no cancer, although 95 of those had a chronic respiratory disease or a disease that could lead to impaired immune function and were excluded. Therefore, the group of patients without complications (the control group) comprised 102 patients.

Table 1 shows the characteristics of the patients. Of the 20 patients in the advanced-stage cancer group, 10 (50.0%) were female, compared with 24 (66.7%) of the 36 patients in the early-stage cancer group and 79 (77.5%) of the 102 patients in the control group, and the difference between the advanced-stage cancer group and the control group was significant ($p = 0.042$). The mean age was significantly higher in the advanced-stage cancer group than in the control group (74.8 ± 7.9 vs. 66.3 ± 11.8 years; $p < 0.01$). In addition, the proportion of never smokers was lower in the advanced-stage cancer group than in the control group (65.0% vs. 81.3%; $p = 0.045$). Furthermore, the mean NICE score at the time of MAC lung disease diagnosis was higher in the advanced-stage cancer group than in the control group (14.8 ± 8.1 vs. 10.2 ± 7.2; $p = 0.013$).

Figure 2 shows the Kaplan-Meier curves for the comparison among the three groups in terms of the

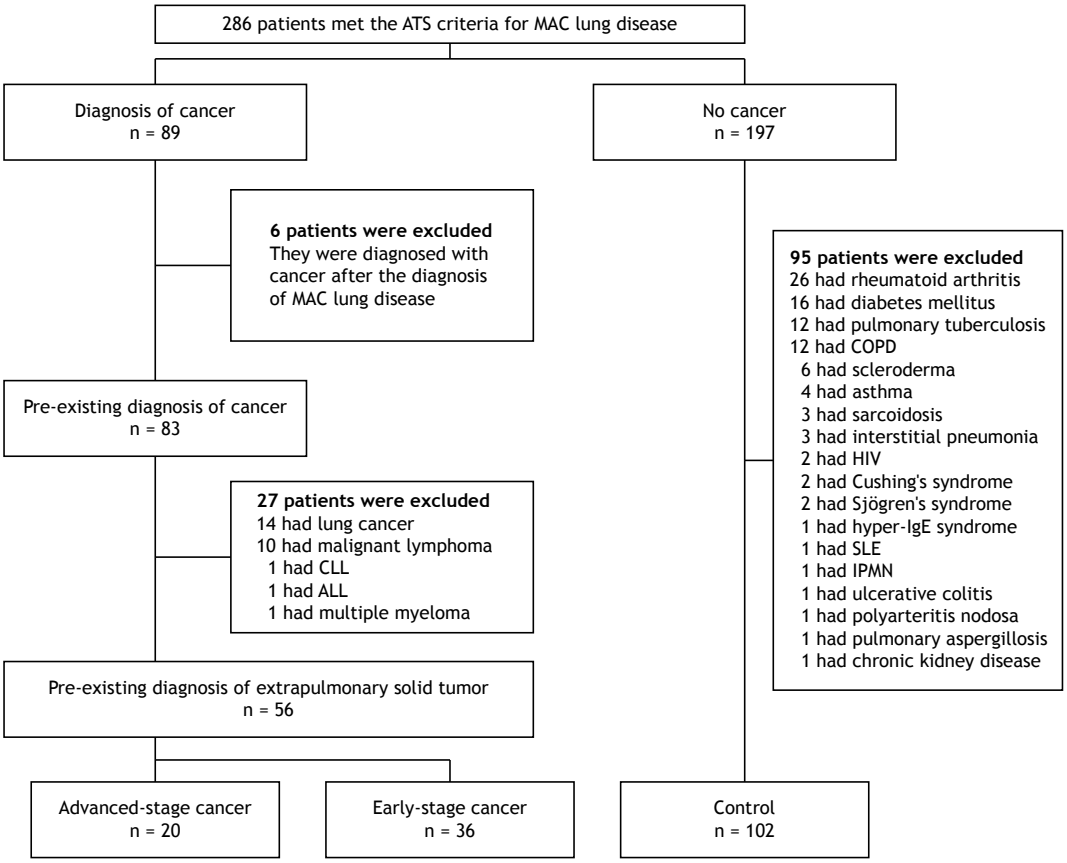

Figure 1. Flow chart of the process of selecting patients with *Mycobacterium avium* complex (MAC) lung disease. ATS: American Thoracic Society; CLL: chronic lymphocytic leukemia; ALL: acute lymphocytic leukemia; SLE: systemic lupus erythematosus; and IPMN: intraductal papillary mucinous neoplasm.

time to progression of MAC lung disease. The median time to progression in the advanced-stage cancer group, early-stage cancer group, and control group was 432, 3,595, and 2,829 days, respectively ($p < 0.01$). In the final analysis, progression of MAC lung disease was seen in 9 (45.0%), 11 (30.6%), and 30 (29.4%) of the patients in the advanced-stage cancer, early-stage cancer, and control groups, respectively. The proportional hazards model with stepwise regression showed that the following were significant predictors of MAC lung disease progression (Table 2): advanced-stage cancer (hazard ratio [HR] = 6.096; 95% CI: 2.688-13.826; $p < 0.01$); cavitary disease (HR = 2.750; 95% CI: 1.306-5.791; $p < 0.01$); and the NICE score (HR = 1.046; 95% CI: 1.004-1.091; $p = 0.033$).

DISCUSSION

The results of the present study suggest that a coexisting advanced extrapulmonary solid tumor can hasten the progression of MAC lung disease. In addition, severely abnormal radiological imaging patterns at the diagnosis of MAC lung disease also seemed to be related to progression.

The incidence of cancer has been shown to be higher at advanced ages and in men.[22] In addition, smoking is thought to be associated with an increased risk of developing not only lung cancer. but also other types of cancer.[23,24] That might explain the fact that the proportions of men and former or current smokers, as well as the mean age, were higher in the advanced-stage cancer group than in the control group. In a search of the literature, we found no clear evidence of an association between chest X-ray severity at the time of MAC lung disease diagnosis and advanced-stage cancer. However, in the present study, the NICE scores were higher in the advanced-stage cancer group patients. That suggests that MAC lung disease can be more severe in patients with an advanced extrapulmonary solid tumor, although further studies are needed in order to test that hypothesis.

In the present study, a coexisting advanced extrapulmonary solid tumor seemed to hasten the progression of MAC lung disease. Previous studies have suggested that a low BMI and the presence of autoimmune diseases can also accelerate the progression of MAC lung disease.[18,25] Coexisting solid tumors, including lung cancer, have also been shown to increase the probability of tuberculosis reactivation.[26] Exposure to chemotherapy has also been shown to accelerate the progression of tuberculosis.[26,27] In

Table 1. Characteristics of patients with *Mycobacterium avium* complex lung disease, by group.[a]

Characteristic	Group			p*
	A-SC (n = 20)	E-SC (n = 36)	Control (n = 102)	
Gender (male/female)	10/10	12/24	23/79	0.042
Age (years)	74.8 ± 7.9	72.1 ± 8.8	66.3 ± 11.8	< 0.01
Smoking status (current/former/never)	0/7/13	1/14/21	0/18/78[†]	0.045
Species[b]	14/6	29/7	92/10	0.055
Symptomatic	9 (45.0)	13 (36.1)	44 (43.1)[‡]	0.642
AFB smear-positive status	13 (65.0)	20 (55.6)	54 (52.9)	0.605
Number of lung segments involved	3 [2-6]	4 [1-6]	4 [1-6]	0.099
NICE score	14.8 ± 8.1	9.9 ± 7.9	10.2 ± 7.2	0.013
Cavitary lesions	6 (30.0)	14 (38.9)	19 (18.6)	0.051
Chemotherapy[c]	7 (35.0)	1 (2.8)	0 (0.0)	< 0.01
Type of cancer[d]				
Gastrointestinal	7 (35.0)	16 (44.4)		
Breast	2 (10.0)	10 (27.8)		
Urinary tract	5 (25.0)	6 (16.7)		
Liver, bile duct, and pancreatic	6 (30.0)			
Gynecologic	3 (15.0)	3 (8.3)		
Head and neck	4 (20.0)	3 (8.3)		
Thyroid		1 (2.8)		
Skin		1 (2.8)		

A-SC: advanced-stage cancer; E-SC: early-stage cancer; and NICE: Nodule-Infiltration-Cavity-Ectasis. [a]Data are presented as n, mean ± SD, median [range], or n (%). [b]*Mycobacterium avium* or *M. intracellulare*. [c]Cytotoxic chemotherapy. [d]In the advanced-stage cancer group, there were six patients who had a history of two or more types of cancer: one had prostate, gastric, and esophageal cancer; one had bladder and laryngeal cancer; one had breast and esophageal cancer; one had hepatocellular and uterine cancer; one had hepatocellular and laryngeal cancer; and one had pancreatic and prostate cancer. In the early-stage cancer group, there were four patients who had a history of two types of cancer: one had renal cell and bladder cancer; one had tongue and esophageal cancer; one had gastric and colorectal cancer; and one had gastric and esophageal cancer. *For the variables age, number of lung segments involved, and NICE score, the p-value represents a comparison between the advanced-stage cancer group and the control group. [†]n = 96. [‡]n = 98.

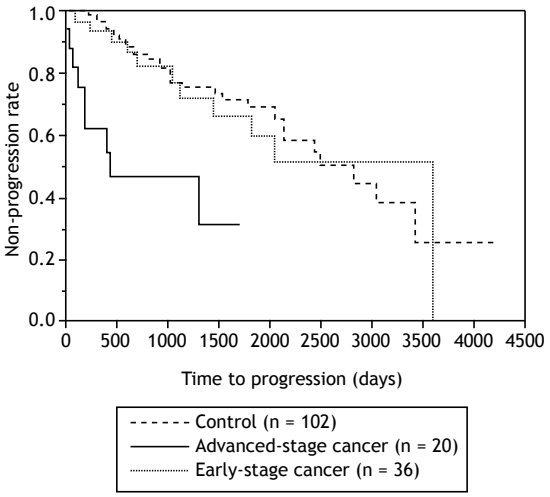

Figure 2. Comparison of the time to progression of *Mycobacterium avium* complex lung disease in each group.

addition, our findings suggest that cavitary lesions and high NICE scores at diagnosis of MAC lung disease favor progression. Previous studies have also shown that the presence of cavitary lesions leads to a worse prognosis in MAC lung disease,[28] as well as that high NICE scores are related to MAC lung disease progression.[18]

Our study has some limitations. First, not all medical records contained complete data regarding smoking status and symptoms. Therefore, the number of patients evaluated was not the same for every variable. In addition, the fact that some of the patients in the advanced-stage cancer group had complications other than the advanced extrapulmonary solid tumor might represent a selection bias. However, the decision was made to include them in order to maintain the statistical power. Furthermore, it was unclear why a coexisting advanced extrapulmonary solid tumor would accelerate the progression of MAC lung disease. Moreover, the small size of our sample of patients with advanced-stage cancer might explain our finding that cytotoxic chemotherapy had no significant influence on MAC lung disease progression. Nevertheless, future studies, including larger patient samples, might reveal such an association.

The reported five-year mortality rate for MAC lung disease exceeds 25%, and the presence of MAC lung disease may be related to an increase in the overall (all-cause) mortality rate and shorter life expectancy.[29,30] In addition, as seen in the present study, MAC lung

Table 2. Multivariate analysis using a proportional hazards model to identify predictors of *Mycobacterium avium* complex lung disease progression.

Variable	HR	95% CI	p
Advanced-stage cancer	6.096	2.688-13.826	< 0.01
Cavitary lesions	2.750	1.306-5.791	< 0.01
NICE score	1.046	1.004-1.091	0.033

HR: hazard ratio; and NICE: Nodule-Infiltration-Cavity-Ectasis.

disease progression may be accelerated by a coexisting advanced extrapulmonary solid tumor, and some patients with MAC lung disease deteriorate rapidly.[31,32] Because advances in treatment have improved the prognosis of patients with cancer year by year,[9,10] it may be necessary to address MAC lung disease that worsens during the treatment of an advanced extrapulmonary solid tumor. Clinicians should consider the possibility of MAC lung disease progression in patients with an advanced extrapulmonary solid tumor.

In conclusion, a coexisting advanced extrapulmonary solid tumor could hasten the progression of MAC lung disease. Therefore, clinicians should exercise caution in the treatment of patients with an advanced extrapulmonary solid tumor who also have MAC lung disease.

AUTHOR CONTRIBUTIONS

RI and KW: conception, administrative support, data collection, data analysis, writing/revision of the manuscript; YS: data collection and analysis; NH: conception and data collection; YH: conception and data analysis; NK and MK: administrative support; and TK: conception and data analysis.

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Diagnostic performance of the Xpert MTB/RIF assay in BAL fluid samples from patients under clinical suspicion of pulmonary tuberculosis: a tertiary care experience in a high-tuberculosis-burden area

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ABSTRACT

Objective: To assess the diagnostic performance of the Xpert MTB/RIF assay, a rapid molecular test for tuberculosis, comparing it with that of AFB staining and culture, in BAL fluid (BALF) samples from patients with clinically suspected pulmonary tuberculosis (PTB) who are sputum smear-negative or produce sputum samples of insufficient quantity. **Methods:** This was a retrospective study of 140 cases of suspected PTB in patients who were smear-negative or produced insufficient sputum samples and were evaluated at a tertiary teaching hospital in the city of Rio de Janeiro, Brazil. All of the patients underwent fiberoptic bronchoscopy with BAL. The BALF specimens were evaluated by AFB staining, mycobacterial culture, and the Xpert MTB/RIF assay. **Results:** Among the 140 patients, results for all three microbiological examinations were available for 73 (52.1%), of whom 22 tested positive on culture, 17 tested positive on AFB staining, and 20 tested positive on the Xpert MTB/RIF assay. The sensitivity, specificity, positive predictive value, negative predictive value, and overall accuracy for AFB staining were 68.1%, 96.1%, 88.2%, 87.5%, and 87.6%, respectively, compared with 81.8%, 96.1%, 90.0%, 92.4%, and 91.8%, respectively, for the Xpert MTB/RIF assay. The agreement between AFB staining and culture was 82.3% (kappa = 0.46; $p < 0.0001$), whereas that between the Xpert MTB/RIF assay and culture was 91.8% (kappa = 0.8; $p < 0.0001$). **Conclusions:** In BALF samples, the Xpert MTB/RIF assay performs better than do traditional methods, providing a reliable alternative to sputum analysis in suspected cases of PTB. However, the rate of discordant results merits careful consideration.

Keywords: Tuberculosis; Molecular diagnostic techniques; Bronchoscopy; Bronchoalveolar lavage fluid; Mycobacterium tuberculosis.

INTRODUCTION

Tuberculosis, a disease caused by infection with *Mycobacterium tuberculosis*, continues to be an alarming public health problem, with high rates of morbidity and mortality worldwide. It has been estimated that there were approximately 10.0 million new cases of tuberculosis in 2019, a year in which 1.2 million and 208,000 tuberculosis-related deaths occurred among non-HIV-infected and HIV-infected individuals, respectively. Although the efforts made have saved millions of lives worldwide, reducing tuberculosis mortality by 42% since 2000, an annual decrease of approximately 4-5%, rather than the current 2%, would be needed in order to reach the End TB Strategy target of a 95% reduction by 2035. In Brazil, which is one of the 30 countries with the highest tuberculosis burden,[1] the estimated number of new cases of tuberculosis in 2019 was more than 90,000.[2]

One major concern regarding the management of cases of tuberculosis is that microbiological confirmation is achieved in only 40-60% of patients with pulmonary tuberculosis (PTB), the main clinical manifestation and the type of tuberculosis that is the most relevant in the chain of transmission. In addition, approximately half of all patients with PTB are sputum smear-negative for AFB or are unable to produce sputum samples of sufficient quantity,[1,3] making the diagnosis quite challenging. In such patients, fiberoptic bronchoscopy with BAL is a reliable, rapid method of collecting useful specimens for the diagnosis of PTB.[3-6] However, conventional methods, such as Ziehl-Neelsen staining, which detects AFB, and mycobacterial cultures, have poor diagnostic yields. Sputum smear microscopy for AFB is limited by its low sensitivity (approximately 40%), whereas mycobacterial culture, which is considered the gold standard, performs better (with a sensitivity of approximately 86%),

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although the latter is time consuming, requiring 6-8 weeks to produce a diagnosis.[7,8] Therefore, new methods have been proposed and in some cases implemented to improve diagnostic accuracy, which would allow the appropriate treatment to be instituted early, thus avoiding the spread of tuberculosis and minimizing the associated deaths. The Xpert MTB/RIF assay (GeneXpert; Cepheid, Sunnyvale, CA, USA), an automated cartridge-based assay that uses quantitative heminested real-time PCR, is a rapid (≤ 2 h) molecular test for the detection of *M. tuberculosis* and of resistance to rifampin.[9,10] The Xpert MTB/RIF assay has proven to have high sensitivity and specificity, as well as being a test of low complexity that is safe and cost-effective for the diagnosis and management of suspected cases of tuberculosis.[11-13] Currently, a range of clinical specimens other than spontaneous or induced sputum, such as pleural fluid, urine, cerebrospinal fluid, tracheal aspirate, and BAL fluid (BALF), have been shown to be suitable for analysis with the Xpert MTB/RIF assay.[14,15] However, there are few data in the literature regarding the analysis of BALF samples by the Xpert MTB/RIF assay for the diagnosis of PTB, especially at tertiary care facilities, as well as regarding its comparison with conventional microbiological methods. Therefore, the present study aimed to assess the performance of Xpert MTB/RIF assays of BALF samples from patients with suspected PTB who are sputum smear-negative or produce insufficient sputum samples. To that end, we evaluated such patients at a university hospital in the city of Rio de Janeiro, which ranks second among Brazilian cities in terms of tuberculosis burden.[2] We also evaluated the Xpert MTB/RIF assay in comparison with AFB staining, processing the BALF samples in parallel and using mycobacterial culture as the reference.

METHODS

Ethical aspects

The study was approved by the Research Ethics Committee of Pedro Ernesto University Hospital of the State University of Rio de Janeiro (Reference no. 2.013.455). All participating patients gave written informed consent.

Study design and participants

This was a retrospective analytical study of 149 patients who were sputum smear-negative, despite clinical and radiological findings suggestive of PTB. The patients were evaluated at Pedro Ernesto University Hospital, a tertiary care referral center in the city of Rio de Janeiro, Brazil, between November of 2015 and October of 2017. All of the patients underwent fiberoptic bronchoscopy. The BALF samples collected were evaluated by AFB staining, mycobacterial culture, and Xpert MTB/RIF assay. The following inclusion criteria were applied: being suspected of having PTB on the basis of clinical, physical, and radiological findings; being sputum smear-negative, producing insufficient sputum samples, or testing negative for *M. tuberculosis* on sputum culture; and having been referred for fiberoptic bronchoscopy. Patients who tested positive for *M. tuberculosis* in sputum samples (by smear microscopy or culture) were excluded, as were those with malignancy, those with fungal infection, those who were on antituberculosis regimens for more than 2 weeks, and those with a confirmed diagnosis of infection with nontuberculous mycobacteria (NTM). A confirmed diagnosis of PTB was defined as *M. tuberculosis* growth on mycobacterial culture of a BALF sample, which was considered the reference method. A probable diagnosis of PTB was defined as not meeting the criteria for a confirmed diagnosis of PTB but having clinical and radiological findings suggestive of tuberculosis, as well as showing a clinical response to antituberculosis treatment. Sociodemographic and clinical characteristics, such as gender, age, smoking status, history of tuberculosis, HIV status, and the presence of cavitary disease, were collected from hospital records. Smokers were defined as individuals who had smoked at least 100 cigarettes (or the equivalent) in their lifetime, and former smokers were defined as those who had quit smoking more than 12 months prior.

Patient evaluation and sample collection

In patients under intravenous sedation, clinical investigators used a flexible fiberoptic bronchoscope to perform transnasal bronchoscopy, during which there was continuous monitoring of heart rate, blood pressure, and SpO_2. In brief, after the bronchial tree had been inspected, BAL was performed by instilling sterile saline (0.9%) in serial 20-mL aliquots (up to a maximum of 200 mL). At least 50% of the total volume of the aspirate was returned, then being divided into three parts and sent to the laboratory for Ziehl-Neelsen (AFB) staining, mycobacterial culture, and Xpert MTB/RIF assay.

Smear microscopy

The BALF specimens collected from all patients were centrifuged at 3,000 × *g* for 15 min, after which they were submitted to microbiological tests according to Brazilian Health Regulatory Agency guidelines.[16] The supernatant was carefully removed, after which it was processed in parallel for each subsequent test. For the AFB staining, a BALF sample was smeared on a glass microscope slide and allowed to dry, after which the staining was performed. After staining, a minimum of 100 fields were examined with a ×100 oil immersion objective and the smear was scanned systematically. The observation of at least one AFB was considered a positive result.

Solid culture

The BALF samples were decontaminated by using sodium hydroxide in a final concentration of 4%. After centrifugation, the supernatant was discarded and the precipitate was inoculated into tubes containing Löwenstein-Jensen solid medium. Cultures were

incubated at 37°C for 60 days, being examined weekly for up to 8 weeks or until growth was observed. The growth of *M. tuberculosis* was identified by using a rapid immunochromatographic MPT64 antigen testing kit (SD Bioline TB Ag MPT64 Rapid test; Standard Diagnostics Inc., Yongin-si, South Korea), according to the manufacturer's instructions.

Xpert MTB/RIF assay

Sediment from the BALF samples was processed with a DNA/RNA extraction protocol, after which the Xpert MTB/RIF platform was employed according to the manufacturer's instructions. In brief, the samples were diluted with the sample reagent provided by the manufacturer. The clinical specimens and reagent mixture were shaken in the vortex mixer for at least 10 s and left to settle at room temperature for 15 min. As recommended, all of the solutions were then transferred to the Xpert cartridge and loaded onto the GeneXpert equipment for analysis.

Statistical analysis

In the comparison of sociodemographic, clinical, and biochemical features between the two groups (culture-confirmed PTB and non-culture-confirmed PTB), we tested the hypothesis that the different samples in the comparison were drawn from the same distribution or distributions with the same median by using Mann-Whitney U tests for continuous variables. Fisher's exact tests were used in order to evaluate frequencies between the two groups, testing the hypothesis of independence between the groups and the categorical variables. The kappa statistic was used in analyses of agreement among mycobacterial culture, the Xpert MTB/RIF assay, and AFB staining. For the detection of *M. tuberculosis* in BALF samples, the performance of the Xpert MTB/RIF assay and AFB staining, as well as combinations of the two, in comparison with the gold-standard (mycobacterial culture), was estimated. We used leave-one-out cross-validation to determine their accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), as well as determining their rates of false-positive and false-negative results, together with the corresponding 95% confidence intervals. All statistical analyses were performed with the program R, version 3.5.2 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Study design and patient characteristics

As depicted in the flow chart in Figure 1, we enrolled 149 patients who presented with clinical and radiological findings suggestive of PTB, who were sputum smear-negative or who produced sputum samples of insufficient quantity, and who underwent fiberoptic bronchoscopy. After the BALF samples had been processed and evaluated, 9 patients were excluded for receiving a final diagnosis of NTM infection. Therefore, the final study population comprised 140 patients for whom BALF test results were available. Mycobacterial culture results were available for 140 patients, *M. tuberculosis* being identified in 22 (15.7%) of those patients, compared with 31 (23.8%) of the 130 patients for whom AFB staining results were available and 20 (24.4%) of the 82 patients for whom Xpert MTB/RIF assay results were available. Results for all three examinations were available for 73 patients, of whom 22 (30.1%) tested positive on culture, 17 (23.2%) tested positive on AFB staining, and 20 (27.4%) tested positive on the Xpert MTB/RIF assay. None of the strains isolated were found to be resistant to rifampin.

Table 1 shows the demographic and clinical features of the study population, by outcome of the mycobacterial culture of the BALF samples. The median age of the patients was 56 years (IQR = 28.25 years). Seventy-eight patients (55.7%) were male, and there were no significant differences between the two groups in terms of gender distribution. All of the patients had at least one symptom suggestive of tuberculosis, the most common symptoms being weight loss (in 59.3%; $p = 0.008$), cough (in 57.1%), and dyspnea (in 53.6%). Cavitary disease was observed in 25 patients (17.9%). Of the 140 patients in the study population, 31 (22.1%) had previously had tuberculosis: 28 in the negative BALF culture group and 3 in the positive BALF culture group.

Performance of AFB staining and the Xpert MTB/RIF assay in BALF samples

Among the patients in the study population, the three methods for *M. tuberculosis* detection were used heterogeneously (Figure 1). Primarily, the test results were analyzed in different combinations (pairs) to evaluate the overall agreement among the Xpert MTB/RIF assay, AFB staining, and mycobacterial culture of BALF samples in suspected cases of PTB. As shown in Table 2, the Xpert MTB/RIF assay showed 91.78% agreement with culture (kappa = 0.8; $p < 0.0001$), compared with 82.31% for AFB staining (kappa = 0.46; $p < 0.0001$), regardless of whether we analyzed the sample as a whole (n = 140) or only those patients for whom results from all three examinations were available (n = 73). The agreement between the Xpert MTB/RIF assay and AFB staining was 82.2% (kappa = 0.53; $p < 0.0001$).

When we compared the Xpert MTB/RIF assay and AFB staining in terms of their individual diagnostic performance in BALF samples, using mycobacterial culture as the reference, we found that the Xpert MTB/RIF assay had an overall accuracy of 92%, a sensitivity of 81%, a PPV of 90%, and an NPV of 92%, compared with only 87%, 68%, 88%, and 87%, respectively, for AFB staining. Two different conditions ("OR" and "AND") were also analyzed. When the two methods were used in combination (Xpert MTB/RIF assay AND AFB staining) the specificity and PPV increased to 100%. However, the false-positive rate was higher when one or the other method was used (Xpert MTB/RIF assay OR AFB staining) than when the two were used in combination (Table 3).

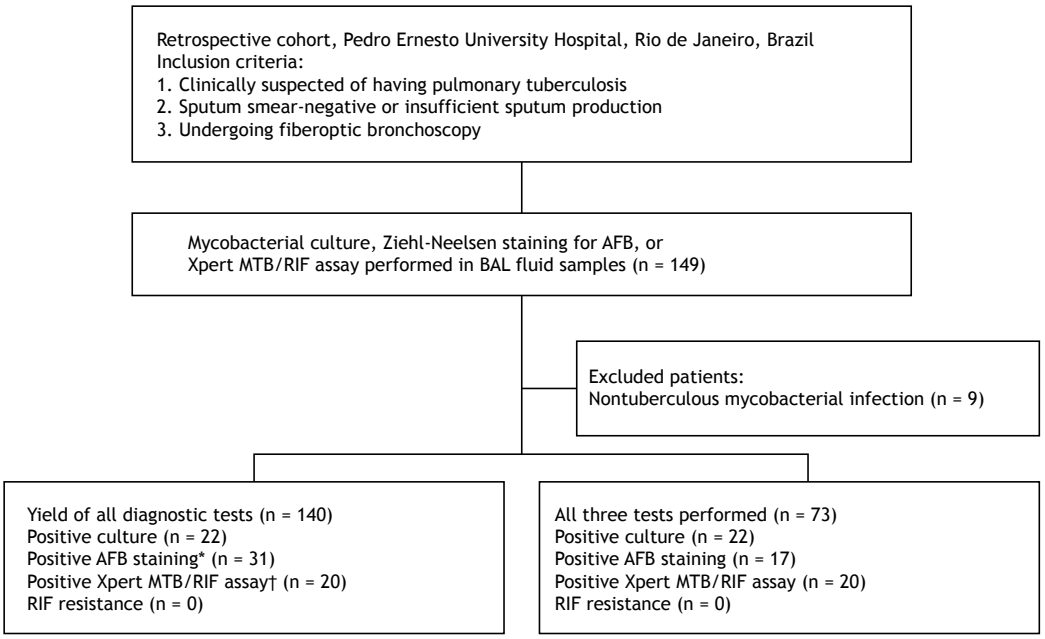

Figure 1. Flow chart of the study design and yield of the tuberculosis diagnostic tests performed in BAL fluid samples. *Performed in only 130 of the 140 patients. †Performed in only 82 of the 140 patients.

Table 1. Sociodemographic and clinical characteristics of the study population, by the results of mycobacterial culture of BAL fluid samples.[a]

Characteristic	Result of BALF culture		Total	p
	Negative (n = 118)	Positive (n = 22)	(N = 140)	
Gender				
Male	69 (49.3)	9 (6.4)	78 (55.7)	0.162
Female	49 (35.0)	13 (9.3)	62 (44.3)	
Age in years, median (IQR)	56 (26.25)	50 (30.00)	56 (28.25)	0.6002
Smoking status				
Never smoker	60 (42.9)	16 (11.4)	76 (54.3)	0.2018
Former smoker	33 (23.6)	4 (2.9)	37 (26.4)	
Current smoker	25 (17.9)	2 (1.4)	27 (19.3)	
Clinical features				
HIV-infected	7 (5.0)	4 (2.9)	11 (7.9)	0.0718
Previous tuberculosis	28 (20.0)	3 (2.1)	31 (22.1)	0.406
Symptoms				
Chest pain	46 (32.9)	8 (5.7)	54 (38.6)	1.00
Dyspnea	66 (47.1)	9 (6.4)	75 (53.6)	0.246
Fever	45 (32.1)	6 (4.3)	51 (36.4)	0.4698
Hemoptysis	49 (35.0)	4 (2.9)	53 (37.9)	0.054
Cough	67 (47.9)	13 (9.3)	80 (57.1)	1.00
Weight loss	76 (54.3)	7 (5.0)	83 (59.3)	0.0081
Cavitary disease[b]				
Yes	19 (13.6)	6 (4.3)	25 (17.9)	0.229
No	99 (70.7)	16 (11.4)	115 (82.1)	

BALF: BAL fluid. [a]Values expressed as n (%), except where otherwise indicated. [b]Determined by chest X-ray examination.

To promote better identification and visualization of the overall performance of the methods evaluated, we created a Venn diagram to illustrate the outcomes of the BAL Xpert MTB/RIF assay, AFB staining, and mycobacterial culture of BALF samples in the 73 patients for whom results from all three examinations were available (Figure 2). The distribution of positive (+) and negative (−) results was as follows: Xpert MTB/RIF

Table 2. Agreement among the results of the Xpert MTB/RIF assay, AFB staining, and mycobacterial culture in BAL fluid samples.[a]

Comparison methods	Results of the comparison methods	Comparator method and results		Agreement	kappa	p
		Culture				
		Negative	Positive			
		118 (84.3)	22 (15.7)			
Xpert MTB/RIF assay	Negative	49 (35.0)	4 (2.9)	91.78%	0.79963	< 0.0001
	Positive	2 (1.4)	18 (12.9)			
AFB staining	Negative	92 (65.7)	7 (5.0)	82.31%	0.45892	< 0.0001
	Positive	16 (11.4)	15 (10.7)			
		AFB staining				
		Negative	Positive			
		99 (70.7)	31 (22.1)			
Culture	Negative	92 (65.7)	16 (11.4)	82.31%	0.45892	< 0.0001
	Positive	7 (5.0)	15 (10.7)			
Xpert MTB/RIF assay	Negative	48 (34.3)	5 (3.6)	82.19%	0.53043	< 0.0001
	Positive	8 (5.7)	12 (8.6)			
		Xpert MTB/RIF assay				
		Negative	Positive			
		53 (37.9)	20 (14.3)			
Culture	Negative	49 (35.0)	2 (1.4)	91.78%	0.79963	< 0.0001
	Positive	4 (2.9)	18 (12.9)			
AFB staining	Negative	48 (34.3)	8 (5.7)	82.19%	0.53043	< 0.0001
	Positive	5 (3.6)	12 (8.6)			

[a]Test results are presented as n (%).

Table 3. Diagnostic performance of the Xpert MTB/RIF assay and AFB staining in BAL fluid samples, in comparison with the reference method (mycobacterial culture).

Measure	Xpert MTB/RIF	AFB staining	Xpert MTB/RIF OR AFB staining	Xpert MTB/RIF AND AFB staining
	% (95% CI)	% (95% CI)	% (95% CI)	% (95% CI)
Accuracy	91.78 (87.35 to 96.21)	87.67 (82.37 to 92.97)	93.15 (89.08 to 97.22)	86.3 (80.76 to 91.85)
Sensitivity	81.82 (70.11 to 93.52)	68.18 (54.05 to 82.32)	95.45 (89.13 to 101.78)	54.55 (39.43 to 69.66)
Specificity	96.08 (92.31 to 99.85)	96.08 (92.31 to 99.85)	92.16 (86.94 to 97.37)	100.00 (100.00 to 100.00)
PPV	90.00 (80.4 to 99.6)	88.24 (76.95 to 99.52)	84.00 (73.62 to 94.38)	100.00 (100.00 to 100.00)
NPV	92.45 (87.43 to 97.48)	87.50 (81.39 to 93.61)	97.92 (95.06 to 100.78)	83.61 (77.06 to 90.16)
FPR	3.92 (0.15 to 7.69)	3.92 (0.15 to 7.69)	7.84 (2.63 to 13.06)	0.00 (0.00 to 0.00)
FNR	18.18 (6.48 to 29.89)	31.82 (17.68 to 45.95)	4.55 (−1.78 to 10.87)	45.45 (30.34 to 60.57)

PPV: positive predictive value; NPV: negative predictive value; FPR: false-positive rate; and FNR: false-negative rate.

assay$^+$/culture$^+$/AFB staining$^+$ = 12 patients; Xpert MTB/RIF assay$^-$/culture$^+$/AFB staining$^-$ = 1 patient; Xpert MTB/RIF assay$^+$/culture$^+$/AFB staining$^-$ = 6 patients; Xpert MTB/RIF assay$^+$/culture$^-$/AFB staining$^-$ = 2 patients; Xpert MTB/RIF assay$^-$/culture$^+$/AFB staining$^+$ = 3 patients; Xpert MTB/RIF assay$^-$/culture$^-$/AFB staining$^+$ = 2 patients. Altogether, the Xpert MTB/RIF assay identified three more cases than did AFB staining.

DISCUSSION

As previously mentioned, even though mycobacterial culture has long been considered the gold standard method for the diagnosis of PTB, 40-50% of cases are not detected by microbiological methods.[1] Sputum smear microscopy has low sensitivity and limited specificity, the latter evidenced by its incapacity to differentiate between *M. tuberculosis* and NTM species. In addition, some patients do not produce significant quantities of spontaneous or induced sputum,[1,3] which makes it difficult to obtain sufficient clinical specimens for microbiological analysis. In this scenario, empirical antituberculosis treatment emerges as a possible strategy to interrupt the spread of the disease and minimize the associated mortality. In the present study, we found that the Xpert MTB/RIF assay—a rapid molecular test for tuberculosis—performed better than did AFB staining in BALF samples from patients with suspected PTB who were sputum smear-negative or produced sputum samples of insufficient quantity, in a high-tuberculosis-burden area.

Recently, the Brazilian National Ministry of Health has recommended the use of the Xpert MTB/RIF assay in

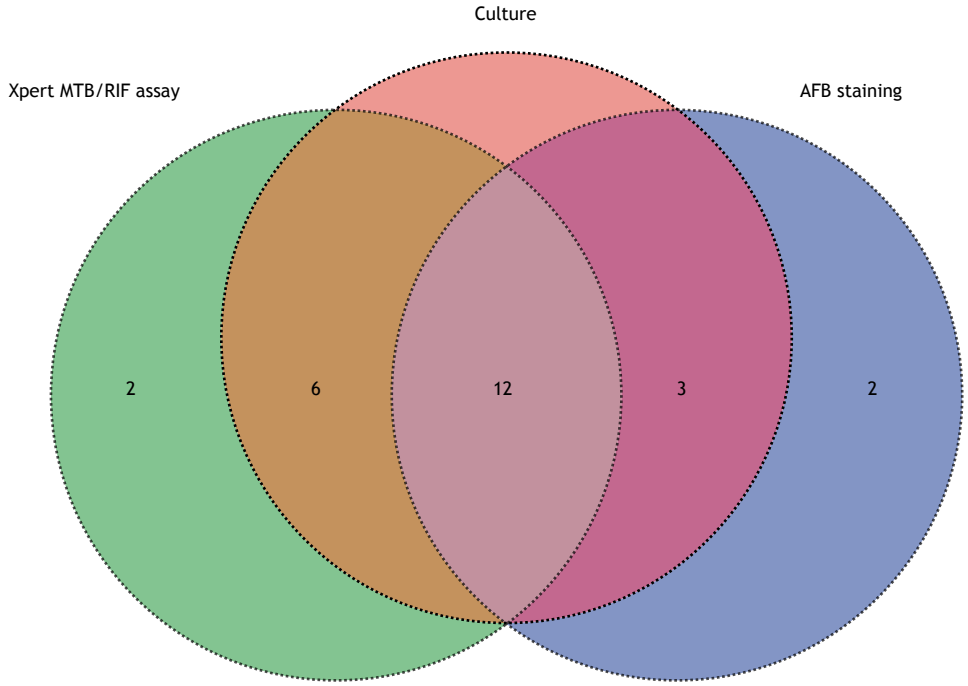

Figure 2. Venn diagram of the positive results of the tuberculosis diagnostic tests performed in BAL fluid samples: Xpert MTB/RIF assay (green), AFB staining (blue), and mycobacterial culture (pink). Note: numerals indicate the number of cases in which *Mycobacterium tuberculosis* was identified.

clinical specimens other than sputum, such as BALF, which is obtained by fiberoptic bronchoscopy, as an alternative way to investigate suspected cases of tuberculosis.[2] The Xpert MTB/RIF assay offers many advantages, such as providing results within 2 h, thus allowing antituberculosis treatment to be initiated sooner; high sensitivity, specificity, and overall accuracy; detecting rifampin-resistant *M. tuberculosis* strains; and high sensitivity and specificity for the detection of tuberculosis in HIV-infected patients.[11,13,17] Despite its limitations, which include a high false-positive rate and the high costs of equipment maintenance and reagents/components, the Xpert MTB/RIF assay has made an essential contribution in clinical practice as a rule-in or rule-out test for the diagnosis of tuberculosis.[18,19]

The performance of the Xpert MTB/RIF assay in sputum samples has been well documented,[13,20,21] as has the value of BALF samples in the diagnosis of tuberculosis, especially in patients who are sputum smear-negative or unable to produce sufficient sputum samples[4,22-24]; however, there have been few studies analyzing and validating the utility of molecular tests for the diagnosis of tuberculosis in BALF specimens. Khalil & Butt[25] demonstrated that, in comparison with mycobacterial culture, the Xpert MTB/RIF assay was superior for detecting *M. tuberculosis* and rifampin resistance showing high sensitivity (91.86%) and PPV (97.53%) in patients with PTB who were sputum smear-negative or unable to produce sufficient sputum samples. In a retrospective study, Agrawal et al.[26] also showed that the Xpert MTB/RIF assay performed better in respiratory samples (sputum and BALF) than did AFB staining. Finally, a recent study conducted at a tertiary care facility in India compared BAL the Xpert MTB/RIF assay, AFB staining, and mycobacterial culture in BALF samples from suspected cases of PTB, in a manner similar to that of the present study. Bashir et al.[27] observed that, although the Xpert MTB/RIF assay and AFB staining had similar overall specificity, the sensitivity of the Xpert MTB/RIF assay was much higher than was that of smear microscopy in BALF samples (97.1% vs. 36.7%). Together with all of that evidence, our data support the use of the Xpert MTB/RIF assay in BALF samples as an interesting and suitable tool to improve the diagnosis of tuberculosis.

In the present study, there were some discordant results among the outcomes of the Xpert MTB/RIF assay, AFB staining, and mycobacterial culture, particularly among the 73 patients for whom results from all three examinations were available. There were two patients in whom the BALF samples tested positive on the Xpert MTB/RIF assay, despite testing negative on AFB staining and culture. It is noteworthy that those samples had higher cycle threshold values (26.6-30.9; probes A-E), which implies low concentrations of *M. tuberculosis* DNA.[28] That could explain the negative results obtained with mycobacterial culture and AFB staining. In two other patients, *M. tuberculosis* was identified only by AFB staining; one of those patients, a female, was HIV-infected. Immunosuppression can favor coinfection with other pathogens, such as NTM.[29,30] However, in that case, there was no growth in mycobacterial culture, which delayed the diagnosis. In addition, there was one case in which *M. tuberculosis*

was identified only in culture. None of those 5 patients reported having had tuberculosis previously. Therefore, on the basis of clinical and radiological criteria, they were treated with an antituberculosis regimen. After six months, all of them showed improvement in the signs and symptoms. All of these discrepancies should be interpreted with caution, the limitations of each method and the clinical status of the patients being taken into consideration.

Our study has some limitations. First, it was a single-center study, which limits the generalizability of the data. Second, because it was a retrospective study, the clinical data were limited to those available in the medical records. Third, there was a relatively small number of cases in which results were available from all three of the methods evaluated. However, the study was performed at a specialized, tertiary, referral teaching hospital in a high-tuberculosis-burden area, where numerous tools are available for the investigation and accurate diagnosis of cases of tuberculosis. In addition, mycobacterial culture results were available for all cases, and we excluded cases of NTM infection in order to avoid bias.

In summary, in BALF samples, the Xpert MTB/RIF assay performed better than did AFB staining for the diagnosis of cases of PTB in patients who were sputum smear-negative or were unable to produce sputum specimens of sufficient quantity. That could have a significant impact on clinical practice and on the management of such cases, particularly those in which the diagnosis is challenging. When the Xpert MTB/RIF assay produces results that are discordant with those of other diagnostic tools, those discrepancies must be carefully analyzed, given that tuberculosis continues to be a significant public health problem worldwide.

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AUTHOR CONTRIBUTIONS

TTM and LSR: conceived and designed the study. GMXB and RSL: performed the experiments. GMXB, MRA, and LSR: analyzed the data. RR and LSR: contributed analysis tools. GMXB, TTM, RSL, MRA, and LSR: drafted and revised the manuscript. RR and JL: supervised patient enrollment. LVT and TTM: performed the bronchoscopy procedures. LSR: coordinated the study. All authors contributed to the discussion of the data and approved the final version of the manuscript.

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Analysis and comparison of tuberculosis treatment outcomes in the homeless population and in the general population of Brazil

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ABSTRACT

Tuberculosis remains a major public health problem deeply influenced by inequality. The present study used data from the Brazilian Tuberculosis Case Registry Database in order to compare the rates of tuberculosis treatment success, loss to follow-up, and tuberculosis mortality between the homeless population and the general population of Brazil. The likelihood of tuberculosis treatment success was reduced by approximately 50% in the homeless population. In addition, the rate of loss to follow-up was 2.9 times higher in the homeless population than in the general population, and the rate of tuberculosis mortality was 2.5 times higher in the former.

Keywords: Tuberculosis; Homeless persons; Health information systems; Health policy.

Worldwide, tuberculosis remains a major public health problem in the 21st century, despite being a treatable and curable disease. In 2015, there were 10.4 million new tuberculosis cases and 1.4 million tuberculosis deaths,[1] tuberculosis being one of the leading causes of death in the world.[2] In Brazil, strategies to fight tuberculosis include several government action plans[3-5] and national initiatives to achieve the United Nations Sustainable Development Goals.[6] Despite an improvement in tuberculosis indicators, Brazil ranked 20th among the countries with the highest tuberculosis burdens and 19th in terms of HIV/tuberculosis coinfection in the world in 2015, therefore remaining on the World Health Organization (WHO) list of priority countries for tuberculosis control in the 2016-2020 period.[3]

Obstacles to the control of tuberculosis in Brazil include historical difficulty in efficiently disseminating tuberculosis-related information, economic crises with negative impacts on poverty rates, unequal distribution of wealth, precarious urbanization, increased HIV infection, poor nutrition, poor sanitation, and an increase in vulnerable populations.[7-9] Vulnerable populations include homeless individuals, who are particularly at risk for tuberculosis because of extreme social exclusion, poor access to health care, violence, and discrimination, as well as strained or no family ties.[7,10,11]

Studies have shown that homeless individuals are at an increased risk for tuberculosis, and rates of comorbidities are higher in the homeless than in the general population.[7-9] However, no studies have examined a wider range of tuberculosis indicators in a large country like Brazil. Therefore, there is a need to study tuberculosis treatment outcomes in the homeless population of Brazil and compare them with those in the general population in order to gain a better understanding of this issue and contribute to the design of effective and equitable health policies. The objective of the present study was to compare the rates of tuberculosis treatment success, loss to follow-up, and tuberculosis mortality[4] between the homeless population and the general population of Brazil (by region) in 2018.

This was a cross-sectional study of data from the Brazilian National Ministry of Health *Sistema de Informação de Agravos de Notificação* (SINAN, Case Registry Database). Reported new cases of tuberculosis (International Classification of Diseases, 10th revision

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codes A15-A16) were analyzed in the homeless and general populations. Confirmed tuberculosis was defined as clinically and laboratory or clinically and epidemiologically confirmed cases of tuberculosis, in accordance with the SINAN Tuberculosis Reporting/Surveillance Form definition.[12] After exclusion of tuberculosis cases in special populations and those with missing data on outcomes of interest, 1,530 cases and 54,608 cases were analyzed in the homeless and general populations, respectively.

Outcomes of the study included treatment success, loss to follow-up, and tuberculosis mortality. All indicators were described for Brazil as a whole and for each region of the country. Case distribution was analyzed by sex, level of education, race, presence or absence of alcoholism, smoking status, HIV status, and presence or absence of mental disorder as recorded in the SINAN.[12] Microdata were analyzed with the Stata statistical software package, version 14 (StataCorp LP, College Station, TX, USA). For the three outcomes, the relative differences between the groups were calculated with Pearson's chi-square test. Because the study used public, anonymized data, no research ethics committee approval was required or sought.

Pulmonary tuberculosis accounted for 91.9% of the tuberculosis cases in the homeless population and 81.7% of those in the general population. In the homeless and general populations, there was a predominance of males (83.5% and 65.1%, respectively), individuals who had had 9 years of schooling (83.2% and 69.8%, respectively), and biracial individuals (52.2% and 53.0%, respectively). The homeless and general populations were significantly different in terms of the presence of alcoholism (58.4% vs. 16.8%), smoking (50.4% vs. 22.4%), HIV infection (21.2% vs. 9.1%), and mental disorder (7.3% vs. 2.3%).

The likelihood of tuberculosis treatment success was reduced by approximately 50% in the homeless population. The rate of loss to follow-up was 2.9 times higher in the homeless population than in the general population, and the rate of tuberculosis mortality was 2.5 times higher in the former (Table 1).

Tuberculosis indicators were found to be worse in the homeless population in all regions of the country (Table 1). The rate of successful tuberculosis treatment was highest in the general population in the southeastern region of the country (75.9%) and lowest in the homeless population in the southern region (33.5%). With regard to reported loss to follow-up, relative inequality was found to be highest in the northeastern region, whereas the northern region showed the highest rate of loss to follow-up in the homeless population. With regard to tuberculosis mortality, the rates were highest in the central-west and northern regions. These differences can be attributed to poor access to health care, failure to trace contacts of patients with confirmed tuberculosis, and poor infrastructure.[13] In addition, according to the Brazilian Institute of Geography and Statistics, socioeconomic inequalities are deep in the northern and northeastern regions of Brazil.[14]

The results of the present study show that the homeless are particularly vulnerable to tuberculosis. These results corroborate those of a study conducted

Table 1. Rates, 95% CIs, and incidence ratios (IR) for tuberculosis treatment success, loss to follow-up, and tuberculosis mortality in the homeless population and in the general population of Brazil (by region) in 2018.

Population	Outcome									p*
	Treatment success			Loss to follow-up			Tuberculosis mortality			
	%	95% CI	IR[a]	%	95% CI	IR[a]	%	95% CI	IR[a]	
Brazil										< 0.001
Homeless (n = 1,530)	39.0	(36.5-41.4)	0.5	28.8	(26.6-31.1)	2.9	8.1	(6.8-9.6)	2.5	
General (n = 54,608)	71.9	(71.6-72.3)		9.9	(9.6-10.1)		3.3	(3.1-3.4)		
Northern region										< 0.001
Homeless (n = 83)	44.6	(34.1-55.6)	0.6	24.7	(16.0-34.7)	2.5	9.6	(4.8-18.3)	3.8	
General (n = 6,318)	72.4	(71.3-73.5)		11.0	(10.2-11.8)		2.6	(2.2-3.0)		
Northeastern region										< 0.001
Homeless (n = 243)	33.7	(28.0-40.0)	0.5	30.0	(24.6-36.1)	3.5	7.0	(4.4-11.0)	1.8	
General (n = 12,997)	68.2	(67.4-69.0)		8.5	(8.0-9.0)		3.8	(3.5-4.1)		
Southeastern region										< 0.001
Homeless (n = 1,869)	41.7	(38.4-45.0)	0.5	31.1	(28.1-34.2)	2.9	7.7	(6.1-9.7)	2.5	
General (n = 26,212)	75.9	(75.3-76.4)		10.6	(10.2-10.9)		3.1	(2.8-3.3)		
Southern region										< 0.001
Homeless (n = 248)	33.5	(27.8-39.6)	0.5	21.8	(17.0-27.4)	2.5	8.1	(5.2-12.2)	2.1	
General (n = 6,674)	66.6	(65.6-67.7)		8.6	(8.0-9.3)		3.9	(3.4-4.4)		
Central-west region										< 0.001
Homeless (n = 87)	36.8	(27.2-47.6)	0.6	27.6	(19.1-38.1)	2.7	13.8	(7.9-23.0)	4.6	
General (n = 2,407)	62.9	(61.0-64.9)		10.2	(9.1-11.5)		3.0	(2.4-3.8)		

Source: *Brasil. Ministério da Saúde. Sistema de Informação de Agravos de Notificação* (Brazilian National Ministry of Health Tuberculosis Case Registry Database).[12] [a]The homeless population was used as reference to calculate ORs. *Pearson's chi-square test.

in the state of São Paulo, Brazil, and showing that tuberculosis treatment failed in 57.3% of the homeless individuals, primarily because of loss to follow-up (39.0%) and death (10.5%).[9]

Data from the Brazilian National Ministry of Health show that approximately 11% of tuberculosis patients do not complete the full course of treatment, being consistent with the findings of the present study.[3] The aforementioned rate is more than twice as high as the mean rate of treatment abandonment considered acceptable by the WHO (i.e., 5%).[2] In the homeless population, the rate of loss to follow-up is 33%, which is approximately three times as high as that considered acceptable by the Brazilian National Ministry of Health and seven times as high as that considered acceptable by the WHO.

Tuberculosis outcomes were found to be worse in the homeless population than in the general population of Brazil in all regions of the country, regardless of social and health inequalities. Homeless individuals are autonomous and have specific health needs. Therefore, there is a need to expand the traditional biomedical approach in order to create bonds of trust and respect between patients and health care teams.[15] In Brazil, street teams known as *Consultórios na Rua* are responsible for providing health care services to the homeless. However, although many Brazilian municipalities meet the criteria for *Consultórios na Rua*,[16] only 30% had implemented street teams by the end of 2016.[17] Although the number of street teams in Brazil has increased between 2016 and 2019,[18] it is still 40% below expected.[16,17] This is due to a lack of available health care professionals, a lack of prioritization of the health needs of the homeless, and a lack of adequate financial investment from the federal government, among other reasons.[17]

It is difficult to address the health needs of the homeless because of poor living conditions, mental health conditions, dependence on legal and illegal drugs, comorbidities, marginalization, and limited access to health care.[19] Therefore, it is important to increase access to health care services for the homeless, their needs being respected and addressed.[4] Despite the efforts of health care professionals, the lack of collaboration among the various sectors involved in health care for the homeless can be an obstacle to providing effective health care[11] and achieving shared worldwide goals. Economic growth and a reduction in socioeconomic inequalities, as well as effective and equitable health policies, are also needed in order to meet the population needs, including housing needs.

Health information systems are important tools for evaluation and surveillance studies. However, they have limitations, including inconsistent and missing data.[20] Another possible limitation is the underreporting of tuberculosis in the SINAN. These limitations can be further exacerbated in specific patient groups, such as the homeless. Nevertheless, government health information systems are the best regular source of nationwide data, and their extensive use is an important strategy to improve data quality.

There is a need to improve current tools and create new ones that can address the complexities of providing health care for the homeless. In addition, there is a need to develop intersectoral collaboration to provide comprehensive and equitable health care to the homeless population, with a view to change the model of care for the homeless and, consequently, improve tuberculosis indicators.

AUTHOR CONTRIBUTIONS

ACES, CB, and LSP conceived and designed the study, analyzed the data, and drafted and revised the manuscript; SSS conceived and designed the study, collected and analyzed the data, and drafted the manuscript; AFB provided expert advice and guidance at all stages of the study and manuscript preparation process.

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Diagnosis of tuberculosis: a consensus statement from the Brazilian Thoracic Association

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ABSTRACT

Early, accurate diagnosis of tuberculosis is one of the major pillars of the control of the disease. The purpose of this consensus statement is to provide health professionals with the most current, useful evidence for the diagnosis of tuberculosis in Brazil. To that end, the Tuberculosis Committee of the Brazilian Thoracic Association brought together 14 members of the Association with recognized expertise in tuberculosis in Brazil to compose the statement. A nonsystematic review of the following topics was carried out: clinical diagnosis, bacteriological diagnosis, radiological diagnosis, histopathological diagnosis, diagnosis of tuberculosis in children, and diagnosis of latent tuberculosis infection.

Keywords: Tuberculosis/diagnosis; Mycobacterium tuberculosis; Tuberculosis, multidrug-resistant/diagnosis; Latent tuberculosis/diagnosis.

INTRODUCTION

The End TB Strategy, approved by the World Health Assembly of the WHO in 2014,[1] set targets for tuberculosis prevention, care, and control from 2015 onward. These targets, to be met by 2035, are to reduce the tuberculosis incidence rate to less than 10 cases/100,000 population and to reduce the number of deaths from tuberculosis by 95%. In Brazil, despite a downward trend in the incidence rate between 2010 and 2016, there was an increase in incidence in the 2017-2018 period, and the rate was 35.0 cases/100,000 population in 2019.[2] The mortality rate has remained stable since 2010, ranging from 2.2 to 2.3 deaths/100,000 population, and was 2.2 deaths/100,000 population in 2019.[2]

Early, accurate diagnosis of tuberculosis is one of the major pillars of the control of the disease.[3] The purpose of this consensus statement is to provide health professionals with the most current, useful evidence for the diagnosis of tuberculosis in Brazil.

METHODOLOGY

The Tuberculosis Committee of the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Association) brought together 14 members of the Association with recognized expertise in tuberculosis in Brazil to compose this consensus statement on the diagnosis of tuberculosis in Brazil. A nonsystematic review of the following topics was carried out: clinical diagnosis, bacteriological diagnosis, radiological diagnosis, histopathological diagnosis, diagnosis of tuberculosis in children, and diagnosis of latent tuberculosis infection.

CLINICAL DIAGNOSIS

Tuberculosis manifests as an infectious syndrome, usually with a chronic course, and most patients present with fever, adynamia, anorexia, weight loss, and night

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sweats, as well as with symptoms that are specific to the affected site.[4-6] Approximately 85% and 15% of patients have pulmonary and extrapulmonary tuberculosis, respectively.[7]

Pulmonary tuberculosis

Cough is one of the major symptoms of patients with pulmonary tuberculosis, and the time since the onset of cough should be considered, depending on the population. Therefore, tuberculosis screening should be performed, regardless of cough duration, in contacts of patients with tuberculosis, people living with HIV (PLHIV), prison inmates, homeless people, individuals living in shelters or long-term care institutions, indigenous people, health professionals, immigrants, and refugees (when there is increased vulnerability). In the general population seeking care at any health care facility and in patients with diabetes mellitus, tuberculosis screening should be performed for individuals in whom a cough has lasted two weeks or more. In cases in which a cough has lasted three weeks or more, health professionals should conduct active case finding in the general population.[4] The cough can initially be dry; as the disease progresses, it can be accompanied by expectoration, blood-streaked sputum, or even hemoptysis, and the patient can develop chest pain and dyspnea.[4-6]

Extrapulmonary tuberculosis

The diagnosis of extrapulmonary tuberculosis is often presumptive because it is a paucibacillary form of the disease. Clinical sample collection depends on the suspected site of disease and requires invasive procedures. Therefore, a clinical diagnosis is not sufficient, and ancillary tests are required for confirmation and refinement of the diagnosis. All clinical samples should undergo bacteriological testing, molecular testing, and histopathological examination, and the patient should undergo imaging examinations.[6]

Pleural tuberculosis is the most common form of extrapulmonary tuberculosis, except in PLHIV. Patients can experience dry cough, pleuritic chest pain, and dyspnea, depending on the volume of pleural fluid.[4,6,8]

Lymph node tuberculosis, which is most common in children and women, is the most common form of extrapulmonary tuberculosis in PLHIV. The most commonly affected lymph node chains are the cervical lymph node chain, either unilaterally or bilaterally (and usually asymmetrically), the supraclavicular lymph node chain, and the mediastinal lymph node chain. Affected lymph nodes have a hard consistency, increase in volume, can coalesce, can adhere to deep planes, and can develop fistulas with secretion (scrofuloderma).[5,6]

Tuberculous meningoencephalitis is a severe form of tuberculosis and is difficult to diagnose. In its subacute form, it can present with diffuse headache, irritability, behavioral changes, sleepiness, photophobia, vomiting, paresthesia, and neck stiffness. It can also present with paralysis of the (second, third, fourth, sixth, or seventh) cranial nerves. In the chronic form of the disease, the headache can last for weeks. In its localized form, tuberculoma, it can present with symptoms of intracranial hypertension, a reduced level of consciousness, or coma.[4,9]

In osteoarticular tuberculosis, the most commonly affected site is the spinal column, followed by the hip/thigh region, the knees, and the ankles. The most common manifestations are spondylitis, arthritis, and osteomyelitis. Tuberculous spondylitis affects the intervertebral disk; anterior involvement is mainly due to infection spreading under the ligaments and periosteum and can lead to involvement of multiple vertebral bodies, in a continuous or discontinuous way. As the spinal disease progresses, there can be destruction and collapse of the vertebral bodies leading to kyphoscoliosis, often causing deformity (Pott's disease). Pain, tumor formation, neurological changes, and gait changes can occur, and, if discovered late, the disease can lead to irreversible neurological deficits.[10]

BACTERIOLOGICAL DIAGNOSIS

Smear microscopy

Sputum smear microscopy is important for the diagnosis of tuberculosis because it identifies patients with active tuberculosis, who feed the chain of disease transmission. Smear testing for AFB is a rapid, inexpensive method.[11] However, although the sensitivity of direct smear microscopy examination of spontaneous sputum is as high as 80% in the presence of extensive cavitary lesions, it ranges, on average, from 40-60% in patients with minimal lesions, and smears are positive in only 20% of those patients.[11] In addition, smear microscopy has lower sensitivity (ranging from 20-60%) in patients coinfected with HIV.[12]

Two to three sputum samples, at least one being collected in the early morning to optimize results, should be sent for smear microscopy.[13] The sputum volume should be greater than 3 mL, the optimal volume being 5-10 mL.[14]

Fluorescence microscopy can increase the capacity to detect mycobacteria by 10%, compared with conventional light microscopy. A 10-20% increase in the sensitivity of smear microscopy can also be achieved by using sputum centrifugation or sedimentation.[13]

Sputum induction with hypertonic saline solution is a useful technique in individuals who have negative sputum smears or who are unable to produce sputum, because it increases the yield of smear microscopy and culture.[13] Sputum induction with hypertonic saline solution has a diagnostic yield similar to that of bronchoscopy with BAL and is more cost-effective. If a diagnosis is not possible on the basis of spontaneous or induced sputum collection and suspicion of pulmonary tuberculosis persists, bronchoscopy and BAL fluid collection can be performed for smear microscopy and culture. Bronchoscopy also plays a role in the

diagnosis of smear-negative pulmonary tuberculosis, in cases of hemoptysis caused by tuberculosis, and in the exclusion of alternative diagnoses.[15-17]

In cases of suspected extrapulmonary tuberculosis, smear microscopy examination of the material collected is also indicated, although its sensitivity is lower. In cases of lymph node tuberculosis, the diagnosis is made by needle puncture-aspiration or lymph node resection. In pleural tuberculosis, the pleural fluid presents as an exudate with a predominance of lymphocytes but with a low yield for the detection of AFB (< 5%). Conversely, the yield of smear microscopy is high in tuberculous empyema. Increased adenosine deaminase levels (> 40 U/L) in the pleural fluid are considered highly suggestive of the diagnosis of pleural tuberculosis.[4]

Culture

Mycobacterial culture of respiratory material has a sensitivity of approximately 80% and a specificity of 98%. In cases of smear-negative pulmonary tuberculosis, culture increases disease detection by 20-40%.[11] Culture methods that use seeding on solid media, such as Löwenstein-Jensen and Ogawa-Kudoh media, are the most commonly used because they have the advantage of being inexpensive and having a low rate of contamination.[4] However, the time to visible growth of mycobacteria on solid media is two to eight weeks. Therefore, if available, liquid media should be used in automated nonradiometric systems, such as the Mycobacteria Growth Indicator Tube (MGIT; Becton Dickinson, Sparks, MD, USA), for faster results (10-42 days).[4] If mycobacterial growth is detected, species identification and antimicrobial susceptibility testing is required.[18]

Species identification is performed using biochemical and phenotypic methods or using molecular techniques and consists in distinguishing mycobacteria of the *Mycobacterium tuberculosis* complex from nontuberculous mycobacteria (NTM).[4] Currently available methods of antimicrobial susceptibility testing include the proportion method, which is performed on solid media and yields results within the first 42 days of incubation, and the automated method, which is performed in liquid media and yields results within 5 to 13 days. The drugs tested include streptomycin, isoniazid, rifampin, ethambutol, and pyrazinamide. For cases of multidrug-resistant tuberculosis (MDR-TB), second-line drugs are tested.[4]

The WHO considers culture using solid or liquid media the gold standard for the diagnosis of tuberculosis.[13] Culture is also indicated in suspected cases of extrapulmonary tuberculosis.[14] In pleural tuberculosis, mycobacterial culture has a low yield (< 15%). In contrast, in tuberculous empyema, the yield of culture is high.[4] Induced sputum culture is positive in up to 50% of cases, even if the only abnormality visible on chest X-ray is pleural effusion.[19]

Molecular testing

The Xpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) is based on nucleic acid amplification for detection of DNA of *M. tuberculosis* complex and screening for rifampin-resistant strains by real-time polymerase chain reaction (PCR), the results being available in approximately 2 h and only one sample being required. In 2011, the WHO endorsed the use of the Xpert MTB/RIF assay for the rapid diagnosis of tuberculosis and identification of rifampin resistance in individuals with suspected tuberculosis, even those infected with HIV. The sensitivity of the test in sputum samples from adults is approximately 90%. For rifampin resistance, its sensitivity is 95%.[4]

In Brazil, the Xpert MTB/RIF assay is known as the rapid molecular test for tuberculosis (RMT-TB) and is indicated for the diagnosis of new cases of pulmonary and laryngeal tuberculosis in adults and adolescents, being used with spontaneous sputum, induced sputum, BAL fluid, and gastric lavage samples; for the diagnosis of extrapulmonary tuberculosis in validated biological materials (i.e., cerebrospinal fluid, lymph nodes, and tissue macerate); for screening for rifampin resistance in cases of retreatment; and for screening for rifampin resistance in cases of suspected treatment failure.[4]

To improve the molecular diagnosis of tuberculosis, the Xpert MTB/RIF Ultra assay (Cepheid) has been developed. It is a new version of the Xpert MTB/RIF assay that has higher sensitivity for detecting tuberculosis, especially in paucibacillary samples. The sensitivity of the Xpert MTB/RIF Ultra assay is comparable to that of liquid culture,[20] and the test is already available in Brazil. The Xpert MTB/RIF Ultra results are reported as *M. tuberculosis* not detected (negative), *M. tuberculosis* detected (positive), and trace *M. tuberculosis* detected. This last result can be interpreted as positive, within the clinical context, in specimens from individuals with HIV/AIDS and children under 10 years of age, as well as in those obtained from the extrapulmonary materials mentioned above, because such materials are more commonly associated with the paucibacillary forms of tuberculosis. In other clinical situations, the result "trace *M. tuberculosis* detected" should be considered inconclusive and the investigation of tuberculosis should continue.[21]

Another type of molecular test approved and recommended by the WHO for use in respiratory material is the line probe assay, which, in addition to identifying the *M. tuberculosis* complex, identifies resistance to rifampin and isoniazid and which, in a separate test, can also detect resistance to fluoroquinolones and injection drugs.[22] In one meta-analysis, the sensitivity and specificity of the line probe assay was 96.7% and 98.8%, respectively, for detecting rifampin resistance, whereas they were 90.2% and 99.2%, respectively, for detecting isoniazid resistance.[23]

RADIOLOGICAL DIAGNOSIS

The initial approach to patients with respiratory diseases should include imaging with chest X-ray and, if necessary, chest CT. These methods are considered

essential because they provide relevant information on the presentation of the disease, its extent, and its course during treatment. Because it is easy to perform, accessible, and inexpensive, as well as because it uses a low dose of radiation, chest X-ray is the method of choice for the initial assessment of patients who present with suspected tuberculosis. Despite having low diagnostic specificity, chest X-ray is extremely useful in defining the presentation, evaluating possible comorbidities, and monitoring the evolution during treatment. In addition, chest X-ray can be used as a screening method for tuberculosis, especially in prison inmates, among whom the incidence of tuberculosis is extremely high.[24] The basic routine X-ray protocol in patients with suspected tuberculosis includes the use of posteroanterior and left lateral views. An apical lordotic (Fleischner) view may complement the routine protocol in cases in which there is uncertainty in interpretation of the lung apices. In suspected infrapulmonary pleural effusion, the horizontal beam lateral decubitus (Hjelm-Laurell) view is being replaced by chest ultrasound.[24-26]

The pulmonary tuberculosis-related changes seen on chest X-rays can be addressed in relation to the following conditions: primary tuberculosis; and secondary tuberculosis (reactivation or exogenous reinfection). Although primary tuberculosis is more common in children, it can also occur in adults. In children, given the difficulty in establishing smear microscopy-based diagnoses, imaging methods play an even more relevant role. Among the multiple presentations of the disease, the most common X-ray findings consist of concurrent changes, including single or multiple parenchymal, segmental, or lobar opacities and enlarged hilar or mediastinal lymph nodes, which cause reduced lung volume (epituberculosis), the most well-known presentation being middle lobe syndrome (Chart 1). Occasionally, there are cavitary lesions with bronchial dissemination and a diffuse/miliary pattern, as well as involvement of other sites, such as the pleura.[26-28]

Secondary tuberculosis, caused by reactivation or exogenous reinfection, is the most common form of the disease among adolescents and adults, and, in such individuals, pulmonary involvement occurs in 85-90% of cases. There are many possible manifestations on X-rays, chief among which are incipient, nodular, pneumonic, cavitary, pseudotumoral, and extrapulmonary forms. Lesions more commonly affect the apical and posterior segments of the upper lobes, as well as the apical segments of the lower lobes. They usually involve more than one lobe and are bilateral. Their manifestations are multiple, including small clustered nodules, heterogeneous segmental or lobar opacities, nodules measuring 1-3 cm in diameter, thick-walled cavities with bronchial dissemination, and areas of fibrosis (Chart 2).[26,27]

Although chest X-ray is the most important imaging method in the diagnosis and follow-up of patients with tuberculosis, chest CT has been increasingly used. Chest CT is more sensitive and more specific than is chest X-ray, being able to show early changes that are undetectable by chest X-ray, and it should be performed in patients with respiratory symptoms and poorly defined or unclear changes in whom the clinical and epidemiological context raises the possibility of tuberculosis. Chest CT should be performed in patients with respiratory symptoms but with negative sputum smear results, in individuals with suspected tuberculosis in whom chest X-ray was inconclusive, in cases in which further evaluation of the mediastinum is required, in cases of diffuse disease, and in patients with endobronchial abnormalities, as well as in those with respiratory symptoms and extensive sequelae that may require surgical intervention. Chest CT, unlike chest X-ray, can show changes suggestive of activity that occur at the level of the secondary pulmonary lobule, such as small airspace nodules exhibiting a tree-in-bud pattern or neatly arranged in a clover pattern ("clover sign"). Chest CT always provides additional information. There is a CT pattern that is consistent with active tuberculosis, characterized by consolidation (with or without air bronchogram), nodules, cavities, airspace nodules (tree-in-bud pattern), and bronchial abnormalities, such as wall thickening and dilatation.[26,27,29-34] Figures 1 and 2 show the X-ray and CT aspects of tuberculosis, respectively.

HISTOPATHOLOGICAL DIAGNOSIS

Histopathology is an important method for diagnosing pulmonary and extrapulmonary tuberculosis on the basis of specimens of tissue infected with *M. tuberculosis*. The typical histopathological lesion in pulmonary tuberculosis is a granuloma with caseous necrosis, composed of epithelioid histiocytes around a necrotic center, usually accompanied by a variable number of multinucleated giant cells and lymphocytes, which are found in up to 80% of cases. Non-necrotic granulomas may also be present, especially in immunocompromised patients when there is an incomplete inflammatory reaction. Granulomas without caseous necrosis should be interpreted with caution and in conjunction with clinical and epidemiological

Chart 1. Most common changes in primary tuberculosis.

- Enlarged hilar or mediastinal lymph nodes
- Reduced lung volume (partial atelectasis)
- Segmental, lobar, or whole lung parenchymal opacities
- Cavities accompanied by airspace nodules (bronchial dissemination)
- Diffuse micronodules (miliary pattern) in children not vaccinated with BCG

Chart 2. Most common changes in secondary tuberculosis.

- Common bilateral involvement, affecting more than one lobe, with multiple lesions
- Faint, clustered, difficult-to-visualize nodular opacities, typically located in the apical, interclavicular-hilar, and axillary regions
- Heterogeneous parenchymal opacities affecting more than one segment or lobe
- Lobar opacity accompanied by lines that converge toward the hilum (hilum overlay sign)
- Well-defined nodule(s) measuring 1-3 cm in diameter
- One or more cavities, of varying size, with a wall thickness of 3 mm or more, with or without parenchymal opacities and satellite nodules
- Architectural distortion resulting from areas of fibrosis or fibrosis/atelectasis, predominantly in the upper lobes
- Diffusely distributed micronodules measuring 2-3 mm in diameter (miliary pattern)

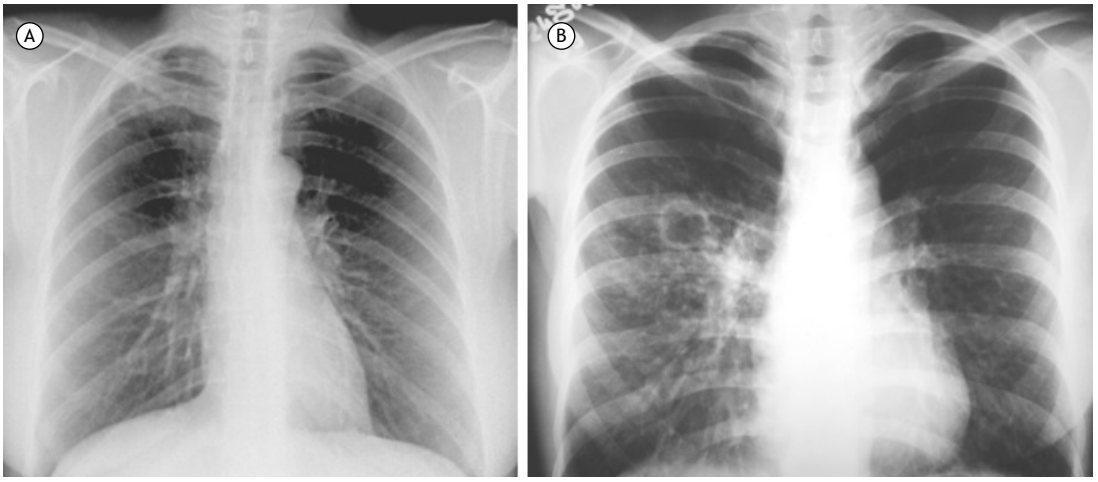


Figure 1. Chest X-ray findings of tuberculosis. In A, small clustered opacities in the right infraclavicular area. In B, a thick-walled cavity located in the middle third of the right lung, accompanied by small airspace nodules, also known as satellite lesions, which are classically representative of bronchial dissemination of the disease.

findings, given that they can be found in other pulmonary and systemic granulomatous diseases, such as silicosis, mycoses, and sarcoidosis.[4,35]

In immunocompetent patients with tuberculosis, smear microscopy of lung tissue is usually negative, whereas it is typically positive in immunocompromised patients. However, the only definitive diagnostic method is culture followed by biochemical or molecular confirmation of *M. tuberculosis*.[4]

The diagnosis of extrapulmonary forms of tuberculosis is more difficult because of the paucibacillary nature of samples, the lack of sufficient sample quantities or volumes, and the fact that samples are fractionated in order to perform several diagnostic tests, such as histology/cytology, biochemical analysis, microbiology, and molecular biology methods.[36]

In pleural tuberculosis, it is recommended that specimens be collected for histopathological examination, AFB testing, mycobacterial culture, and PCR. A definitive etiological diagnosis requires culture or PCR detection of *M. tuberculosis* in pleural fluid or pleural tissue. However, the presence of caseating granulomas, even in the absence of AFB or in the presence of negative culture, is considered highly suggestive of tuberculosis. Pleural biopsy shows granulomas in 50-97% of cases, and culture is positive in 40-80% of cases. Noncaseating granulomas can also be seen, at which point it is necessary to make a differential diagnosis from sarcoidosis, fungal diseases, and rheumatoid disease. It is also necessary to test pleural fluid and pleural tissue for neoplastic cells, especially in older patients.[4,37]

Histopathology yields findings that are nonspecific for the diagnosis of lymph node tuberculosis in the absence of AFB, because they mimic those of other diseases, such as sarcoidosis and fungal infections. Fine-needle aspiration biopsy plays an important role in the diagnosis of lymph node tuberculosis. However, the amount of material obtained is usually insufficient for AFB testing and culture. Fine-needle aspiration biopsy cytology also has difficulty in differentiating tuberculosis from other granulomatous or NTM diseases. PCR methods in combination with cytology reduce the need for an open biopsy. Lymph node aspirate smears are positive in 10-25% of cases, lymph node aspirate culture is positive in 50-90% of cases, and granulomas can be seen in up to 90% of cases. Molecular biology methods, such as Xpert MTB/RIF Ultra (Cepheid), allow detection of *M.*

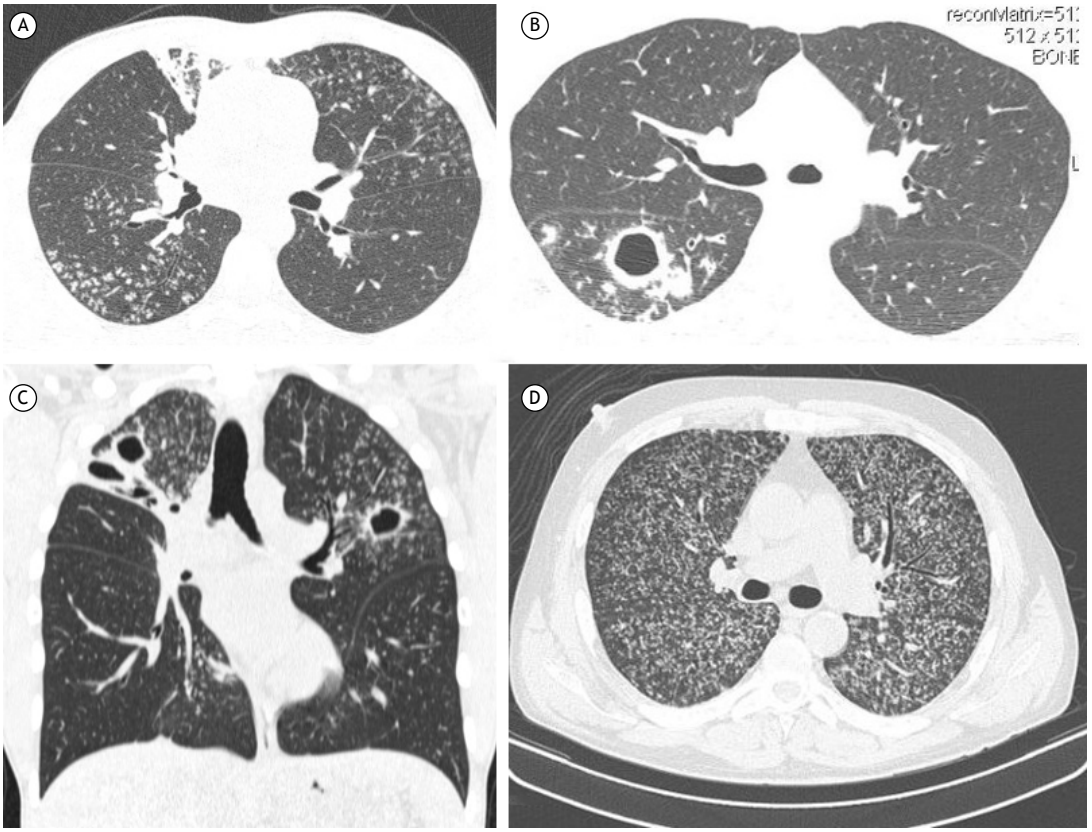


Figure 2. CT findings of tuberculosis. In A, diffuse airspace nodules, some of which are dichotomous, resulting in a tree-in-bud pattern. In B (same case as Figure 1B), a thick-walled cavity, accompanied by satellite nodules and marked bronchial wall thickening, in the apical segment of the right lower lobe. In C, coronal reconstruction showing thick-walled cavities and satellite nodules, bilaterally. In D, a miliary pattern of diffuse micronodules.

tuberculosis DNA and rifampin resistance in biopsy macerates. In a study involving 140 patients with lymph node tuberculosis, the rates of detection of *M. tuberculosis* by Xpert MTB/RIF, conventional PCR, and MGIT 960 culture were 25.71%, 20.71%, and 17.85%, respectively.[36]

In cutaneous tuberculosis of exogenous origin, there is at first a neutrophilic reaction with areas of necrosis accompanied by AFB. A granuloma with caseous necrosis is evident after three to six weeks, and AFB may or may not be present. In cutaneous tuberculosis of endogenous origin, there are granulomas with caseous necrosis, and AFB may be present. As the lesion progresses, granulomas may be replaced by a nonspecific chronic inflammatory infiltrate, and AFB may be scarce. In cutaneous tuberculosis resulting from hematogenous spread, there is a nonspecific inflammatory infiltrate with areas of necrotizing vasculitis, signs of thrombosis, and numerous AFB. Tuberculids (cutaneous manifestations of a distant paucibacillary focus) present as nodular vasculitis (erythema induratum of Bazin) and erythema nodosum.[38]

Intestinal tuberculosis primarily affects the ileocecal region, probably because there is a high density of lymphoid tissue in this region, as well as neutral pH, and transport mechanisms that favor the absorption and persistence of *M. tuberculosis*. The most common histopathological finding is the presence of characteristically large (> 200 µm) granulomas with caseous necrosis in the intestinal mucosa and submucosa. Positive PCR results can be seen in 72-87% of cases, with greater sensitivity and specificity than those of smear microscopy and mycobacterial culture.[39,40]

Bone puncture biopsy is the most common invasive procedure for the diagnosis of bone tuberculosis. Because of the density of bone structures, the limited sample volumes, the paucibacillary nature of samples, and the atypical puncture sites, it is difficult to make the histopathological and bacteriological diagnosis of bone tuberculosis. The most common finding is granuloma, with or without caseous necrosis, and smear microscopy, culture, and molecular biology methods have varying yields. Because of the difficulties inherent in such procedures, the diagnosis is often based on epidemiological, clinical, and radiological findings.[41]

Figures 3 and 4 show diagnostic algorithms for pulmonary and laryngeal tuberculosis in adults, for new cases and cases of retreatment, respectively. Where the RMT-TB is unavailable, the diagnosis of

tuberculosis should be based on smear microscopy and culture.

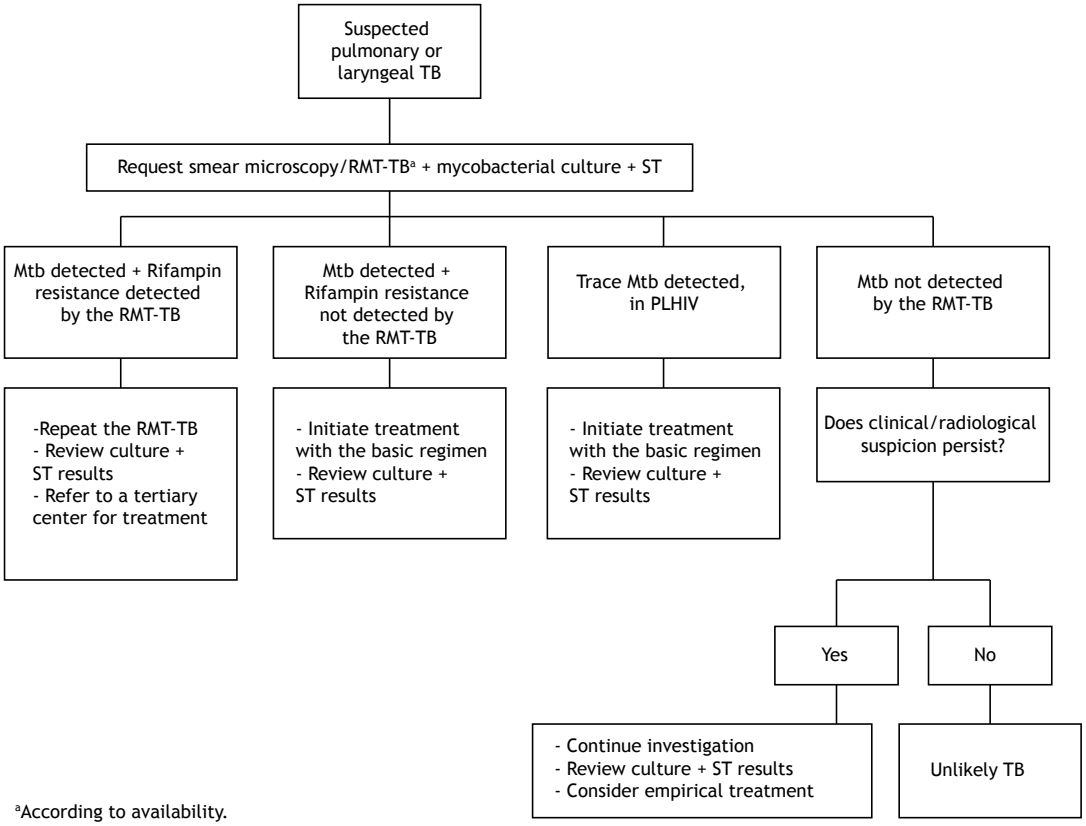
DIAGNOSIS OF TUBERCULOSIS IN CHILDREN

The WHO estimates that each year more than one million children become ill with tuberculosis worldwide—approximately 10% of the total number of cases—and that the incidence of childhood tuberculosis is underestimated because of the difficulty in diagnosing the disease in children. There are approximately 200,000 tuberculosis deaths per year among children and adolescents aged 0-14 years. Approximately 80% of those deaths occur among children under 5 years of age, and 17% occur in HIV-infected patients. Twenty-five thousand children under 14 years of age develop MDR-TB each year, although only approximately 5% receive treatment. The difficulties in diagnosis, contact tracing, and access to health care facilities would explain this challenge from a public health standpoint.[7,42]

In Brazil, the tuberculosis incidence rate in 2018 was higher among children 0-4 years of age than among those 5-14 years of age. In that same year, 75,709 new cases of tuberculosis were reported, 3.3% of which were in children under 14 years of age. It is estimated that 6-7% of tuberculosis patients have HIV coinfection.[43]

Children under 10 years of age typically have paucibacillary disease, which makes it difficult to detect *M. tuberculosis* in clinical specimens. Antituberculosis treatment is almost always started on the basis of clinical history, symptoms, and signs, as well as, when possible, on the basis of radiological findings and tuberculin skin test (TST) results.[4,44] Figures 5 and 6 show radiological features of tuberculosis in children.

The diagnosis of pulmonary tuberculosis in children is mainly based on clinical and radiological findings, epidemiological history of contact with adults with tuberculosis (typically active tuberculosis), and the interpretation of individual TST results. In a small number of cases, the diagnosis is based on bacteriological findings, because they are mostly cases of latent tuberculosis. The recent introduction of nucleic acid amplification methods has resulted in an increase in the rate of case confirmation. Slowly progressive infection, often showing no signs of being localized, with weight loss, anorexia, and occasionally sweating, is more common in children under 10 years of age than in children and adolescents 10-18 years age. Typically, those are cases of primary tuberculosis. Persistent cough and a history of contact with an adult with tuberculosis are clinical findings that are



[a]According to availability.

Figure 3. Diagnostic algorithm for new cases of pulmonary and laryngeal tuberculosis in adults. TB: tuberculosis; RMT-TB: rapid molecular test for tuberculosis; ST: susceptibility test; Mtb: *Mycobacterium tuberculosis*; and PLHIV: people living with HIV.

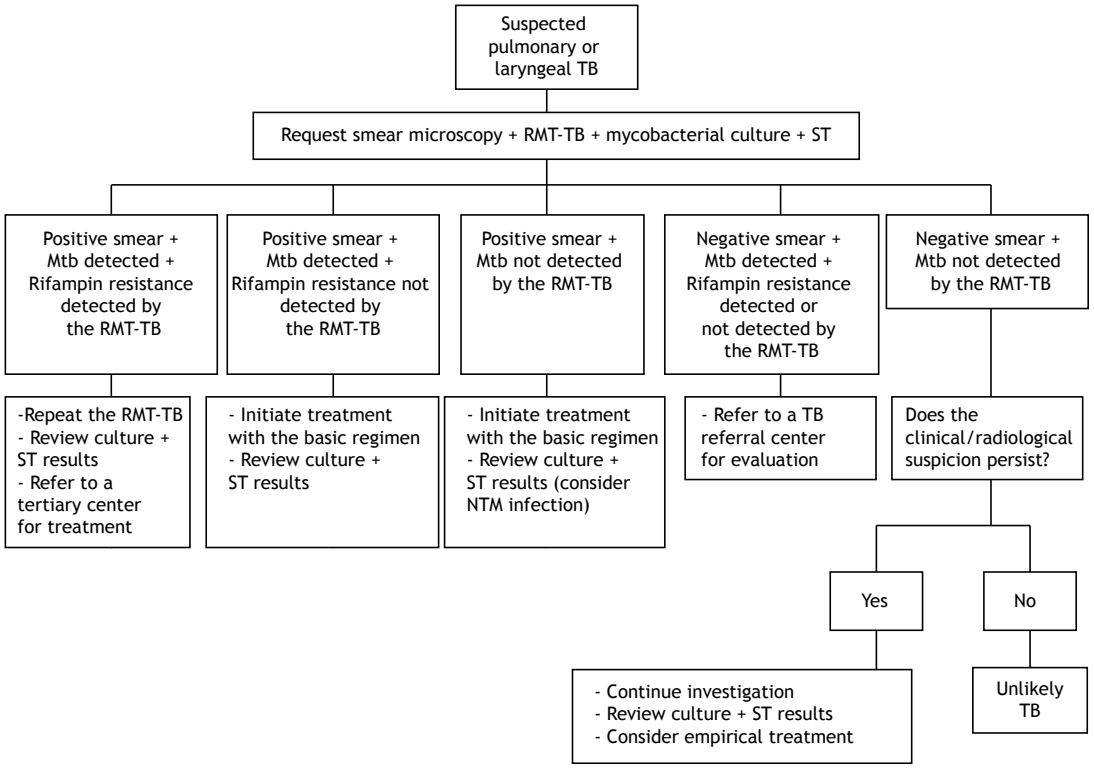


Figure 4. Diagnostic algorithm for cases of pulmonary and laryngeal tuberculosis requiring retreatment in adults. TB: tuberculosis; RMT-TB: rapid molecular test for tuberculosis; ST: susceptibility test; Mtb: *Mycobacterium tuberculosis*; and NTM: nontuberculous mycobacteria.

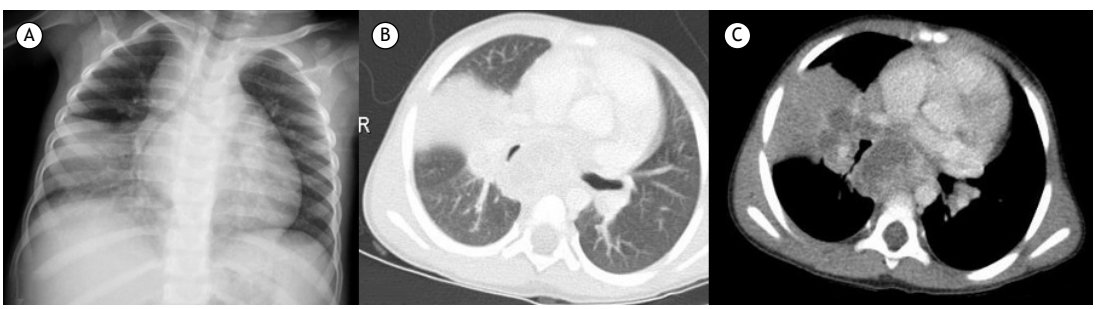


Figure 5. Primary tuberculosis in a child aged four years and nine months. In A, chest X-ray showing opacity in the right middle lower third accompanied by widening of the right paratracheal stripe, consistent with enlarged lymph nodes. In B, chest CT (lung window) showing opacity and extrinsic obstruction of the intermediate bronchus by enlarged lymph nodes, which are indicative of middle lobe syndrome. In C, chest CT (mediastinal window settings) showing enlarged lymph nodes of varying density in the right hilum and posterior mediastinum.

of great practical value in relation to tuberculosis in children.[4,44,45] However, some findings have been the subject of discussion. For example, prolonged cough (> 15 days) is thought to be a finding suggestive of pulmonary tuberculosis in children. However, children who have had a cough for a few days may also have pulmonary tuberculosis and go undetected. A history of contact with a person with tuberculosis and some chest X-ray features, such as unilateral enlarged hilar lymph nodes and a miliary pattern, are more common in children than in adolescents. In their daily lives, children are in closer contact with index cases of tuberculosis (usually adults) than are adolescents. Although the latter have greater autonomy in society, they may engage in rebellious or challenging behavior and show poor adherence to tuberculosis treatment. The classical concept of tuberculosis transmission has been challenged in studies showing that, among children who are household contacts of patients with tuberculosis, less than 30% become infected. Another feature that is of value in the clinical diagnosis of tuberculosis in children is malnutrition or lack of weight gain. Studies have addressed malnutrition as either a cause or a consequence of tuberculosis, depending on the epidemiological scenario in question.[42]

Adolescents commonly develop adult-type tuberculosis. Extensive forms of tuberculosis are

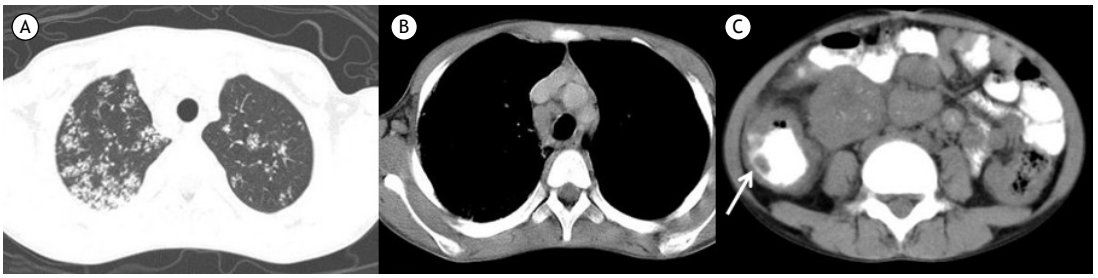


Figure 6. Chest CT scans showing disseminated tuberculosis in a nine-year-old child. In A, airspace nodules exhibiting a tree-in-bud pattern. In B, enlarged right paratracheal lymph nodes. In C, marked thickening of the cecum (arrow).

common in this age group, and more than half of such patients have active tuberculosis.[4,44,46] The differences in findings between children and adolescents are summarized in Chart 3.

In view of the relative complexity of diagnosing pulmonary tuberculosis in children, the Brazilian National Tuberculosis Control Program of the Brazilian National Ministry of Health adopted, in 2002, a scoring system for the diagnosis of pulmonary tuberculosis in children and adolescents (when bacteriological findings or molecular test results are negative). The scoring system does not rely on procedures for the collection of material for bacteriological examination (e.g., sputum induction and gastric lavage) to establish the diagnosis. The Brazilian scoring system is one of the few that have been validated in HIV-infected and HIV-uninfected children, and it has performed well in real-life studies.[47,48] Over the years, changes have been made to the scoring system with regard to the interpretation of TST results. A TST induration ≥ 5 mm indicates infection with *M. tuberculosis*, even in patients vaccinated with BCG at birth. The latest version of the scoring system is summarized in Chart 4.[4]

Pulmonary tuberculosis may be suspected in children and adolescents with slowly progressive pneumonia; that is, pneumonia that is presumably caused by common germs and does not improve as expected with antimicrobial treatment. Often, what is of note is the clinical and radiological dissociation, that is, there may be improvement in symptoms and persistence or worsening of radiological findings. In adolescents, the diagnosis can be attempted by sputum examination either using conventional bacteriological methods or molecular methods. In Brazil, the standard method is the RMT-TB.[4,44]

One study of pediatric patients with pulmonary tuberculosis at a tertiary care hospital showed that RMT-TB positivity was 33% and 64% among the children and adolescents, respectively, whereas culture positivity was approximately 42% in both groups. The rate of rifampin resistance among the patients was 10%. However, the rate of rifampin resistance among only the patients with an RMT-TB result of "*M. tuberculosis* detected" was 17%, which is similar to that reported in the literature.[42] In 2017, the WHO started to recommend the use of Xpert Ultra, which is more sensitive than its predecessor, with good prospects for use in paucibacillary cases, such as in children and individuals living with HIV/AIDS.[49]

In HIV-infected patients, the clinical presentation of tuberculosis may vary according to their degree of immunosuppression. The extrapulmonary and disseminated forms are more common in HIV-infected children. In general, the diagnostic workup requires the use invasive methods, such as thoracentesis and lumbar puncture, as well as biopsy of solid organs, such as lymph nodes and the pleura.[4] In HIV-infected children, raising a diagnostic suspicion of pulmonary tuberculosis can be more complex because it is necessary to make a differential diagnosis from some HIV-related lung diseases, such as pneumocystosis, other mycoses, and lymphocytic interstitial pneumonia. In addition, TST sensitivity can be affected by HIV-induced anergy.[4,48]

DIAGNOSIS OF LATENT *M. TUBERCULOSIS* INFECTION

The state of an individual in the "window period" between becoming infected with *M. tuberculosis* and developing active tuberculosis is known as latent tuberculosis infection (LTBI), that is, the individual is infected with the tuberculosis bacillus but shows no signs or symptoms of active disease.[4,50]

There are currently no methods capable of measuring the global prevalence of LTBI; however, one quarter of the global population is estimated to be infected with *M. tuberculosis*.[51] Being infected does not necessarily mean that the individual will develop active tuberculosis at some point in the future. However, we can infer that infected individuals are reservoirs of tuberculosis bacilli, which can be reactivated under conditions that alter the competence of the immune system, such as HIV infection.[4] In addition, the greatest risk of developing active disease occurs within the first 2 years after primary infection, which is why contacts of active tuberculosis cases should also be included in LTBI case finding.[52] The presence of other immunosuppressive conditions or conditions considered to be risk factors should be evaluated within the context of each epidemiological scenario.[53]

With the advent of biologic agents, greater attention has come to be focused on the LTBI status of patients on biologic therapy. Not all biologic agents currently

Chart 3. Clinical findings, radiological findings, and history of contact in children and adolescents with pulmonary tuberculosis.

		Children[a]	Adolescents[a]
Clinical findings	Persistent fever		
	Weight loss (or lack of weight gain)		
	Irritability		
	Persistent cough		
	Expectoration (sometimes streaked with blood)		
Contact	History of contact with tuberculosis		
Radiological findings	Pulmonary lymph node involvement		
	Opacity		
	Nodules		
	Cavitations		
	Pleural effusion		
	Miliary pattern		

[a]In gray: less common; and in blue: more common.

Chart 4. Diagnosis of pulmonary tuberculosis in children and adolescents with negative smear and/or rapid test results.

Clinical profile	Radiological profile	Contact with an adult with tuberculosis	TST	Nutritional status
Fever or symptoms such as cough, adynamia, expectoration, weight loss, and sweating for > 2 weeks (15 points)	Enlarged hilar lymph nodes or miliary pattern Condensation or infiltrate (with or without cavitation) that remains unchanged for > 2 weeks Condensation or infiltrate (with or without cavitation) for > 2 weeks, with worsening of symptoms or lack of improvement with the use of antibiotics for common germs (15 points)	Close contact within the past two years (10 points)	Induration between 5-9 mm (5 points) Induration ≥ 10 mm (10 points)	Severe malnutrition (5 points)
Asymptomatic or symptomatic for < 2 weeks (0 points) Improvement in respiratory infection with the use of antibiotics for common germs or without the use of antibiotics (10 points)	Condensation or infiltrate of any type for < 2 weeks (5 points) Normal chest X-ray (5 points)	Occasional or no contact (0 points)	Induration < 5 mm (0 points)	Weight ≥ 10th percentile (0 points)

TST: tuberculin skin test. Interpretation: ≥ 40 points (very likely diagnosis) → it is recommended that tuberculosis treatment be initiated; 30-35 points (possible diagnosis) → treatment should be initiated at the discretion of the physician; < 25 points (unlikely diagnosis) → further investigation of the child/adolescent should be undertaken.

used in clinical practice exponentially increase the risk of reactivation of tuberculosis in patients with LTBI. AntiTNF-α biologic agents (anti-TNF-α antibodies and recombinant TNF-α-blocking proteins), which are mainly used in the treatment of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis, are the most significant contributors to increasing the risk of LTBI progressing to active tuberculosis.[54,55] Nevertheless, the risks posed by other immunosuppressive agents, such as corticosteroids, methotrexate, and leflunomide, should not be overlooked.[56]

The WHO and the Brazilian National Ministry of Health differ in their lists of indications for investigation of LTBI (Chart 5).[4,53] There is currently no gold standard test for the diagnosis of LTBI, which is based not only on the result of a diagnostic test but also on the exclusion of active tuberculosis. At present, the two methods that have been validated and are recommended in clinical practice are the TST and interferon gamma release assays (IGRAs). Both are imperfect and indirect methods, that is, they assess the response of an individual to exposure to mycobacterial antigens rather than detecting latent mycobacterial antigens in the body.[57] In addition, neither can predict disease progression nor differentiate latent from active tuberculosis.[58]

The TST is the oldest and most classically used method.[59] TST results reflect a delayed-type hypersensitivity reaction to the mycobacterial antigen, the standard positivity cutoff in Brazil being a 5-mm induration.[4]

Like the TST, IGRAs assess the cell-mediated immune response. However, unlike the TST, IGRAs assess this in vitro by measuring the IFN-γ released by T lymphocytes in response to *M. tuberculosis*-specific antigens, overcoming the main limitations of the TST (BCG vaccination cross-reactivity and NTM infection).[53]

At present, the TST is the only method available via the Brazilian Unified Health Care System for the management of LTBI at public health care facilities. The only IGRA that is cleared by the Brazilian National Health Oversight Agency is QuantiFERON-TB (QFT; QIAGEN, Hilden, Germany). Although QuantiFERON-TB is approved by the Brazilian National Commission for the Incorporation of Technologies into the Brazilian Unified Health Care System, it is, at this writing, available only at private health care facilities and not at public ones, despite the fact that it has been cleared and is recommended by the Brazilian National Ministry of Health for use in the country.[4]

The advantages and disadvantages of the TST and IGRAs are well known and are summarized in Chart 6. The choice of which method to use should take into account the availability and accessibility of the methods.[53,60]

From a review of the literature and international recommendations, the following can be concluded:

- The TST and IGRAs can both be used as methods to diagnose LTBI, and the presence of active tuberculosis should be ruled out before recommending treatment for LTBI.
- There are insufficient data to recommend the use of either the TST or IGRAs as a first-line method to diagnose LTBI.
- Neither the TST nor IGRAs can predict LTBI progression to active tuberculosis.
- Neither the TST nor IGRAs can differentiate LTBI from active tuberculosis.
- BCG vaccination in childhood should not be a determining factor in deciding whether to use the TST, because it has a limited effect on the interpretation of TST results later in life.

Regardless of which method is used, individuals with documented TST or IGRA positivity should not be retested, even after a new exposure to *M. tuberculosis*.[4] That is because TST and IGRA results both reflect the response of an individual to previous exposure to mycobacterial antigens, rather than detecting mycobacterial antigens. Conversion of a TST or IGRA (from positive to negative) can occur as a result of intrinsic or drug-induced immunosuppression, errors in test administration, or

Chart 5. Indications for investigation of latent tuberculosis infection according to the Brazilian National Ministry of Health (NMH) and the WHO.

Indication	Brazilian NMH	WHO
Being a contact of an adult or child with pulmonary or laryngeal TB (in the past two years)	✓	✓
Being HIV-infected and having a CD4+ T-lymphocyte count ≥ 350 cells/mm^3	✓	✓
Being on a TNF-α inhibitor or a CCS (> 15 mg/day of prednisone or equivalent for more than one month)	✓	✓
Having fibrotic radiological changes suggestive of sequelae of TB	✓	Not mentioned
Being a pre-transplant patient who is likely on immunosuppressive therapy	✓	✓
Having silicosis	✓	✓
Having head or neck cancer, lymphoma, or any other hematologic malignancy	✓	Not mentioned
Being a cancer patient on immunosuppressive therapy	✓	Not mentioned
Being a kidney failure patient on dialysis	✓	✓
Having diabetes mellitus	✓	Not an indication
Having a low body weight (< 85% of ideal body weight)	✓	Not an indication
Having an isolated calcification (without fibrosis) on chest X-ray	✓	Not mentioned
Being a smoker (≥ 1 pack per day)	✓	Not an indication
Being a health professional or living or working in the prison system or long-term care institutions	✓	✓

TB: tuberculosis; and CCS: corticosteroid.

Chart 6. Advantages and disadvantages of the tuberculin skin test and IFN-γ release assays.

TST	IGRAs
Requires complex training	Require simple training
Requires patients to return for the reading	Require just one patient visit for blood draw
Does not require special laboratory infrastructure	Require special laboratory infrastructure
Is inexpensive	Are expensive
Does not yield indeterminate results	Can yield indeterminate results
Is affected by BCG vaccination and NTM infection	Use Mtb-specific antigens

TST: tuberculin skin test; IGRAs: interferon gamma release assays; Mtb: *Mycobacterium tuberculosis*; and NTM: nontuberculous mycobacteria.

problems with the test. In the case of IGRAs, spontaneous conversion can reflect dynamic immunological processes, difficulties in the reproducibility of the test, or simply variations from person to person.[61]

AUTHOR CONTRIBUTIONS

All authors participated in all stages of the development of this consensus statement, from conception to final approval.

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REVIEW ARTICLE

Tuberculosis and COVID-19, the new cursed duet: what differs between Brazil and Europe?

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ABSTRACT

On April 1st, 2020, COVID-19 surpassed tuberculosis regarding the number of deaths per day worldwide. The combination of tuberculosis and COVID-19 has great potential for morbidity and mortality. In addition, the COVID-19 pandemic has had a significant impact on the diagnosis and treatment of tuberculosis. In this review article, we address concurrent tuberculosis and COVID-19, with particular regard to the differences between Brazil and Europe. In addition, we discuss priorities in clinical care, public health, and research.

Keywords: Tuberculosis; COVID-19; SARS-CoV-2; Coronavirus.

INTRODUCTION

Tuberculosis became the leading cause of death from infectious disease worldwide in 2015, when it surpassed HIV infection.[1] However, on April 1, 2020, COVID-19 surpassed tuberculosis in terms of the number of deaths per day.[2]

Since the beginning of the COVID-19 pandemic, cases of concurrent tuberculosis and COVID-19 have been reported.[3,4] The combination has great potential for morbidity and mortality. In addition, the COVID-19 pandemic has had a significant impact on the diagnosis and treatment of tuberculosis. The reduction in demand for the diagnosis and treatment of tuberculosis may be reflected in future incidence and mortality rates.[5]

In this review article, we address concurrent tuberculosis and COVID-19, with particular regard to the differences between Brazil and Europe. In addition, we discuss priorities in the management of clinical care and public health, as well as in research.

INTERACTIONS BETWEEN TUBERCULOSIS AND COVID-19

A review article published in 2021[6] summarized what is known on the interactions between tuberculosis and COVID-19. That review subdivided the topic into epidemiology, clinical presentation, prognosis, mortality, and impact on health care services.

CLINICAL PRESENTATION OF CONCURRENT TUBERCULOSIS AND COVID-19

The first obvious aspect of the clinical presentation of concurrent tuberculosis and COVID-19 is that the majority of patients with COVID-19 report signs and symptoms that largely correspond to those of tuberculosis, making the differential diagnosis difficult.[6-8]

Since the publication of the first cohort study of patients with tuberculosis and COVID-19,[9] it has been unclear whether and to what extent COVID-19 might increase the risk of the development of active tuberculosis in patients previously infected with *Mycobacterium tuberculosis*. Such a mechanism played a role when HIV infection boosted the tuberculosis epidemic. Preliminary data do not support that hypothesis for infection with SARS-CoV-2, although it remains an open question.[7]

PROGNOSIS AND MORTALITY

The real effect of COVID-19 as an additional risk factor for tuberculosis mortality (and vice-versa) has yet to be clearly established in different settings.[4] The main difficulty is to "clean" the interaction between the two diseases that form this "cursed duet" from the effect of age and, especially, of comorbidities (which, in turn, tend to increase with age), as well as of social determinants, such as poverty and malnutrition.[6,10] Similarly, the effect of COVID-19 in the probability

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of achieving a satisfactory outcome has yet to be described adequately.[7]

PREVENTION

Mycobacterium tuberculosis and SARS-CoV-2 are both spread through airborne transmission, although SARS-CoV-2 is much more infectious. In theory, the classical infection control measures,[11-13] including the use of personal protection equipment, environmental control, and administrative measures, should be effective. Physical distancing measures use concepts from tuberculosis infection control, adapting them to the context of the pandemic and the high transmissibility of SARS-CoV-2.[14]

Another major area of current debate concerns the role of vaccines. With regard to tuberculosis, we still rely on an old vaccine that has only relative/incomplete effectiveness (the BCG vaccine), whereas new, rapidly developed vaccines against SARS-CoV-2 are presently being used. The potential protective effect of the BCG vaccine against COVID-19 is still controversial.[15]

CLINICAL MANAGEMENT

Preliminary evidence suggests that there is a specific need for oxygen supply and invasive or noninvasive ventilation in patients with tuberculosis and COVID-19,[6,14] which further complicates the management of such patients. The subsequent waves of COVID-19 have differently burdened the ICUs in the affected countries, and the cadres traditionally involved in the clinical management of tuberculosis (pulmonologists and specialists in infectious diseases) seem to play a central role in the first-line response to the COVID-19 pandemic.[6,16,17]

SEQUELAE OF TUBERCULOSIS: EVALUATION AND REHABILITATION

The rehabilitation of individuals with sequelae of tuberculosis is an important area that has garnered more and more interest over time.[18-23] After completing antituberculosis treatment, patients often suffer from a variety of health problems, including difficulty engaging in physical exercise or even performing activities of daily living, resulting in deterioration of their quality of life.[24] A proportion of those patients can benefit from pulmonary rehabilitation, as recently demonstrated.[18-20] The core of the problem is how to evaluate the patients completing antituberculosis treatment by using simple, inexpensive tools, such as spirometry, oximetry, and the six-minute walk test, in order to identify those who are eligible for pulmonary rehabilitation.[25] Quality of life can also be evaluated with simple questionnaires.[24-26] Because COVID-19 can increase the number of sequelae, it is of utmost importance to evaluate patients with tuberculosis and COVID-19, as well as to determine their need for pulmonary rehabilitation.[23]

IMPACT ON HEALTH CARE SERVICES AND ON RESEARCH ACTIVITIES

The impact that the combination of tuberculosis and COVID-19 has had on health care services and research activities has been clearly highlighted in various studies, although the real overall economic impact is yet to be known.[27-35] A recent Global Tuberculosis Network study[5] clearly indicated that the rate at which active and latent tuberculosis are diagnosed has decreased during the COVID-19 pandemic in many countries, and that could have serious consequences for tuberculosis incidence and mortality in the future. One interesting study recently addressed aspects of the issue in Brazil.[36] The authors demonstrated that the cumulative number of new tuberculosis cases in the State of Bahia was 26.4% lower in the period from January to July of 2020 than in the same period in 2019.[36]

TUBERCULOSIS IN BRAZIL AND EUROPE

In Brazil, 73,864 cases of tuberculosis were diagnosed in 2019 (35.0 cases/100,000 population). In 2018, 4,490 tuberculosis-related deaths were reported in the country (2.2 deaths/100,000 population). Since 2010, the tuberculosis mortality rate has remained stable (2.2-2.3 deaths/100,000 population). The cure rates of new cases of pulmonary tuberculosis, retreatment of pulmonary tuberculosis, and rifampin-resistant/multidrug-resistant tuberculosis (MDR-TB) were 71.9%, 51.9%, and 55.7%, respectively. In general, there is a trend toward an improvement in the cure rates of new tuberculosis cases.[37]

In the WHO Region of the Americas, a gradual increase in the incidence of tuberculosis has been attributed to an upward trend observed in Brazil. Although a consistent trend toward a decrease was observed between 2010 and 2016, the tuberculosis incidence rate in the country increased in 2017 and 2018 when compared with the previous period.[37,38]

In 2018, 52,862 tuberculosis cases were reported in 30 countries in the European Union and European Economic Area. The joint European Centre for Disease Prevention and Control/WHO report[39] showed a decrease of 4% in the overall rate reported over the last five years in those countries. Of all of the tuberculosis cases reported, 40,625 (76.9%) were newly diagnosed, and 35.0% were of foreign origin. In 999 cases (3.7%), MDR-TB was detected (by drug susceptibility testing). Of those, 808 were tested for second-line drug susceptibility and extensively drug-resistant tuberculosis was detected in 19.6%. The rate of reported MDR-TB cases decreased from 0.3/100,000 population in the 2014-2016 period to 0.2/100,000 population in 2017 and remained unchanged in 2018. Among all of the reported cases of tuberculosis, the final outcome was cure in 67.6% and death in 6.9%, compared with 49.9% and 15.7%, respectively, among the reported cases of MDR-TB.[39]

In the WHO European Region, the mean annual decline in the tuberculosis incidence rate between 2014 and 2018 was 5.1%. The WHO European Region almost reached the 2020 End TB Strategy milestone (i.e., to reduce the tuberculosis incidence rate by 20% in 2020 against the 2015 baseline rate), with a reduction of 19% in the tuberculosis incidence rate, and is on track to reach the 2020 milestone for tuberculosis mortality (a 31% reduction). Although progress has been made in reducing the number of cases of tuberculosis and the mortality rate, treatment success rates in the region are still below regional and global targets.[38]

COVID-19 IN BRAZIL AND EUROPE

The incidence of SARS-CoV-2 infection and the number of deaths due to COVID-19 between January of 2020 and January of 2021 are shown in Figures 1 and 2, respectively, for Brazil and for five major European countries (France, Germany, Italy, Spain, and the United Kingdom). The first wave was more pronounced in Brazil than in those European countries (Figure 1). In Brazil and in the United Kingdom, the peaks of new infections were highest between the end of 2020 and the beginning of 2021. The situation is similar in terms of mortality, the United Kingdom reporting the highest peak. With the exception of Germany, two peaks in the number of deaths were observed in all countries, those peaks being more prolonged in Brazil (Figure 2). The epidemiological patterns described in the various countries result from specific features of the pandemic, the response by health care facilities, and the preventive measures adopted.[40] Figure 3 summarizes the information available, by WHO Region.

PRIORITIES FOR CLINICAL MANAGEMENT

Diagnosing tuberculosis during the COVID-19 pandemic requires a high degree of clinical suspicion, because the two diseases have similar characteristics, such as fever and respiratory symptoms. In addition, tuberculosis and COVID-19 can present simultaneously, as previously demonstrated in the first cohort study of patients with tuberculosis and COVID-19.[9] Often, the investigation carried out for the diagnosis of COVID-19, such as a CT of the chest, detects an undiagnosed pre-existing tuberculosis infection.[3]

In settings with a high tuberculosis burden, the possibility of a concomitant diagnosis of tuberculosis and COVID-19 should always be considered in order to ensure the appropriate management of both diseases.[41] It has been suggested that the development of algorithms for the management of the tuberculosis/COVID-19 combination could improve outcomes.[42]

Some of the drugs used in the treatment of COVID-19 (such as hydroxychloroquine, remdesivir, dexamethasone, and anticoagulants) may interfere with the treatment of tuberculosis. Although the short-term use of corticosteroids is indicated in some

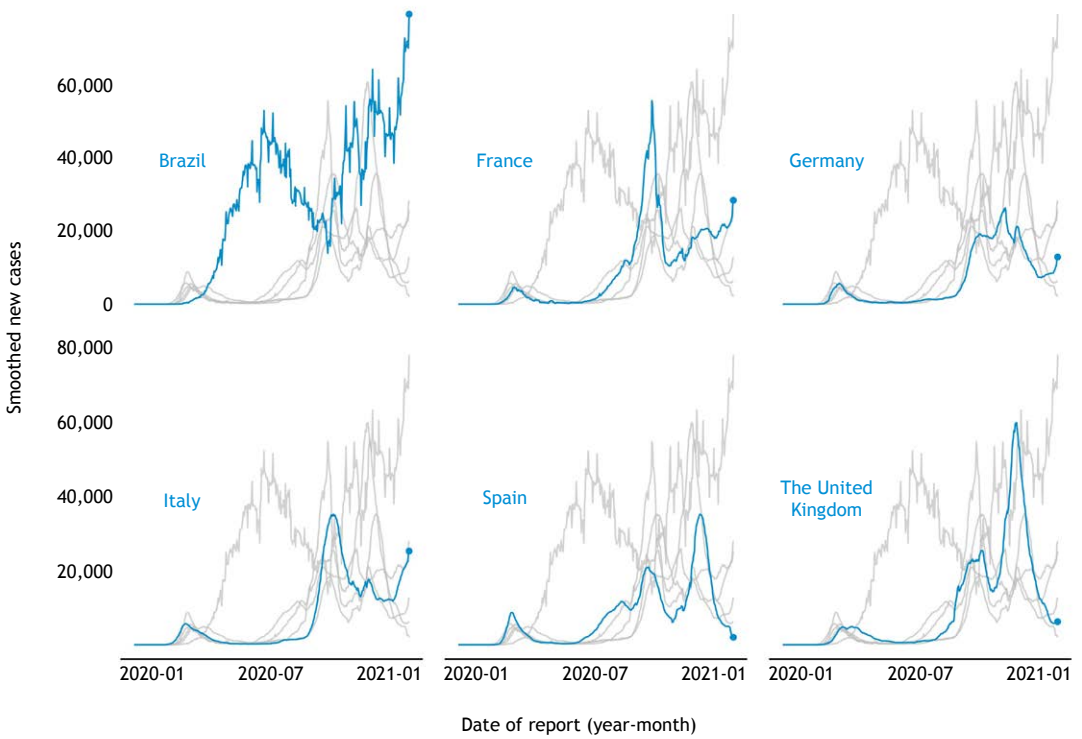

Figure 1. Number of new COVID-19 cases in six countries between January of 2020 and January of 2021. Source: COVID Intel database; data retrieved on March 15, 2021.

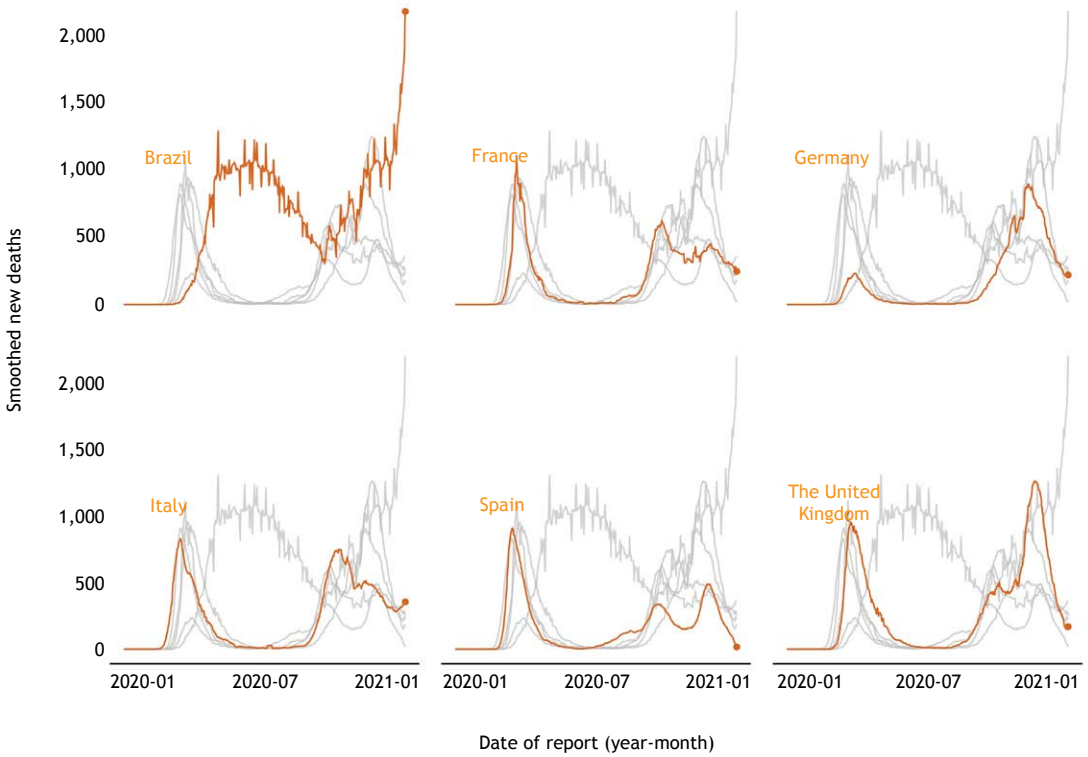

Figure 2. Number of new deaths in six countries between January of 2020 and January of 2021. Source: COVID Intel database; data retrieved on March 15, 2021.

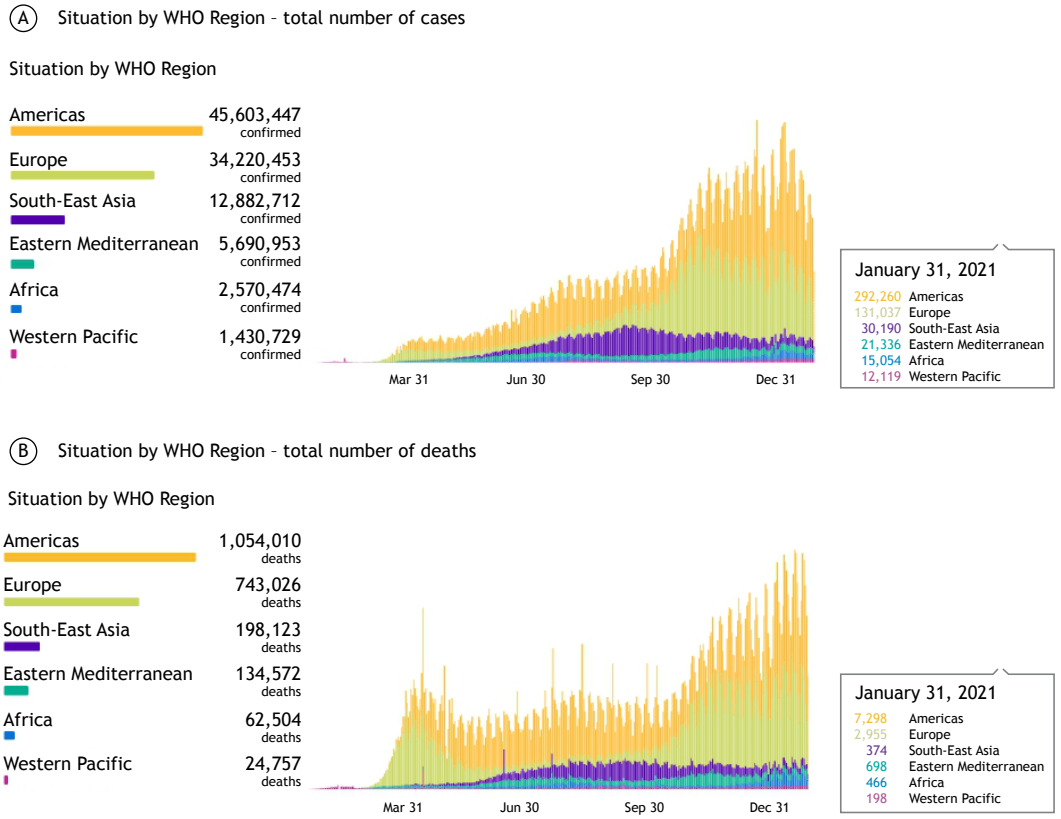

Figure 3. Total number of cases (in A) and total number of deaths (in B), by WHO Region, from the beginning of the COVID-19 pandemic to January 31, 2021. Source: World Health Organization. https://covid19.who.int/

situations in COVID-19 patients, their prolonged use for the treatment of post-COVID-19 organizing pneumonia may result in tuberculosis reactivation. In addition, the doses of antituberculosis drugs that have hepatotoxic or nephrotoxic potential should be adjusted in cases of patients with severe COVID-19 who show changes in liver and kidney function.[42,43] It is also important to bear in mind that COVID-19 can lead to sequelae, such as pulmonary fibrosis, which can reduce the penetration of antituberculosis drugs in the lungs, thus contributing to poor outcomes, especially in patients with MDR-TB.[42]

Patients with tuberculosis and COVID-19 may be at a greater risk of poor outcomes and death than are those with COVID-19 alone.[3,4,44,45] One study showed that the risk of death was 2.17 times higher in patients with tuberculosis and COVID-19 than in those with COVID-19 only.[44] Therefore, early detection of the combination is important for the proper management of both diseases. In addition, adequate isolation of tuberculosis patients, thus minimizing their exposure to SARS-CoV-2, can prevent coinfection.[46] It has been demonstrated that patients with tuberculosis and COVID-19 are 25% less likely to recover from the latter.[44] In addition, patients with pulmonary sequelae due to COVID-19 may have a higher risk of developing tuberculosis in the future.[42]

COVID-19 can also have a negative impact on latent tuberculosis infection (LTBI). The immune dysregulation caused by COVID-19 can affect the diagnosis and management of LTBI.[47] In that sense, many questions remain open. It is unknown, for example, whether there is a need to screen patients with severe COVID-19 with a tuberculin skin test/IFN-γ release assay before prescribing immunosuppressant drugs and, in the case of a positive result on the tuberculin skin test/IFN-γ release assay, whether immunosuppressant drugs currently in use should be discontinued. Additional studies are also needed in order to understand the role of SARS-CoV-2 in the progression from LTBI to active tuberculosis and to plan the post-COVID-19 follow-up of such patients.[3] Chart 1 summarizes the priorities for clinical management.

PRIORITIES FOR PUBLIC HEALTH MANAGEMENT

Given that tuberculosis is a major public health problem in Brazil and that COVID-19 is a health emergency with increasing numbers of cases in our country, we need to identify strategies for the best management of these two infectious diseases of the respiratory tract in our country.

The control of COVID-19 is based on the same strategies as those of tuberculosis control: early detection of infectious cases, infection prevention, and contact tracing.[48] Therefore, by adapting and integrating existing control programs, we can reduce the spread of COVID-19 and improve tuberculosis control.[48,49] However, to achieve this goal, some priorities should be addressed.

Regarding patient care, physicians and nurses should be trained in COVID-19 diagnosis and control.[48] Patients with respiratory symptoms can be tested for both pathogens, depending on clinical presentation. In addition, close contacts can be screened for *M. tuberculosis* and SARS-CoV-2 infection in order to control the spread of disease.[50]

The tuberculosis control program can share its laboratory network to support the diagnosis of COVID-19 efficiently if microbiological safety cabinets become widely available in our country. In addition, the implementation of automated molecular tests, such as the Xpert Xpress SARS-CoV-2 assay (Cepheid, Sunnyvale, CA, USA), could be an alternative for our laboratories, because the Xpert MTB/RIF Ultra

Chart 1. Priorities for clinical management.

• High degree of clinical suspicion for the diagnosis of tuberculosis due to the similarity of symptoms with those of COVID-19.
• In settings with a high tuberculosis burden, the possibility of a concomitant diagnosis of tuberculosis and COVID-19 should always be considered.
• Development of algorithms for the management of the tuberculosis/COVID-19 combination can improve outcomes.
• The doses of antituberculosis drugs with hepatotoxic or nephrotoxic potential should be adjusted in patients with severe COVID-19 who show changes in liver and kidney function.
• Remember that the prolonged use of corticosteroids for the treatment of post-COVID-19 organizing pneumonia may result in tuberculosis reactivation.
• Remember that COVID-19 can lead to sequelae, such as pulmonary fibrosis, which can reduce the penetration of antituberculosis drugs in the lungs, contributing to poor outcomes, as well as to the development of multidrug-resistant tuberculosis.
• Patients with tuberculosis and COVID-19 may be at a greater risk of poor outcomes and death than are those with COVID-19 alone. Therefore, early detection of the combination is important for the proper management of both diseases.
• Adequate isolation of tuberculosis patients, thus minimizing their exposure to SARS-CoV-2, can prevent coinfection.
• Remember that patients with pulmonary sequelae due to COVID-19 may have a higher risk of developing tuberculosis in the future.
• The diagnosis and management of latent tuberculosis infection can be affected by the immune dysregulation caused by COVID-19.

assay (Cepheid) has already been incorporated for the diagnosis of tuberculosis and both tests use the same equipment.

The community also has an important role to play, and community-wide education on behavioral practices, such as the use of masks, may be reinforced to reduce the transmission of *M. tuberculosis* and SARS-CoV-2.[48,50]

The integration of tuberculosis into the geospatial mapping system set up to report cases of COVID-19 could be useful to improve the tracing of tuberculosis cases and their contacts.[50] In addition, COVID-19 has necessitated the use of virtual tools for the in-home management of cases. These tools can help increase adherence to tuberculosis treatment and should be incorporated into tuberculosis control programs. Finally, the economic support provided during the

Chart 2. Main research questions on COVID-19 and tuberculosis, by field of study.

Field of study	Research question
Human exposure and immunology	When and where did COVID-19 first appear? What are the main immunological consequences of exposure to *Mycobacterium tuberculosis* and SARS-CoV-2?
Epidemiology	What is the real impact of COVID-19 on the epidemiology of tuberculosis and vice-versa? To what extent can SARS-CoV-2 trigger latent tuberculosis to evolve into active tuberculosis?
Transmission	What is the relevance of COVID-19 transmission via surface contamination, fecal-oral route, and aerosols versus droplet transmission? What is the relevance of transmission occurring from asymptomatic individuals? What are the implications for the prevention of transmission?
Signs and symptoms	What are the signs and symptoms possibly supporting the initial differential diagnosis between the two diseases?
Comorbidities	What is the role of different comorbidities on the incidence and mortality of the two diseases separately and when they are combined?
Vaccine	What is the real effectiveness and epidemiological impact of the COVID-19 vaccination program that has recently begun? What about vaccination of specific groups, such as the elderly and immunocompromised individuals? Is the BCG vaccine protective against COVID-19?
Other preventive measures	What are the most effective prevention measures (hand washing, use of personal protection equipment, physical distancing, other mitigation measures such as curfews and lockdowns, etc.) in different COVID-19 epidemiological scenarios?
Rapid diagnostics	What are the feasibility, importance, and potential impact of combined rapid diagnostics?
Treatment	What treatment is effective against COVID-19? Are corticosteroids necessary? Is there a relevant drug-to-drug interaction to monitor specifically? What is the importance of providing oxygen supplementation or invasive/noninvasive ventilation, and when should they be initiated? Are treatment outcomes different in patients with the tuberculosis/COVID-19 combination? What is the need for pulmonary rehabilitation following tuberculosis or COVID-19? Is pulmonary rehabilitation effective?
Case definition	What is the final case definition and associated criteria for classification of COVID-19, which are still subject to updates?
Stigma	What types of stigma are associated with the two diseases, and what can be done to prevent that?
Policy development	What have we learned in terms of policy development, risk communication, rapid implementation of travel policies, and quarantine restrictions, etc., one year after the beginning of the COVID-19 pandemic?
Resource mobilization	Can the rapid but sometimes chaotic resource mobilization experienced during the COVID-19 pandemic be used in order to prepare rational, comprehensive epidemic prevention/control plans for the future? Can this resource mobilization include benefits for tuberculosis prevention as well?
Economic impact	What is the overall cost of the COVID-19 pandemic to the global economy? To what extent will the COVID-19 epidemic create an additional economic burden that will impact the tuberculosis epidemic in the future?
Stress on health care systems	What is the real stress imposed by the two diseases on health care systems presently and in the coming future?
Data availability	How can we improve surveillance data to make evidence-based decisions?

COVID-19 pandemic should continue for patients with tuberculosis, prioritizing those living in poverty.[50]

PRIORITIES FOR RESEARCH

Although much has been written on the topic of tuberculosis and COVID-19, the quantity of evidence in the literature is still modest. An international study has recently been initiated with the objective of describing the interactions between the two diseases using a large individual cohort (over 600 patients) in approximately 40 countries in all continents.[7]

As summarized in Chart 2, important research questions can be derived from the studies available.[4-7,9,11,15,42,44-46,49,51,52] Those questions are related to the following major areas of interest: human exposure and immunology; epidemiology; transmission; signs and symptoms; comorbidities; vaccines and other preventive measures; rapid diagnostics; treatment; case definition; stigma; policy development; resource mobilization; economic impact; stress on health care systems; and data availability.

FINAL CONSIDERATIONS

This review article describes specific features of tuberculosis and COVID-19 according to what is known in Brazil and in Europe to date. Because the COVID-19 pandemic is still in progress, much needs to be known in order to maximize the impact of new discoveries and the implementation of best practices.

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AUTHOR CONTRIBUTIONS

DRS and GBM: conception and planning of the study; drafting and revision of preliminary and final versions; and approval of the final version. FCQM, LD, RC, and MPD: drafting and revision of preliminary and final versions; and approval of the final version.

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Association between Xpert MTB/RIF cycle threshold values and sputum smear microscopy in patients with pulmonary tuberculosis

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TO THE EDITOR:

In 2010, the WHO endorsed the use of the Xpert MTB/RIF assay (Cepheid; Sunnyvale, CA, USA) in countries with a high burden of tuberculosis, considering it to be a technology capable of revolutionizing the diagnosis of the disease.[1] Xpert MTB/RIF assay results are automatically generated and are reported as either negative or positive for *Mycobacterium tuberculosis*, and in the latter case, as whether the strain is susceptible or resistant to rifampin. Xpert MTB/RIF assay results are also reported as cycle threshold (C_T) values, which correspond to the number of PCR cycles required to detect *M. tuberculosis*. Each additional cycle represents an approximate 50% decrease in the amount of material present in a sample over the previous cycle, thus providing a semiquantitative measure of bacillary burden, and higher C_T values correspond to lower bacillary burden.[2]

Given the WHO recommendation to replace sputum smear microscopy with Xpert MTB/RIF as an initial diagnostic test for tuberculosis (although smear microscopy is still used in some countries), because culture results take several weeks, Xpert MTB/RIF C_T values may be the only way to assess bacillary burden.[3-6] The objective of the present study was to assess the association between Xpert MTB/RIF C_T values and sputum smear microscopy and to assess the diagnostic performance of Xpert MTB/RIF C_T values.

This was a cross-sectional study of prospectively collected data, conducted at the tuberculosis outpatient clinic of a health care center in the city of Alvorada, Brazil, where the incidence of tuberculosis was 84.4 cases/100,000 population between 2017 and 2019.[7] The study was approved by the Research Ethics Committee of the Porto Alegre *Hospital de Clínicas*, located in the city of Porto Alegre (Protocol no. 160063).

Patients aged 18 years or older who had respiratory symptoms suggestive of pulmonary tuberculosis and were able to produce sputum were invited to participate. Those who could not produce sputum were excluded, as were patients with extrapulmonary tuberculosis. The diagnosis of pulmonary tuberculosis was established in accordance with the Third Brazilian Thoracic Association Guidelines on Tuberculosis.[8]

Data were collected on demographic characteristics, smoking, alcohol abuse, symptoms, and comorbidities. Chest X-rays were classified either as being typical of tuberculosis or as being consistent with tuberculosis.[9] Sputum smears were stained by the Ziehl-Neelsen technique for identification of AFB, and culture was performed using the Ogawa-Kudoh method.[8] The Xpert MTB/RIF assay was performed in accordance with the manufacturer's instructions.[2]

Data analysis was performed with IBM SPSS Statistics, version 18.0 (IBM Corporation, Armonk, NY, USA), and MedCalc, version 16.4.3 (MedCalc Software, Mariakerke, Belgium). On the basis of smear microscopy results (positive or negative), we calculated the sensitivity, specificity, positive predictive value, and negative predictive value of Xpert MTB/RIF C_T values, with the corresponding 95% CIs. We also constructed ROC curves to determine the optimal cutoff. In order to calculate sample size, we considered the fact that the sensitivity of a given Xpert MTB/RIF C_T cutoff was 85% in a previous study.[4] Therefore, using a 95% CI and a power of 80%, the required sample size was estimated to be 100 patients at least.

During the study period, 407 patients underwent Xpert MTB/RIF testing. Of those, 150 had a positive Xpert MTB/RIF result and were included in the study. Table 1 describes the characteristics of the study participants. There was a statistically significant difference in mean C_T between sputum smear-positive and sputum smear-negative patients (17.8 ± 4.8 and 22.3 ± 6.7, respectively; p = 0.002). Sensitivity, specificity, positive predictive value, and negative predictive value of an Xpert C_T cutoff of 22.7 were 83.6% (95% CI: 75.8-89.7), 60.7% (95% CI: 40.6-78.5), 90.3% (95% CI: 85.3-93.7), and 45.9% (95% CI: 34.0-58.3), respectively. The area under the ROC curve for this cutoff was 0.70 (95% CI: 0.62-0.77; p = 0.002).

Few studies[4-6] have assessed C_T cutoffs as a measure of bacillary burden. The C_T cutoffs that have been most widely studied are 28[5,6] and 31.8.[4] Hanrahan et al.[6] demonstrated that a C_T cutoff of 28 had good predictive value for smear positivity, with a sensitivity of 89.9% and a specificity of 67.0%. In another study,[5] the authors showed that lower C_T values were associated with HIV negativity and low BMI and also used a cutoff of 28, reporting a sensitivity of 95% and a specificity of 54.1%. In the present study, a C_T value of 22.7 was found to be the optimal cutoff, which is lower than the

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Table 1. Characteristics of the study participants.

Characteristic	(N = 150)
Demographic characteristics	
Age, years	40.9 ± 15.3
Male gender	108 (72.0)
White ethnicity	102 (68.0)
Active smoking	84 (56.0)
Alcohol abuse	31 (20.7)
Symptoms	
Cough	145 (96.7)
Weight loss	112 (74.7)
Dyspnea	62 (41.3)
Fever	72 (48.0)
Night sweats	97 (64.7)
Hemoptysis	13 (8.7)
HIV positivity	31 (20.7)
Diabetes	18 (12.0)
Radiological features	
Typical of tuberculosis	103 (68.7)
Consistent with tuberculosis	47 (31.3)
Sputum smear positivity	122 (81.3)
Cycle threshold, Xpert MTB/RIF	
	18.7 ± 5.5
Ccpositi(detected)	

*Data presented as mean ± SD or as n (%).

cutoffs used in most studies. However, the decision regarding the optimal C_T cutoff differs according to the context and the objectives of testing. In order to identify as many smear-positive patients as possible, higher C_T values should be chosen. In the context of limited resources, however, patients with lower C_T values should be prioritized for respiratory isolation.[4]

In one meta-analysis,[4] cutoffs of 27.7 and 31.8 were shown to have a sensitivity of 85% and 95%, respectively, as well as a specificity of 67% and 35%, for smear-positive samples. However, the authors concluded that the moderate diagnostic accuracy of C_T values compared with that of sputum smear microscopy, as well as different needs in contexts with varying prevalence of sputum smear positivity, may preclude the use of C_T values as a surrogate for sputum smear microscopy in all contexts.

One of the limitations of the present study was the fact that participants were recruited at a single tuberculosis outpatient clinic. However, we believe that the findings are applicable to similar contexts. In addition, we did not assess whether C_T values can predict infectiousness and transmission, although smear positivity alone has been shown to be an imperfect measure of infectiousness, with evidence of transmission from smear-negative but culture-positive cases.[10] Despite these limitations, to our knowledge, this is the first study in Brazil to assess the accuracy of C_T values as a surrogate for sputum smear microscopy.

In conclusion, Xpert MTB/RIF C_T values are associated with sputum smear results and are lower in smear-positive patients. A C_T value cutoff of 22.7 showed good predictive value for smear positivity.

AUTHOR CONTRIBUTIONS

GCP: study design, methodology, investigation, formal analysis, and writing of the original draft; GRP, KGD, and LRM: methodology, investigation, writing, revision, and editing; and DRS: study design, methodology, investigation, formal analysis, and writing of the original draft.

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Fighting tuberculosis: from 1993 to 2035 during the COVID-19 era

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TO THE EDITOR:

Since the declaration of tuberculosis as a "global emergency" in 1993 and the United Nations General Assembly high-level meeting on tuberculosis in September of 2018,[1] we recognize that progress has been made. However, this progress is fragile given the magnitude of the challenge put to world leaders, particularly the goal of eliminating tuberculosis as a public health problem by 2030 in order to achieve the United Nations Sustainable Development Goals.[1] An enormous effort is required in order to end the tuberculosis epidemic in all countries by 2035 as outlined in the WHO End TB Strategy, which is aimed at reducing tuberculosis mortality by 95%, tuberculosis incidence by 90%, and catastrophic costs by 100%.[2] Tuberculosis remains a serious cause of illness and death worldwide, especially in developing countries. The year 2020 was the first WHO milestone for ending tuberculosis by 2030, but it was also the year in which COVID-19 was declared a pandemic, making 2021 a crucial year for tuberculosis elimination. Each year, we recognize the 24th of March as the World Tuberculosis Day.

Given the serious nature of the tuberculosis epidemic in Brazil, a multisectoral approach is required in order to control it. The *Rede Brasileira de Pesquisas em Tuberculose* (REDE-TB, Brazilian Tuberculosis Research Network)[3] was launched in 2001 and has been a model for other countries since then. The REDE-TB has had a significant role in tuberculosis control in Brazil, especially in the last decade, contributing to the inclusion of research and innovation in the Brazilian National Tuberculosis Control Program agenda. The REDE-TB has changed the research scenario in Brazil over the last decade, with a significant number of new studies and collaborations resulting in the 2015 Brazilian National Tuberculosis Research Agenda, in response to the WHO End TB Strategy.[4-6] The REDE-TB is currently part of the Brazil-Russia-India-China-South Africa Tuberculosis (BRICS TB) Research Network, with a research representative from Brazil.

Brazil did not achieve the 2020 WHO milestone for ending tuberculosis by 2030, and, at this rate, it is unlikely that it will achieve the 2030 and 2035 targets. Unfortunately, at a time when intensified research is needed, Brazil is facing a dramatic reduction in federal funding for basic research. It must be recognized that the burden of tuberculosis in Brazil contributes to the high burden of the disease in the world. In addition, health services in Brazil have been affected by the COVID-19 pandemic, particularly tuberculosis services. Actions taken in response to the COVID-19 pandemic will have far-reaching consequences. Hogan et al.[7] found that disruptions to tuberculosis services during the COVID-19 pandemic could increase the number of deaths from tuberculosis by up to 20% over five years. This might be due to reductions in timely diagnosis and treatment of new cases.

The fact that many tuberculosis health care providers in Brazil were assigned to provide COVID-19 care had a major negative impact on tuberculosis care. As a consequence of the negative impact of the COVID-19 pandemic on tuberculosis services, the Brazilian National Tuberculosis Control Program has reduced screening for latent tuberculosis infection among asymptomatic adults and adolescents in contact with individuals with active tuberculosis; this can lead to delayed diagnosis and treatment of new cases.[8]

Another challenge presented by the COVID-19 pandemic is the increased poverty in Brazil, which will have a negative impact on the indicator of catastrophic total costs due to tuberculosis. The current economic recession can have a significant impact on household financial capacity because of a reduction in income and an increase in unemployment, close monitoring, and effective actions to fight poverty being required.[1]

The scenarios described herein will require a joint effort from the government, academia, and society in general. There is a need to improve tuberculosis testing, treatment, prevention, and research. In order to do that, a massive and committed investment in research and immediate knowledge transfer to society are required.

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Pulmonary disease and the autonomic nervous system: a new pathophysiological mechanism for Lady Windermere syndrome

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TO THE EDITOR:

Lady Windermere syndrome (LWS) is the eponym for a nodular bronchiolocentric form of lung disease caused by nontuberculous mycobacteria (NTM) and occurring predominantly in tall thin White elderly women without previous lung disease. CT findings of LWS include centrilobular nodules, tree-in-bud opacities, and bronchiectasis. Lesions occur predominantly in the middle lobe and lingula (Figure 1). Although *Mycobacterium avium* complex is the most common causative agent, other species can cause LWS. The disease usually has a chronic course and an indolent behavior, as well as being characterized by a progressive increase in lesion size and number. Certain clinical and laboratory characteristics are more common in patients with LWS than in the general population, including scoliosis, pectus excavatum, mitral valve prolapse, benign joint hypermobility syndrome, and genetic mutations (related to cystic fibrosis, affecting ciliary function, causing connective tissue disorders, and involving immune function). Endocrine changes (such as reduced estrogen, leptin, and dehydroepiandrosterone, as well as increased adiponectin and cortisol) have also been reported. Most LWS patients are nonsmokers, and LWS can also affect men, albeit much less commonly. The mean age at diagnosis is usually higher in men than in women. Impaired bronchial clearance is part of the pathophysiological process. LWS is multifactorial, involving genetic, environmental, and aging-related factors.

Here, we hypothesize a pathophysiological mechanism for LWS based on knowledge of the physiology and pathophysiology of the autonomic nervous system, the aging process, and menopause. We suggest that changes in respiratory mechanics and autonomic dysfunction participate in the disease process, LWS occurring predominantly in women because of sex-specific autonomic differences, together with the effects of aging and menopause. A relative reduction in parasympathetic activity, as well as changes in lung and chest wall elasticity, together with a reduction in respiratory muscle strength, can predispose to NTM colonization and disease. Autonomic changes can reduce mucus production and modify the viscoelastic characteristics of the mucus, compromising airway smooth muscle function and cough reflex. Vagotomy significantly inhibits or suppresses cough reflex. Atropine and vagal blockade reduce basal tracheobronchial submucosal gland secretion. The fact that inhaled atropine slows mucociliary transport suggests that vagal tone influences secretion, clearance of tracheobronchial secretions, or both. The parasympathetic nervous system also acts by locally regulating pulmonary inflammation and immunity.

Denervation generates hypersensitivity to stimuli, which is at least partially attributable to an increase in the number of receptors in the postsynaptic membrane. Methacholine acts on muscarinic receptors. In a study comparing asthma patients undergoing methacholine challenge testing, elderly patients had a greater reduction in FVC and a lower perception of bronchoconstriction than did younger patients.[1] In a study of COPD patients undergoing methacholine challenge testing, the prevalence of airway hyperresponsiveness was found to be higher in women than in men.[2] These findings could be at least partially due to autonomic dysfunction. Systemic and local factors are associated with infections in lung transplant recipients, as well as with denervation. Among solid organ transplant recipients, NTM infection is most common in lung transplant recipients.

Differences in autonomic balance between men and women are related to female hormonal changes, autonomic changes also being related to aging. Alterations in extracellular matrix collagen can compromise autonomic activity. Many parasympathetic nerve fibers and almost all sympathetic nerve fibers touch effector cells or, in some cases, end up in the connective tissue adjacent to the cells to be stimulated. Acetylcholinesterase is linked to collagen and glycosaminoglycans in the local connective tissue. One study reported the interactions of acetylcholinesterase with collagen, sphingomyelin, and phosphatidylcholine.[3] Differences in collagen turnover biomarkers have been reported between menopausal and premenopausal women, as well as between menopausal women and men.[4] Other biochemical metabolites also change during menopause, including sphingomyelin (a component of the cell membrane, particularly nerve cells), leucine, and phosphatidylcholine.[5] In a multicenter population-based study conducted in Europe, lung function (particularly FVC) was found to decline more rapidly in transitional and postmenopausal women, beyond the expected age change.[6]

Autonomic changes have been described in joint hypermobility syndrome, Ehlers-Danlos syndrome, and mitral valve prolapse syndrome. LWS can present with similar manifestations as these diseases.

Autonomic differences might be responsible for the difference between men and women with cystic fibrosis regarding average life expectancy, which is 2 years and 7 months shorter for women.[7,8] This hypothesis is

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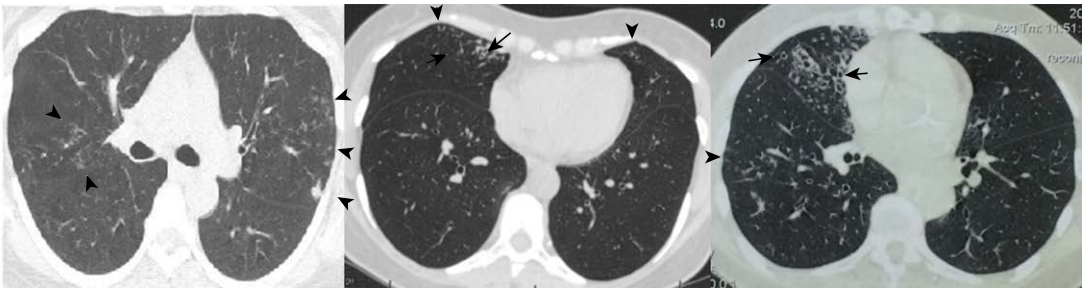

Figure 1. Common chest CT findings for Lady Windermere syndrome. Note centrilobular nodules with a linear branching pattern (tree-in-bud pattern; arrowheads) and bronchiectasis, the latter occurring predominantly in the middle lobe and lingula (arrows). The nodules in the middle of the secondary pulmonary lobule occur where the bronchioles are small in diameter, without cartilaginous support, and with relatively more developed musculature than that of the bronchi (an area theoretically subject to an earlier complication of neuromuscular damage).

consistent with the fact that, although women with cystic fibrosis undergo lung transplantation earlier than men, post–lung transplant survival is the same for men and women and independent of the gender of the donor.[7] It is also of note that girls with cystic fibrosis have infections at a younger age than boys, and the difference in age at onset between males and females is greatest for NTM infections.[8]

Although COPD is associated with fibrocavitary NTM lung disease, most LWS patients are nonsmokers. Nicotine acts on nicotinic acetylcholine receptors. There are also differences between men and women regarding the effects of smoking on nicotinic acetylcholine receptors.[9] A lack of nicotinic receptor stimulation might be associated with a predisposition to LWS.

In an animal study, nebulized hypertonic saline was reported to stimulate pulmonary vagal afferent receptors.[10] This could partially explain the therapeutic effect of nebulized hypertonic saline on humans infected with NTM.

The increase in the number of diagnosed cases of NTM lung disease in the world and the current therapy for this disease (long courses of antibiotics, resulting in side effects, resistance, and relapse) reinforce the need for new lines of research. Studies of the autonomic nervous and respiratory systems could provide a better understanding of the pathophysiological mechanism of LWS and have an impact on pulmonary and systemic conditions such as post–lung transplant follow-up, cystic fibrosis, smoking, and decline in lung function at menopause, as well as other diseases that behave differently in men and women, such as idiopathic pulmonary arterial hypertension and the COVID-19 inflammatory response.

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Giant Rasmussen's aneurysm

Mauro Terra Branco[1], Denise Fabri Engracia Mello[2,3], Ibrahim Nabil Abdel Fattah Ibrahim[4], Edson Marchiori[5], Marcus Vinicius Nascimento Valentin[2,3,4]

TO THE EDITOR:

A 58-year-old man was admitted to the emergency room with a three-month history of cough, expectoration, and weight loss. He reported two episodes of hemoptysis in the last 30 days. Physical examination revealed rhonchi and decreased breath sounds on the right side. A complete blood count was normal. A chest X-ray showed extensive opacification of the right hemithorax, with apical sparing and obliteration of the outline of the ipsilateral heart, hemidiaphragm, and costophrenic sinus (Figure 1A).

A CT scan of the chest showed extensive cavitary consolidation in the right lung parenchyma, with air surrounding a nodule of approximately 9.5 cm × 7.0 cm within the consolidation, characterizing the air crescent sign (Figures 1B and 1C). The nodule showed intense enhancement after intravenous administration of iodinated contrast medium, being consistent with aneurysm formation (Figures 1D and 1E). Sputum examination and bronchoalveolar lavage were positive for AFB, confirming the presence of *Mycobacterium tuberculosis* and establishing a diagnosis of Rasmussen's aneurysm (RA). The patient was started on antituberculosis treatment. He was referred for endovascular embolization but died before the procedure was performed.

An air crescent is a collection of air in a crescentic shape that separates the wall of a cavity from an inner mass or nodule. Although aspergilloma (a fungus ball caused by *Aspergillus* spp. colonization) is the most common cause of an intracavitary nodule, a number of other conditions should be included in the differential diagnosis, including neoplasms (particularly bronchial carcinoma), recovery from angioinvasive aspergillosis, RA, and clots. Other, rarer, causes include foreign bodies, thick pus, dehydrated caseous material, teratoma, and hydatidosis. A useful imaging criterion for the differential diagnosis is a change in the position of the nodule in the cavity when patient position is changed, especially during examination in the supine and prone positions. 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 RA present as masses that are fixed to the cavity wall; that is, they do not move when patient position is changed.[1-3] However, this technique is not useful in the evaluation of large intracavitary masses, as in the case of our patient.

Given the recent rise in reported cases of *M. tuberculosis* infection worldwide, it is extremely important to recognize the complications and sequelae of tuberculosis. In patients with confirmed tuberculosis, aspergilloma is the most common cause of an intracavitary mass/nodule. Other, less common, causes include RA. RA is a rare condition that primarily affects young men and represents a

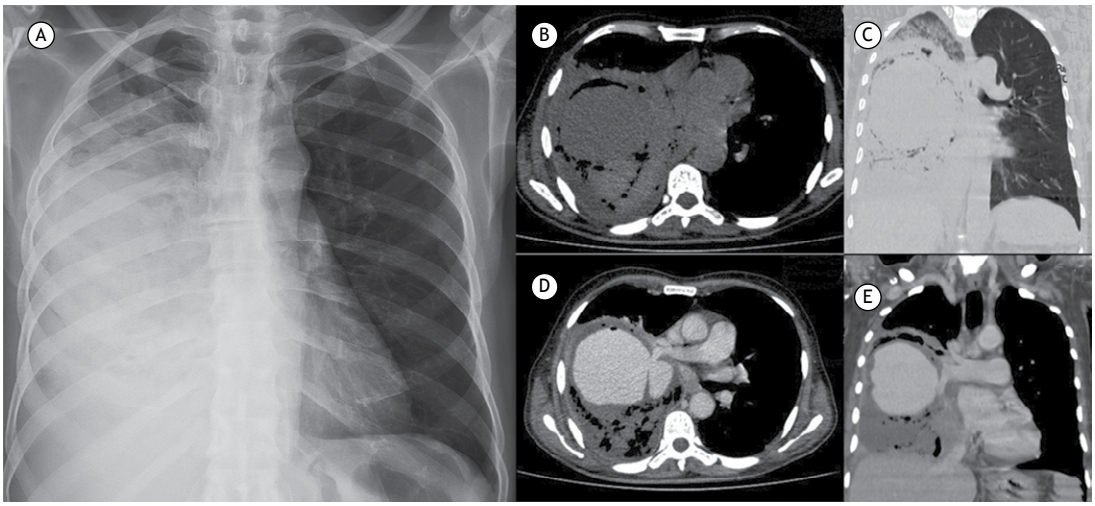

Figure 1. Anteroposterior chest X-ray (in A) showing opacification of the lower two thirds of the right lung. Unenhanced axial CT scan (in B) and coronal reconstruction (in C) showing extensive parenchymal consolidation, with air surrounding a nodule within the consolidation (the air crescent sign). Intravenous contrast-enhanced axial CT scan (in D) and coronal reconstruction (in E) showing intense enhancement of the intracavitary mass, leading to a diagnosis of aneurysm formation.

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pulmonary artery pseudoaneurysm secondary to pulmonary tuberculosis. Progressive weakening of the arterial wall occurs as tuberculous granulation tissue replaces the adventitia and media of the artery. The granulation tissue in the vessel wall is then gradually replaced by fibrin, resulting in arterial wall thinning. Hemoptysis is often the initial clinical manifestation of RA, and can be massive and fatal. In patients with tuberculosis, hemoptysis can be due to aspergilloma, bronchiectasis, neoplasms, chronic bronchitis, and vascular complications such as pseudoaneurysms. Contrast-enhanced chest CT is the preferred imaging technique for the evaluation of pulmonary hemorrhage. RA appears as a markedly enhanced nodule within the wall of a tuberculous cavity or consolidation. The optimal treatment of massive hemoptysis in patients with RA is a matter of debate. Endovascular occlusion of the neck of the aneurysm can provide a positive outcome in the treatment of RA. Surgical excision is recommended when specialized radiological procedures are unavailable or when there is considerable lung destruction.[4,5]

In summary, although aspergilloma is the most common cause of intracavitary nodules in patients with tuberculosis, a number of other conditions should be included in the differential diagnosis, including RA. Early diagnosis allows appropriate treatment, reducing the risk of death from massive bleeding.

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Mosaic attenuation in a patient with COVID-19 pneumonia

Bruno Hochhegger[1], Juliane Mattos[1], Edson Marchiori[2]

An 80-year-old woman with no history of smoking, asthma, or other lung diseases presented to the emergency department with fever, nausea, and intense tiredness. She was diagnosed with COVID-19 by RT-PCR. Her SpO_2 was 85% on room air. She continued to experience dyspnea on moderate and severe exertion two and a half months after discharge. Her cardiac evaluation was normal. A CT scan of the chest was requested, showing a pattern of mosaic attenuation (Figures 1A, 1B, and 1C). Expiratory CT scans showed air trapping (Figures 1D and 1E). A chest CT scan performed ten months earlier (in November of 2019) showed normal lung parenchyma (Figure 1F).

Mosaic attenuation is a CT pattern that is defined as heterogeneous areas of differing lung attenuation. It can be seen in patients with vascular disease, small airway disease, or parenchymal lung disease. In the case of our patient, CT findings of air trapping and normal pulmonary vasculature led to a diagnosis of small airway disease. Bronchiolitis, hypersensitivity pneumonitis, and bronchial asthma are some of the diseases of the small airways that are most commonly associated with mosaic attenuation.[1] Air trapping has been described in patients recovering from COVID-19, and histopathological studies have shown acute bronchiolitis and necrotizing bronchiolitis.[2]

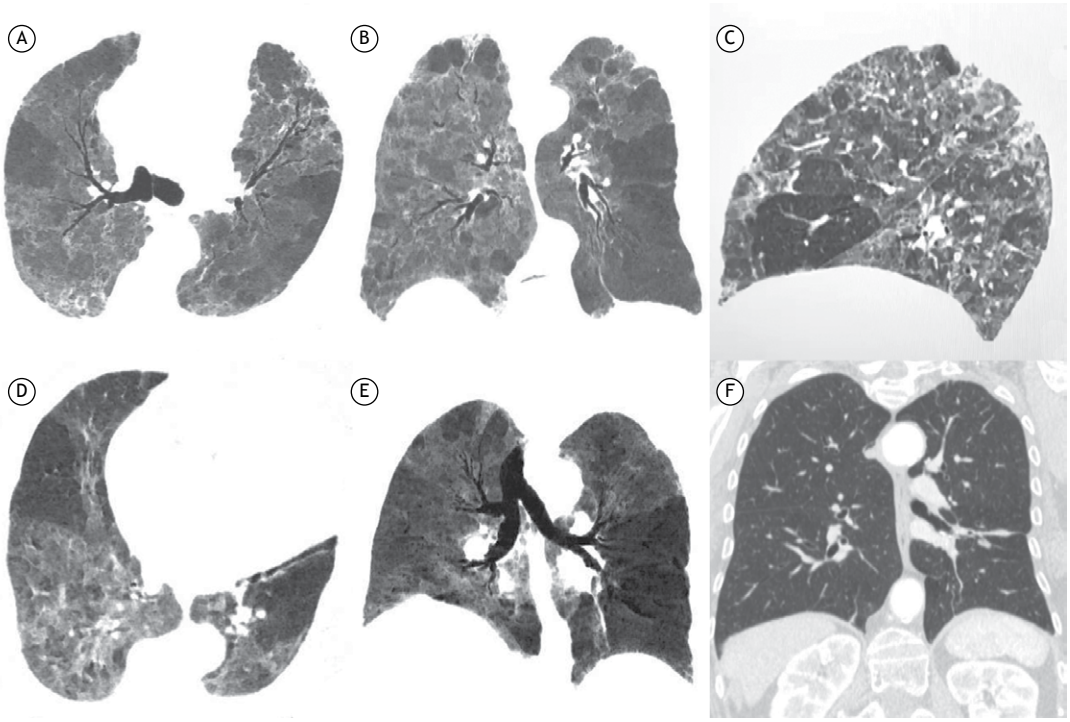

Figure 1. Axial, coronal, and sagittal chest CT reconstructions (in A, B, and C, respectively) showing areas of varying attenuation within the lung parenchyma. In D and E, expiratory CT scans showing air trapping. In F, chest CT scan performed ten months earlier and showing normal lung parenchyma, the exception being a small band-like opacity in the middle third of the left lung.

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Polymethyl methacrylate balls: an unexpected and surprising finding during an autopsy

Eduardo Manuel Barata Coutinho[1], Rosa Henriques de Gouveia[1,2], João Emanuel Santos Pinheiro[1,3]

Before the emergence of antituberculosis drugs, rest and plombage were some of the treatments available for pulmonary tuberculosis.[1] Plombage is a historical and surgical treatment used in order to collapse the lungs and limit the spread of the tuberculosis infection by creating a space under the ribs in the upper chest wall and filling that space with inert material, such as rubber balloons, paraffin wax, and polymethyl methacrylate (commercially known as Lucite) balls.[2] The presence of such material might result in early or late complications, especially infections.[1]

When performing an autopsy at the National Institute of Legal Medicine and Forensic Sciences in Coimbra, Portugal, in a 76-year-old man, whose cause of death was suicide by hanging, a conglomerate of synthetic translucent balls was unexpectedly found (Figure 1). An inquiry to the family revealed that the victim had a personal history of pulmonary tuberculosis during his youth that was treated by plombage with Lucite balls.[3] In this case, the autopsy and the post-mortem histopathological examination revealed no sign of infection.

The authors aim to draw the attention of young medical generations to the possibility of coming across such incidental findings and to the complications due to such therapeutic interventions, which can ultimately cause death.

AUTHOR CONTRIBUTIONS

EMBC: autopsy; drafting and revision of preliminary and final versions; and approval of the final version. RHG and JESP: autopsy and histology; revision of preliminary and final versions; and approval of the final version.

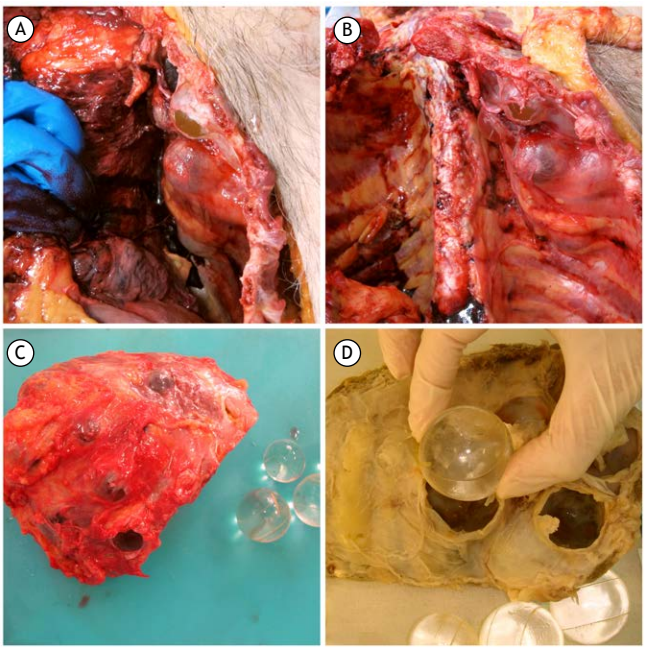

Figure 1. In A and B, polymethyl methacrylate balls located in the costal arches that practically occupy the entire upper half of the left pleural cavity, replacing some ribs. In C and D, a conglomerate of costal arches interspersed with those balls during the autopsy (in C) and after being fixed with 10% formaldehyde (in D).

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

Abstracts

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

Chapter in a Book

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

Official Publications

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

Theses

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

Electronic publications

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

Homepages/URLs

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

Other situations:

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

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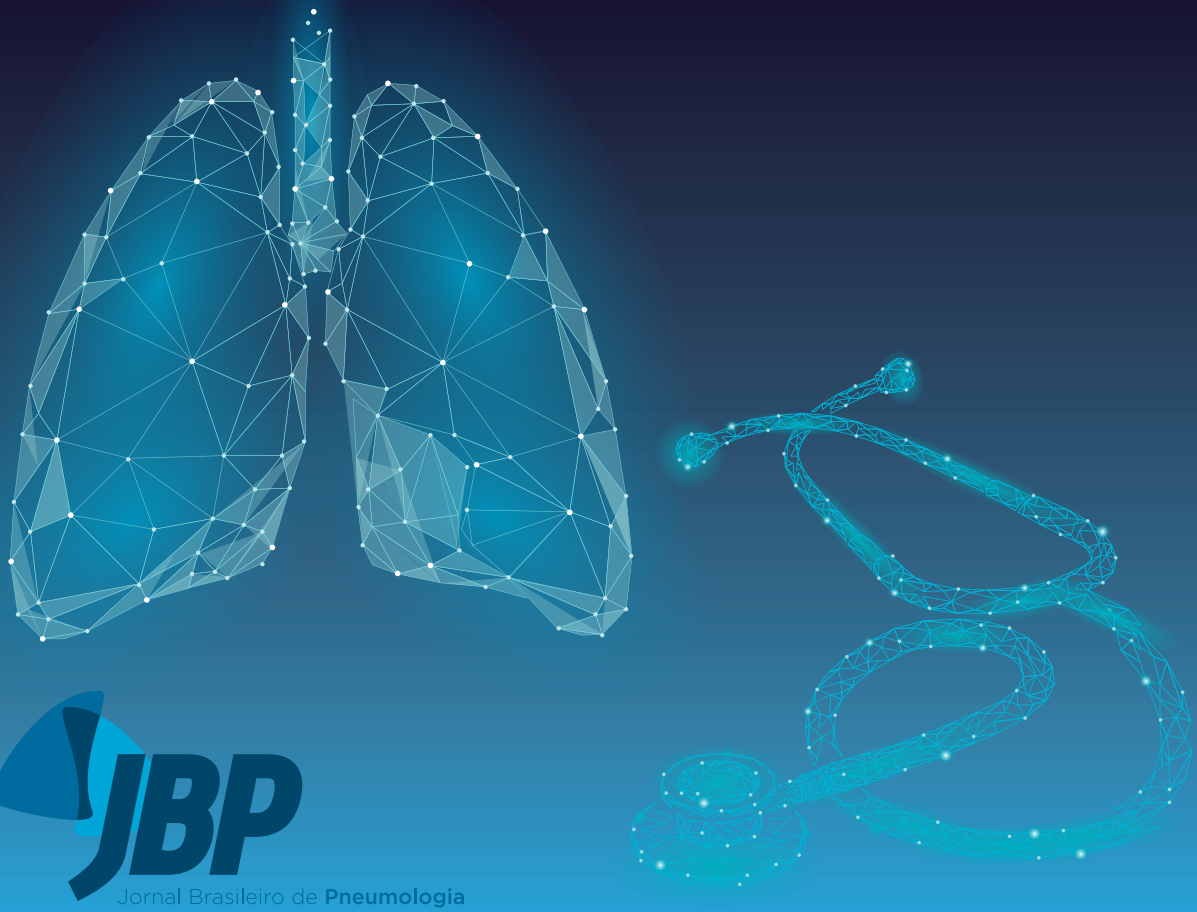

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