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HIGHLIGHT

Thymidine-dependent Staphylococcus aureus and lung function in patients with cystic fibrosist

Tumor spread through air spaces in lung cancer: intraoperative frozen section examination

External validation of the parsimonious EuroLung risk models: analysis of the Brazilian Lung Cancer Registry

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
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The new metrics and additional objectives of the Jornal Brasileiro de Pneumologia

Marcia Pizzichini[1], Bruno Guedes Baldi[2]

The *Jornal Brasileiro de Pneumologia* (JBP) is about to celebrate 50 years of existence. However, it was only in the last two decades that the JBP embarked on a consistent trajectory towards increasing international recognition. This was possible because of the enormous effort of investigators, academicians, and public health professionals who engaged with editors, associated editors, and reviewers in a journey to increase the excellence of the dissemination of knowledge on respiratory medicine and correlated areas in the JBP.

The recent publication of indicators for the JBP by the two major international indexing agencies—-Scimago Journal & Country Rank (SJR) and Journal Citation Reports (JCR) Web of Knowledge, Clarivate Analytics—supports this statement and is a source of pleasure for our scientific community because the JBP have continued attaining higher levels when compared with previous years.[1,2] Therefore, these results certainly expand our attention for the submission of manuscripts by national and international authors, who may contribute to increase the quality of our Journal.

According to the 2023 SJR, the JBP ranked 18th among 443 scientific Brazilian journals within all subject areas. In 2022, the JBP ranked 47th. Additionally, according to the JCR, a database that includes international pulmonary medicine journals from different countries, the two-year citation index of the JBP increased from 2.7 in 2022 to 2.9 in 2023. It is important to reinforce that the trend for many journals was to have a decrease in the impact factor that coincided with the end of the COVID-19 pandemics. Consequently, the JBP ranking in the JCR rose from 47th to 39th among 107 international journals in the area of respiratory medicine, and from 14th to 9th among the 391 Brazilian journals in all subject areas. Given these newly issued indicators, we expect that the JBP will move up to category A4 in Medicine I in the journal ranking system of the Brazilian Office for the Advancement of Higher Education, a system known as Qualis.[3]

Another aspect worth mentioning is that although most manuscripts submitted to the JBP are from Brazil (70%), we have increasingly been receiving submissions from countries of all continents. Despite international visibility is always in the JBP editors' mind, we will continue to encourage submissions and publications of translational pulmonary and respiratory medicine that have novel, ethical, and strong methodology from local and international researchers. Additionally, the JBP aims to publish other articles that have clinical applicability for pulmonologists and specialists in related areas, obviously maintaining scientific rigor.

The JBP is the only Latin American journal in the pulmonary and respiratory medicine field; its continuous publication and the access to all of the articles is free of charge. To be fully free of charge, the JBP is financially supported by the *Sociedade Brasileira de Pneumologia e Tisiologia* (SBPT, Brazilian Thoracic Society), the largest Latin American Respiratory Society, comprising about 4,000 associates and, occasionally, by Governmental Funding Agencies such as the *Brazilian Conselho Nacional de Desenvolvimento Científico e Tecnológico* (CNPq, National Council for Scientific and Technological Development).[4] However, these very agencies have budget constraints that limit the growing capacity of Brazilian researchers. In synthesis, we urgently need improvements to support meaningful research across the inequalities of our country to increase the quality of our publications even more.

There are also other invisible aspects of the JBP that are related to the quality of publications and, consequently, to the impact factor. The board of editors has national and international researchers, the reviewers of the articles submitted are blinded regarding authorship, and the JBP follows the WHO and the International Committee of Medical Journal Editors (ICMJE) policies in regard to authorship, registrations of clinical trials, use of artificial intelligence in research, knowledge dissemination, ethical principles, and rules for publication transparency.[5]

Finally, a recent trend for and a future direction of the JBP has been the expansion of its educational arm to graduate students through appraisal of selected papers and invitation of young academic researchers to become associated reviewers. We also seek to continue debating topics on issues of importance in pulmonary and correlated areas that are relevant for public health policies in underdeveloped countries. Other recent achievements are the publication of manuscripts only in English, the inclusion of a series related to pediatric respiratory care, the increase in social media dissemination of knowledge with periodic podcasts about relevant publications, and the effort to increase the number of guidelines and consensuses on relevant issues published according to priorities established in accordance with the SBPT agenda. The focus and direction of the JBP are to expand our international status of excellence in respiratory and pulmonary medicine and, in a certain way, to meet the needs of the SBPT planning and respiratory researchers. In addition, we hope to help the practice of professionals related to the respiratory area whenever possible.

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Latent tuberculosis infection and biologic agents other than TNF-α inhibitors: "over-screening and over-treatment?"

Ana Paula Santos[1,2], Fernanda Carvalho de Queiroz Mello[1]

The advent of biological therapy to treat many conditions, including autoimmune diseases, asthma, and even cancer, has changed the prognosis of millions of patients, decreasing morbidity and mortality and increasing quality of life.[1] However, because of their mechanism of action, biological therapy can increase the risk of some infections, including tuberculosis.[2]

Latent tuberculosis infection (LTBI), or tuberculosis infection (TBI), as defined in the original article published by Sultana et al.[3] in this issue of the Journal, has a risk of reactivation increased by almost 30 times in patients using TNF-α inhibitors.[2] This happens because such inhibitors block one of the most important cytokines responsible for the integrity of the tuberculous granuloma.[4] However, it is still unclear whether biological therapy with other agents are associated or not with the risk of turning LTBI into active tuberculosis.[5] Additionally, clinical practice is largely heterogeneous, given different scenarios and tuberculosis burdens, which hinders the generalization of guidelines.

Sultana et al.[3] bring a very interesting and timely topic by describing the different clinical practices regarding the approach to TBI worldwide and by evaluating if they are in line with their respective national or international guidelines. In that study,[3] 163 responders in 27 countries completed the survey. According to the authors, "TBI screening rates in patients treated with TNF-α inhibitors were high, especially for older TNF-α inhibitors. Most participants supported TBI screening in patients treated with B- or T-cell inhibitors but not in those treated with interleukin inhibitors. Guideline awareness was higher for TNF-α inhibitors than for other biologic classes." They came to the conclusion that there was a "tendency to recommend TBI screening in patients treated with biologics not known to be associated with an increased risk of TBI" and, as a result, "there is a potential risk of over-screening and over-treatment of TBI, potentially causing harm, in patients treated with biologics other than TNF-α inhibitors." Finally, they conclude that there is a need to investigate the risk of TBI associated with biologics and to develop guidelines to address the spectrum of TBI risk across all types of biologics.

After the initial increasing number of active tuberculosis in the beginning of 2000s associated with TNF-α inhibitors,[6] the scientific community, including physicians, researchers, and even the pharmaceutical industry, became really concerned about this serious adverse event related to these drugs. Since then, each biological therapy approved for use has been considered to be likely to increase active tuberculosis risks, with regard to their different mechanisms of action and potential interference in tuberculosis immunopathogenesis. This concern, although proven to be minimal, pushed all of us to recommend screening and TBI treatment for every patient under biological treatment.[5,7] Now, some years after clinical use, more expertise with all these biological drugs and new researches have shown the safety of biologics other than TNF-α inhibitors. It is time to ask if we still should continue screening and treating those with low or even no risk of tuberculosis reactivation.[5]

Indeed, there is no doubt regarding the over-screening and treatment, especially considering the possible adverse effects related to the TBI treatment, known not to be free from severe complications such as hepatotoxicity. However, TBI is a recurring topic on the "End TB Strategy"[8] agenda, aiming to contribute to achieving the difficult targets of reducing the incidence and mortality of tuberculosis. A backward step, reducing preventive measures, should be discussed. The argument for this concern about TBI treatment in patients on biological therapy relies on the fact that the indication is not only related to the mechanism of action of these drugs, but also to the immunosuppressive condition inherited by autoimmunity. Since the beginning of the last century, studies have shown a higher incidence of active tuberculosis in patients with rheumatoid arthritis, psoriasis, and inflammatory bowel disease, for example.[9] Besides that, there is the possibility of combining these non-TNF-α inhibitor biological therapy with other non-biological disease modifying antirheumatic drugs, which also increase the risk of TBI activation, such as corticosteroids, methotrexate, and leflunomide.[10] Furthermore, patients can have more than one condition that indicate TBI screening.[11]

Differences in how and when to screen for TBI according to the results of Sultana's research are highlighted. Although interferon gamma release assays and tuberculin skin tests were correctly mentioned in different percentages, almost 40% of the respondents were not in favor of performing chest X-rays in all patients during screening, regardless of the presence of symptoms or test results.[3] This should be a reflection of the different recommendations on screening for LTBI around the world. In addition, the responses on when to repeat screening were heterogeneous, probably also reflecting the different origins of the respondents and their different practices according to the tuberculosis burden at their place of practice.[11,12]

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◄ Voltar ao sumário

Although there are well-established indications for TBI screening and treatment, another concern is related to clinical practitioner adherence to guidelines and recommendations proposed by different official societies and organizations.[3] In the study by Sultana et al.,[3] current practice did not always align with national guidelines regarding screening for TBI in patients under immunosuppressive treatment. Also, in some countries, the national guidelines were not updated, which could explain such divergences. Standardized conducts are important, especially in continental and medium-to-high burden countries such as Brazil.

There are several issues to be taken into consideration when deciding to screen and treat TBI in patients on immunosuppressive therapy. When it comes to *Mycobacterium tuberculosis*, one size does not fit all, and many aspects must be relevant. First, the diagnostic methods available for TBI are not perfect. In addition to their expected false negative results, which any test can have, until today, we have no test to diagnose reinfection after treatment, which can be common in high burden tuberculosis countries.[12] Second, we should take into consideration TBI treatment regimens and risks of drug interactions. Finally, we must know the tuberculosis prevalence in different scenarios, the patients' comorbidities, and the risks of adverse events.[11]

In times of so many questions, Sultana et al [3] hit the target bringing this discussion and making us understand the urgent need for new researches to assess the risk of tuberculosis activation according to the immunosuppressive treatment, and mostly, for updated guidelines to address the spectrum of TBI in specific populations and different scenarios.

AUTHOR CONTRIBUTIONS

Both authors equally contributed to this editorial.

CONFLICTS OF INTEREST

None declared.

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Multiple cystic/cavitated metastases

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

A 58-year-old female patient diagnosed with cervical carcinoma reported dyspnea and cough for about one month. A CT of the chest (Figure 1) showed multiple cystic/cavitated nodular images in both lungs.

Cavitated lesions can be the result of a series of pathological processes, especially necrosis, and is defined as a gas-filled space, evidenced on CT as an area of low attenuation within a lung consolidation, mass, or nodule. The differential diagnosis of multiple cavitated nodular lung lesions is broad, including infectious diseases such as septic embolism, tuberculosis, and fungal and parasitic infections, as well as neoplastic lesions (metastases, lymphoma, etc.), in addition to other less common etiologies (tracheobronchial papillomatosis, rheumatoid nodules, Wegener's granulomatosis, and nodular amyloidosis, among others). The most common causes are septic embolism and cavitated metastases.

Septic embolism occurs due to embolization of fragments infected with microorganisms into the lungs. The disease is most commonly secondary to right endocarditis or septic thrombophlebitis, but it may occur secondary to infected endovascular catheters, suppurative processes of the skin, head, or neck, or contamination related to the use of intravenous drugs. CT imaging reveals multiple bilateral nodules, well or poorly defined, predominantly with peripheral distribution, showing varying degrees of cavitation. Associated peripheral triangular images often correspond to infarcts due to vascular occlusion. Septic embolism can occur together with unilateral or bilateral pleural effusion.[1-3]

Cavitated metastases occur most commonly in squamous cell carcinomas, corresponding to 70% of the cases on average. Head and neck tumors, pelvic tumors (uterus, ovary, prostate), and adenocarcinomas of the large intestine are the most common primary sites, although any primitive tumor, in principle, can give rise to cavitated metastases. In metastases, the cavitations originate both from tumor necrosis and from the formation of a valvular mechanism due to neoplastic infiltration into the distal airways. The walls of the cavitations are most often thick and irregular, but they can also be thin, similar to cysts. Clinical aspects are very important for the differential diagnosis. Septic embolism clinically presents with fever, dyspnea, cough, and pleuritic pain. Blood culture may be positive. The presence of a previously known primary tumor may lead to the suspicion of pulmonary metastases. Patients with metastases are often asymptomatic from a respiratory point of view. Our patient had a previous diagnosis of cervical carcinoma. The final diagnosis was cavitated metastases from uterine carcinoma.[1-3]

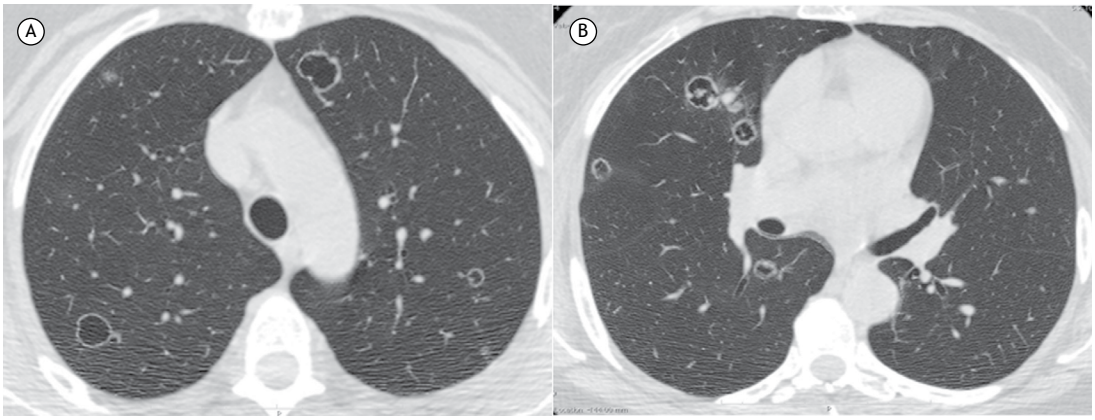

Figure 1. CT scans with lung window settings at the level of the upper lobes (in A) and lung bases (in B) showing multiple nodules of varying sizes, many of them cavitated, predominantly with peripheral distribution. Note solid content inside some of the nodules.

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Enhancing research integrity and data quality through standardized electronic case report forms

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PRACTICAL SCENARIO

The Brazilian Research in Intensive Care Network (BRICNet) designed a multicenter, multinational, cohort study with a 28-day follow-up that will include patients with acute respiratory failure, in transition to spontaneous ventilation in intensive care units in Latin America.[1] Given the multicentric nature of the study and the need to collect data in several countries, which also speak different languages, they were concerned that collecting data in paper forms could lead to errors and opted for using an electronic case report form (CRF) on the Research Electronic Data Capture (REDCap) platform.[2]

DATA COLLECTION

Data collection is a crucial step in the scientific research process, as the quality of the data obtained directly influences the validity of the results and the reliability of conclusions of the study. Researchers must be meticulous in selecting the appropriate method for data collection to ensure that the collected data effectively address the research question.

The use of CRFs ensures standardization in obtaining information and allows for systematic data collection, minimizing variability and bias that may arise from non-standardized collection methods. CRFs should be well-structured, easy to complete, and designed to collect high-quality data. Only the minimum amount of data necessary to address the research question should be collected, avoiding the inclusion of excessive or irrelevant information.

A significant advancement in data collection has been the use of electronic forms instead of paper forms, as data collected on paper forms must be transferred to an electronic database to perform data analysis, and data entry errors can occur.[3] The use of electronic forms significantly improves data quality control, as it verifies invalid responses and missing data in real time (Chart 1). Electronic CRFs serve as an interface that feeds data into a database and avoid the need to type data directly into a spreadsheet, which is prone to mistakes and should not be an option in research studies. When researchers type data directly into a spreadsheet, they can accidentally type data into the wrong column or line, type over data, and mistakes can go unnoticed. There are several methods for collecting data in electronic forms that directly feed a database, including some that are free of charge and used for informal surveys. However, in order to be reliable for collecting data in research studies, electronic forms need to be built to ensure the integrity of the data, protecting the database from unintended data changes or deletions, and protecting the confidentiality of patient data.

REDCAP

The REDCap software,[2] developed by Vanderbilt University, is a web-based platform designed to facilitate the development of electronic data capture forms to be used in research. With REDCap, users can create customized data collection forms and questionnaires according to the specific needs of their studies or download instruments from a shared online library, saving time and resources.

To ensure the quality and integrity of the data collected, REDCap has a series of functionalities that assist data verification in real time. The platform allows the configuration of validation rules that automatically check data consistency and alert users in cases of missing or invalid data, such as text response in a numeric field or values out of range. Additionally, REDCap includes the branching logic feature, which automatically displays only the relevant questions based on previous responses. For example, if data being entered corresponds to a male participant, the question regarding pregnancy status will not appear. This ensures that only pertinent questions are presented, enhancing the respondent's experience and minimizing the collection of irrelevant data.

Another important feature of REDCap is that different access permission levels can be defined for team members, ensuring that only authorized personnel have access to sensitive information collected, maintaining data confidentiality.

REDCap provides a multi-language feature in which the language of the form is displayed in the language of the person collecting the data but feed the same database. In the study described in our practical scenario, the investigators translated the forms from Portuguese to Spanish, and users collecting data in each of the 41 centers chose which language they preferred; data from centers in Peru and Brazil, for example, are saved on a single database for posterior data analysis.

Electronic CRF platforms such as REDCap should be relatively easy to use and feature an intuitive interface that allows users to set up their studies quickly and efficiently.

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Chart 1. Comparison of paper and electronic data collection forms.

Aspect	Paper data collection forms	Electronic data collection forms
Implementation	Simple to implement without the need for technological infrastructure	Needs access to technological resources
Initial cost	Generally lower, as it does not require electronic equipment	May be more expensive initially due to the need for electronic devices (computers, tablets, mobiles)
Accessibility	Can be used in locations with limited or no access to electronic devices or the Internet.	Allows easy sharing and remote completion via Internet-connected devices
Human Error in Transcription	Increased risk of errors when transcribing data into an electronic database	Minimizes transcription errors by allowing direct entry of data in electronic format
Collection and Processing Time	The process of collecting and subsequently digitizing data is time-consuming and can delay data analysis	Faster data collection and processing, with the possibility of direct export for statistical analysis
Quality Control	Difficulty in applying automatic quality controls; manual review is required	Better quality control with real-time data validation, alerting to missing or invalid data
Security and Confidentiality	Paper-based data is more vulnerable to losses, physical damage, and unauthorized access	Increased security with data encryption, access control, and automatic backups, complying with data protection regulations
Scalability	Difficult to scale for large studies, as it requires physical storage of large volumes of paper	Easily scalable for studies of any size, with digital storage and database expansion capabilities

KEY MESSAGES

- High-quality data collection is essential for the validity and reliability of research, and using standardized CRFs minimizes variability and bias.
- Electronic forms, particularly platforms like REDCap, enhance data quality by enabling real-time data verification, reducing errors associated with manual data entry, and ensuring data integrity and confidentiality.
- REDCap offers customizable data collection forms, validation rules, branching logic, multi-language support, and differential access permission levels, making it a powerful tool for research data management.

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The role of the exercise physiology laboratory in disease management: pulmonary arterial hypertension

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Pulmonary arterial hypertension (PAH) is a rare disease associated with exercise intolerance due to right ventricular dysfunction. Risk stratification in PAH is essential in defining the prognosis, and cardiopulmonary exercise testing (CPET) provides valuable information about the severity of the disease, with direct implications for clinical management.

OVERVIEW

A 33-year-old woman, diagnosed with PAH 11 years prior, currently using triple combination therapy, and on the waiting list for lung transplantation, underwent CPET at the time of diagnosis (Figure 1—Panel I) and again at one year before lung transplantation (Figure 1—Panel II). Although both examinations revealed reduced aerobic capacity, signs of cardiocirculatory limitation, and excessive ventilatory responses with gas exchange disturbance, the latter also showed indirect signs of a right-to-left shunt. In patients with PAH, CPET is a valuable tool in assessing prognosis.[1] The primary variable is the peak $\dot{V}O_2$ ($\dot{V}O_{2peak}$), which is related to oxygen delivery and consumption. If the oxygen delivery is low, the first response of the muscle is to increase the oxygen consumption. However, in PAH, this mechanism could fail with a high dependence on non-oxidative pathways, low energy production, and increased exercise intolerance. In addition, patients with PAH have low type I muscle fiber density, which impairs peripheral oxygen use and limits muscle strength. During high metabolic demand, patients with PAH have a lower $\dot{V}O_{2peak}$, early anaerobic threshold (AT), and low aerobic efficiency with a low $\dot{V}O_2$-work rate ($\Delta\dot{V}O_2/\Delta WR$) or a plateau response.[2] Ultimately, PAH leads to a reduction in stroke volume that requires a compensatory increase in HR to maintain cardiac output, which leads to a steeper $\Delta HR/\Delta\dot{V}O_2$ response, a reduced $\dot{V}O_{2peak}$, and O_2 pulse ($\dot{V}O_2/HR$) with a curve plateau before or after the AT.[3] In the PAH lungs, low perfusion with adequate alveolar ventilation results in ventilation-perfusion mismatch and gas exchange disturbance during exercise, increasing ventilatory demand. This augmented response is also related to lactic acid accumulation, signaling peripheral chemoreceptors and increasing the feedback for ventilation. In this context, a high minute ventilation to carbon dioxide production ratio ($\dot{V}E/\dot{V}CO_2$) and lower end-tidal carbon dioxide partial pressure ($PETCO_2$) values have been reported, suggesting signs of ventilatory inefficiency in PAH.[3] In addition, PAH patients usually experience decreased SpO_2 from rest to peak exercise, also related to exercise-induced shunt (EIS).[2] Right-to-left shunting during exercise is attributable to an abnormally high pulmonary vascular resistance to right atrial pressure exceeding left atrial pressure, forcing systemic venous blood through a patent foramen ovale directly into the systemic arterial circulation.[4] An abrupt and sustained decrease in $PETCO_2$ associated with a simultaneous and sustained increase in $PETO_2$, in the ventilatory equivalents of oxygen and carbon dioxide ($\dot{V}E/\dot{V}O_2$ and $\dot{V}E/\dot{V}CO_2$), and in the respiratory exchange ratio (RER), together with a decline in SpO_2, are findings present in patients with EIS.[5] The persistence or development of an EIS strongly predicts death or transplantation regardless of the hemodynamics and all other CPET variables.[4] In the European Respiratory Society guideline, the peak $\dot{V}O_{2peak}$ and the $\dot{V}E/\dot{V}CO_2$ slope have established cutoff values for prognosis assessment. However, other analyses are not considered in the guideline but have provided pathophysiological evidence of an impact on disease severity, such analyses including the assessment of a right-to-left shunt.[5]

CLINICAL MESSAGE

In PAH risk stratification, CPET can play an important role, having the advantage of being noninvasive. This tool might facilitate the decision-making process and clinical management in patients with PAH.

AUTHOR CONTRIBUTIONS

EVMF: Participated in the conception; writing; and revision. JSL: Participated in the conception; and writing. RKFO: Participated in the revision. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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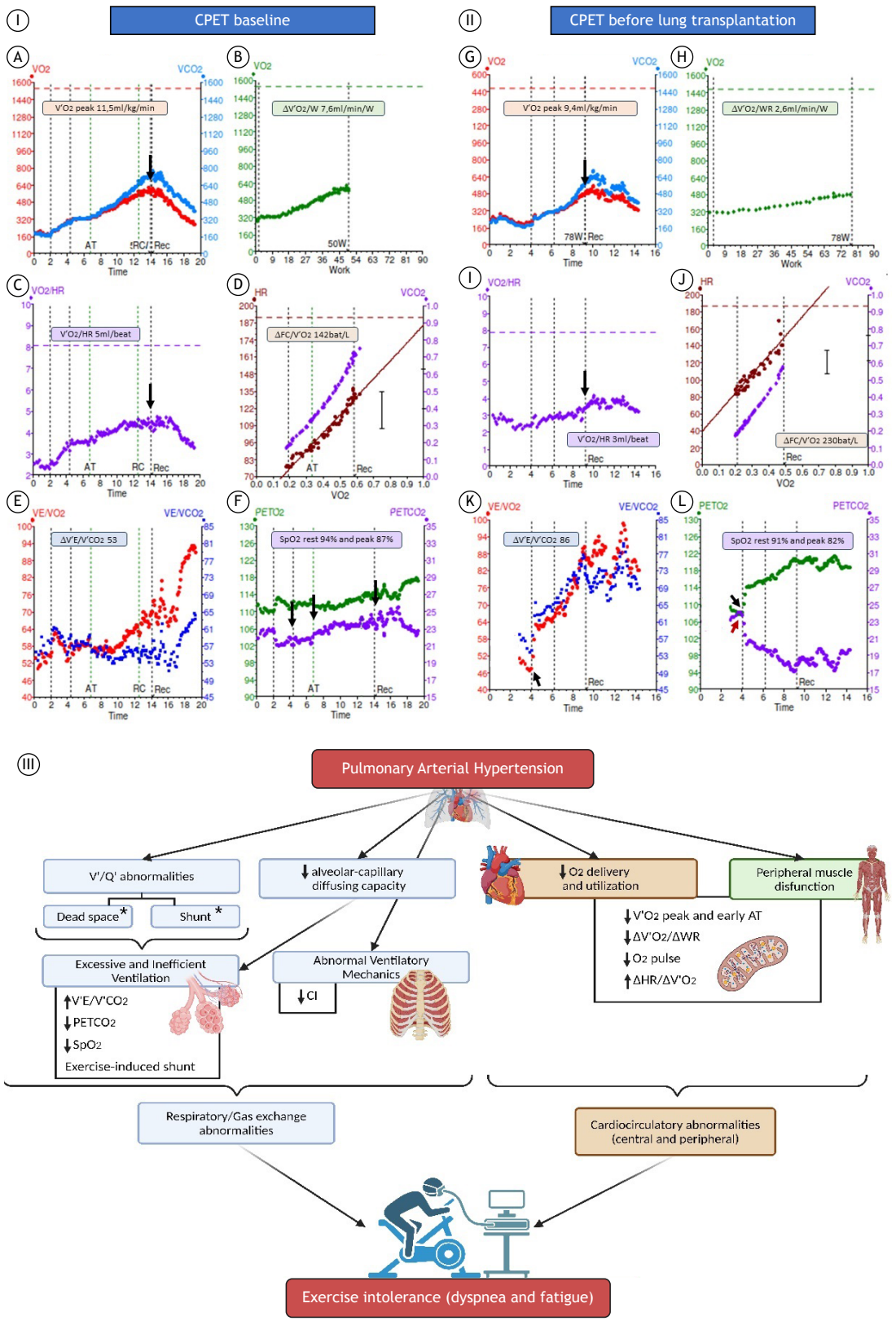

Figure 1. A 33-year-old woman diagnosed with pulmonary arterial hypertension (PAH) 11 years prior, using triple therapy, and on the waiting list for lung transplantation. Panel I (A-F) - Cardiopulmonary exercise testing (CPET) at baseline showed the following: markedly reduced aerobic capacity and signs of cardiocirculatory limitation analyzed by a reduced peak VO_2 (VO_{2peak}) with slow recovery (A); $\Delta VO_2/\Delta WR$ with a plateau at the end of exercise (B); early

anaerobic threshold (AT), and a steeper response of the $\Delta HR/\Delta \dot{V}O_{2peak}$, corresponding to a tachycardic pattern (D); and O_2 pulse ($\dot{V}O_2/HR$) with an early plateau (C) ; excessive ventilatory responses (increased $\Delta \dot{V}E/\Delta \dot{V}CO_2$) suggestive of ventilation-perfusion (V/Q) mismatch (E); and reduced $PETCO_2$ associated with exercise-induced desaturation (F). The Borg scale scores were 4 for dyspnea, 7 for fatigue, and 1.21 for the respiratory exchange ratio (RER) peak. Panel II (G-L) - CPET performed at one year before lung transplantation showed worsening of all of the responses and add-on signs of right-to-left shunt marked by an abrupt decrease in $PETCO_2$ (red arrow in L) simultaneous to an abrupt increase in $\dot{V}E/\dot{V}CO_2$ and $\dot{V}E/\dot{V}O_2$ (black arrow in K) and $PETO_2$ (black arrow in L) with a rise in RER and worsening of exercise-induced desaturation. The Borg scale scores were 9 for dyspnea, 9 for fatigue, and 1.19 for the RER peak. Panel III - Summary of the main CPET findings in patients with PAH. *It is necessary to collect blood samples to perform gas exchange analysis and calculate the ratio of dead space to tidal volume.

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Chronic lung disease of prematurity and bronchopulmonary dysplasia

Gabriela de Azevedo Bastian de Souza[1], Maria Paula Hanel[1], Eduardo da Costa Herter[1], Leonardo Araujo Pinto[1-2], Marcus Herbert Jones[1-2]

DEFINITION AND PHENOTYPES

Chronic lung disease of prematurity (CLDP) refers to various respiratory disorders resulting from prematurity. With the continuous rise in birth and survival rates of premature infants, the incidence of CLDP has increased. In Brazil, 11.94% (302,528) of live births in 2023 were premature (born at < 37 weeks of gestation), and 0.59% (15,134) were extremely premature (born at < 28 weeks).[1] This improved survival of extremely preterm newborns is largely due to advancements in neonatal intensive care over recent decades. Strategies to enhance preterm infant survival include new antimicrobials, corticosteroid therapy for high-risk pregnancies, artificial surfactants, and assisted ventilation methods that are more effective, like CPAP.[2]

Although survival rates have improved, morbidity and mortality have shifted to later stages, often due to sequelae of prematurity such as CLDP, which involves changes in lung structure, including altered septation, vascularization, and a reduced number of alveoli. Those changes, which lead to impaired gas exchange and reduced lung function, can persist into adulthood.[2,3]

As detailed in Chart 1, CLDP encompasses a spectrum of respiratory conditions in premature infants, from minimal symptoms to severe conditions like bronchopulmonary dysplasia (BPD). Inflammatory processes significantly influence those conditions, with cytokine storms exacerbating disease progression. Medical interventions, particularly invasive ventilation, contribute to pro-inflammatory cascades and play a crucial role in CLDP pathogenesis.

During the intrauterine period, airway development progresses through several stages. Many preterm infants are born during the saccular stage (24-36 weeks gestation), with compromised surfactant production and underdeveloped bronchioles and airways. Prenatal factors, such as fetal growth and gestation duration, and postnatal factors, such as ventilatory interventions, can significantly affect lung development into adulthood.[2]

The most severe form of CLDP is BPD, defined by the need for supplemental oxygen or ventilation for 28 days or more, up to 36 weeks post-conception. The etiology of BPD is multifactorial, with inflammation and prolonged mechanical ventilation as key contributors. It is characterized by chronic respiratory disease, with consequences lasting beyond the neonatal period. Children with BPD are at higher risk for lower respiratory tract infections, airway hyperresponsiveness, and hospitalization in the first two years of life.

Within BPD, there are various phenotypes. Some preterm infants exhibit significant lung function impairment without meeting the criteria for BPD or showing signs of neonatal respiratory disease. Others may have severe lung disease, requiring long-term mechanical ventilation or oxygen supplementation. With less aggressive neonatal ventilation techniques, the histological phenotype of BPD has shifted from post-traumatic conditions to a form characterized by arrested alveolar development. Recent studies suggest that patients with BPD are at increased risk for subclinical pulmonary hypertension, exercise-induced lung disease, hypertension, right ventricular dysfunction, and autonomic dysfunction.

Premature birth alters lung structure, increasing vulnerability to acute viral infections in early life. These infections, typically mild in full-term infants, are more severe in preterm infants, with a higher risk of hospitalization and ventilatory support, particularly in infants infected with respiratory syncytial virus (RSV). Many preterm infants develop recurrent wheezing and asthma-like symptoms, often treated with bronchodilators and inhaled steroids, though the response is generally poor. Symptom management should be tailored to individual severity, including RSV prevention and inhaled steroids for patients with atopy and asthma symptoms. Immunostimulants like bacterial lysates may also be considered.

MANAGEMENT

Various treatments for BPD are under study, including inhaled or systemic corticosteroids, bronchodilators, and supplemental oxygen, though interventional studies are limited.[4] The 2020 European Respiratory Society consensus recommends lung function tests for monitoring BPD in children, with pulmonary imaging reserved for severe cases. Bronchodilators should be used for patients with recurrent hospitalizations, exercise intolerance, or asthma-like symptoms, while inhaled corticosteroids should not be used for BPD treatment. If supplemental oxygen is needed, the target saturation should be at least 90%.[4] Palivizumab and, in the future, nirsevimab, can be used to prevent severe RSV infection in high-risk populations, including those with congenital heart disease, BPD, and prematurity.[5]

The main limitations in BPD treatment stem from the scarcity of high-quality studies, leading to a low level of evidence for many guidelines. More prospective studies are needed in order to monitor development of preterm children into school age and adulthood, as well

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Chart 1. Differences in definition and management between chronic lung disease of prematurity and bronchopulmonary dysplasia.

Disease	Definition	Management
CLDP	This comprises a spectrum of respiratory pathologies resulting from prematurity, ranging from minimal respiratory symptoms with some loss of lung function to more severe cases. Viral bronchiolitis caused by RSV or other viral infections, recurrent wheezing, and asthma in school-age children are major causes of morbidity associated with CLDP.	• RSV prevention • Inhaled steroids for patients with atopy and symptoms of asthma • The use of immunostimulants like bacterial lysate as an option to prevent recurrent respiratory infections
BDP	This is the most severe clinical complication within the CLDP spectrum, defined as the need for supplemental oxygen or ventilation for 28 days or more from birth to 36 weeks post-conception.	• Follow-up with pulmonary function tests • RSV monoclonal antibodies • Asthma treatments only for specific groups • If supplemental oxygen use is recommended, a target saturation of >90%

CLDP: chronic lung disease of prematurity; RSV: respiratory syncytial virus; and BDP: bronchopulmonary dysplasia.

as randomized clinical trials to determine the most effective treatments.[4]

AUTHOR CONTRIBUTIONS

GABS, MPH, and ECH contributed to data collection and drafting of the manuscript. MHJ and LAP contributed to drafting, reviewing and editing the manuscript.

CONFLICTS OF INTEREST

None declared.

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Thymidine-dependent *Staphylococcus aureus* and lung function in patients with cystic fibrosis: a 10-year retrospective case-control study

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ABSTRACT

Objective: Thymidine-dependent small-colony variants (TD-SCVs) of *Staphylococcus aureus* are being isolated with increasing frequency from patients with cystic fibrosis (CF). The aim of this study was to evaluate the relationship between TD-SCV isolation and pulmonary function in patients with CF, as well as to determine whether the emergence of TD-SCVs was associated with trimethoprim-sulfamethoxazole (TMP-SMX) use and with coinfection with other microorganisms. **Methods:** This was a retrospective case-control study including patients with CF who visited the Clinical Hospital Complex of the Federal University of Paraná, in Curitiba, Brazil, between 2013 and 2022. Demographic, clinical, and spirometric data, as well as information on TD-SCVs and other isolated microorganisms, were collected from the medical records of patients with CF and TD-SCVs (TD-SCV group; n = 32) and compared with those of a matched group of patients with CF without TD-SCVs (control group; n = 64). **Results:** Isolation of TD-SCVs was positively associated with TMP-SMX use ($p = 0.009$), hospitalization ($p < 0.001$), and impaired pulmonary function ($p = 0.04$). **Conclusions:** The use of TMP-SMX seems to contribute to the emergence of TD-SCVs, the isolation of which was directly associated with worse pulmonary function in our sample.

Keywords: *Staphylococcus aureus*/drug effects; Thymidine/metabolism; Trimethoprim, sulfamethoxazole drug combination/adverse effects; Lung/physiopathology; Cystic fibrosis/complications.

INTRODUCTION

Cystic fibrosis (CF) is a multisystemic disease affecting the digestive, reproductive, and respiratory systems.[1] In the respiratory tract, CF is associated with chronic obstructive bronchial disease caused by recurrent infections.[2] This disease is caused by mutations in the CF transmembrane regulator (CFTR) gene, which encodes a CFTR protein that transports chloride ions outside cells.[3] Because of the hypertonicity of chloride ions in the lungs, thick mucus favors colonization and infection by various microorganisms. Important pathogens in patients with CF include *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Burkholderia cepacia* complex, *Stenotrophomonas maltophilia*, and *Achromobacter xylosoxidans*.[4,5]

It is not uncommon for *S. aureus* to be implicated in initial pulmonary infections in patients with CF.[6] In such patients, small-colony variants (SCVs) of *S. aureus* are being isolated with increasing frequency.[7,8] Colonies of SCVs arise because of multiple conditions that lead to the induction and selection of this phenotype, including auxotrophism caused by genetic mutations that determine the dependence on hemin and menadione due to aminoglycoside use and on thymidine due to trimethoprim-sulfamethoxazole (TMP-SMX) use.[9] Due to this metabolic deficiency, it is difficult to identify *S. aureus* SCVs by routine laboratory microbiology. The colonies grown are 10-fold smaller than normal, non-pigmented, and non-hemolytic on blood agar. SCVs may also produce

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false-negative results on catalase and coagulase tests and fail to grow on Mueller-Hinton agar.[8,9]

The use of TMP-SMX contributes to the introduction of mutations in the *thyA* gene of *S. aureus*; this gene encodes thymidylate synthase, an essential enzyme for bacterial DNA synthesis. Those mutations characterize the thymidine-dependent SCV (TD-SCV) phenotype.[10,11] In some isolates, the SCV phenotype is reversed to a normal phenotype, which may be related to persistent infections[12] and treatment difficulties.[6] Some studies have demonstrated that coinfection of TD-SCVs with other microorganisms, such as *P. aeruginosa*, *S. maltophilia*, and *A. xylosoxidans*, can worsen lung function.[4,13]

To evaluate pulmonary function, spirometry is performed in individuals with CF who are over five years of age.[14] A decline in FEV_1, as measured on spirometry, indicates a higher risk of hospitalization and death.[15]

Given that CF is associated with high morbidity and mortality in young patients and is often linked with recurrent infections, improving the understanding of *S. aureus* TD-SCVs and their clinical role may contribute to improving the prognosis of patients with the disease. This study was conducted to investigate the relationship between TD-SCV isolation and pulmonary function in patients with CF. In addition, we evaluated whether TMP-SMX use is related to the emergence of TD-SCVs.

METHODS

Study design

A total of 286 patients visited the CF clinic of the Clinical Hospital Complex (CHC) of the *Universidade Federal do Paraná* (UFPR) in the city of Curitiba, Brazil, between July 2013 and September 2022. Of those, 96 patients with CF were selected for this case-control study. The presence of TD-SCVs was determined by analyzing respiratory tract cultures (sputum or oropharyngeal swab samples). The TD-SCV group (n = 32) comprised patients with at least one positive culture for TD-SCVs, whereas the control group (n = 64) comprised patients with CF who had a negative culture for TD-SCVs (ratio 1:2). Control group subjects were selected, on the basis of sex and age, from among other patients with CF in whom *S. aureus* had been isolated and who were coinfected with another microorganism.

SCV identification and auxotrophic characterization

Respiratory tract samples were cultured on mannitol salt agar and blood agar. Smaller colonies were identified as *S. aureus* by using standard biochemical tests, and identification was confirmed with matrix-assisted laser desorption ionization time-of-flight mass spectrometry (Bruker Daltonics, Billerica, MA, USA).[8]

The nutritional dependence of the SCVs was tested by inoculating a suspension adjusted to a 0.5 McFarland standard on Mueller-Hinton agar (Oxoid; Thermo Fisher Scientific, Waltham, MA, USA) supplemented with hemin, menadione, or thymidine (10, 25, and 100 µg/mL, respectively; Sigma-Aldrich, St. Louis, MO, USA).[16] The plates were incubated under aerobic conditions at 35°C for 24-72 h. Isolates of *S. aureus* SCVs were characterized as nutritionally dependent when they grew on a specific substrate but did not grow in its absence.[8]

Demographic, clinical, and microbiological data

Demographic and clinical data were obtained by reviewing patient medical records. Age, sex, the results of CF detection tests (for immunoreactive trypsinogen, sweat electrolytes, and CFTR mutations), bronchiectasis, pancreatic insufficiency, hospitalization, death, spirometric values, and TMP-SMX use were evaluated. To determine the frequency of coinfection or colonization between other microorganisms and TD-SCVs, we evaluated *S. aureus*, *P. aeruginosa*, *B. cepacia* complex, *A. xylosoxidans*, and *S. maltophilia*, which were isolated at the time of their emergence.

Pulmonary function was evaluated by determining the percent of predicted FEV_1 (FEV_1%). The FEV_1 values were obtained from spirometric tests performed closest to time of isolation of TD-SCVs, with a maximum period of one year before TD-SCV isolation. The control group comprised patients infected with *S. aureus* with a normal phenotype.

Pulmonary function testing was performed according to the standards established by the American Thoracic Society. Pulmonary function was categorized on the basis of the FEV_1%, as follows[17]: normal, ≥ 90%; mild impairment, 70-89%; moderate impairment, 40-69%; and severe impairment, < 40%.

Statistical analysis

Statistical tests were employed to evaluate demographic, clinical, and spirometric data, as well as the isolated microorganisms. Descriptive data were analyzed as absolute and relative frequencies for qualitative variables and as medians (ranges) for quantitative variables. Data normality was investigated with the Shapiro-Wilk test, and associations between variables were detected with Pearson's chi-square or Fisher's exact tests, as appropriate. In addition, differences between quantitative variables were evaluated with Mann-Whitney U tests. The significance level was set at 5% ($p < 0.05$). Data were analyzed with R software (R Core Team, 2022), version 4.2.1.[18]

This study was approved by the Institutional Ethics Review Board of the CHC/UFPR (Reference no. 45063115.9.0000.0096). The requirement for informed consent was waived because of the retrospective nature of the study.

RESULTS

Among the 286 patients treated at the CF clinic of the CHC/UFPR, *S. aureus* was isolated from respiratory

samples in 254 (88.8%) and TD-SCVs were isolated in 36 (14.2%). In 23 patients, TD-SCVs were isolated only once, whereas in nine patients, they were isolated multiple times over the 10-year follow-up period, as shown in Figure 1.

Demographic data and clinical characteristics of the patients, by group, are shown in Table 1. The table also shows the association between the emergence of TD-SCVs and TMP-SMX use; hospitalization rates; and coinfection with other microorganisms. The mutation most commonly identified among patients in the TD-SCV and control groups was the F508del mutation, followed by the G542X mutation. We found no association between the isolation of other microorganisms and coinfection with TD-SCVs. We detected a positive association between previous use of TMP-SMX and isolation of a TD-SCV. The proportion of patients that had been hospitalized was higher in the TD-SCV group (Table 1). Isolation of a TD-SCV was also associated with lower pulmonary function (FEV_1%), as shown in Table 2.

At the time of TD-SCV isolation, impaired lung function was more common among the patients in the TD-SCV group than among those in the control group. As can be seen in Figure 2, severe air flow obstruction was observed in 19.2% of the TD-SCV group patients (vs. 13.7% of the control group patients) and moderate air flow obstruction was observed in 34.6% of the TD-SCV group patients (vs. 21.6% of the control group patients). Pulmonary function impairment was found to correlate with the isolation of TD-SCVs (Table 2 and Figure 2).

DISCUSSION

This case-control study involved patients at a referral center for CF who were colonized by or infected with TD-SCVs. The results show that the presence of these

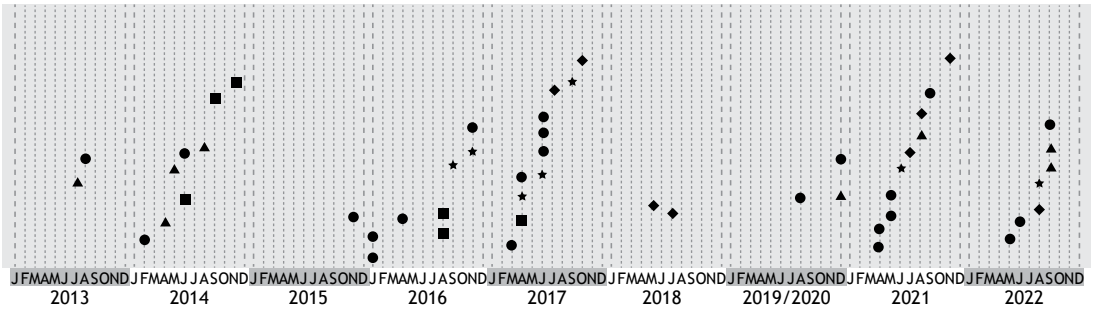

Figure 1. Timeline of the appearance of thymidine-dependent small-colony variants (TD-SCVs) in patients with cystic fibrosis during the study period. Number of times that TD-SCVs were isolated in each patient (P): ●only once (P2, P3, P5, P7-P10, P13-P18, P20, P22-P26, and P29-P32); ▲twice (P1, P4, P21, and P28); ■three times (P6 and P11); ◆four times (P19 and P27); and ★seven times (P12).

Table 1. Demographic and clinical characteristics of patients with cystic fibrosis, with and without thymidine-dependent small-colony variants of *Staphylococcus aureus*.

Characteristic	TD-SCV group n/N (%)	Control group n/N (%)	*p*-value
Male	16/32 (50.0)	32/64 (50.0)	1.00
CFTR gene mutation[a]			
F508del	17/29 (58.6)	39/60 (65.0)	0.653
Homozygous F508del	3/17 (17.6)	17/39 (43.6)	0.205
G542X	7/29 (24.1)	24/60 (40.0)	0.100
Homozygous G542X	3/7 (42.9)	6/24 (25.0)	0.163
Other	7/29 (24.1)	6/59 (10.2)	0.109
Pancreatic insufficiency	28/32 (87.5)	57/64 (89.0)	1.00
Bronchiectasis	27/32 (84.4)	53/64 (82.8)	0.768
Hospitalization	14/32 (43.8)	6/64 (9.4)	< 0.001
Death	3/32 (9.4)	1/64 (1.6)	0.106
Use of TMP-SMX[a]	28/32 (87.5)	39/64 (60.9)	0.009
TD-SCVs and coinfection			
P. aeruginosa	13/32 (40.6)	22/64 (34.4)	0.708
B. cepacia complex	5/32 (15.6)	3/64 (4.7)	0.112
A. xylosoxidans	4/32 (12.5)	3/64 (4.7)	0.217
S. maltophilia	3/32 (9.4)	2/64 (3.1)	0.329

TD-SCV: thymidine-dependent small-colony variant; and TMP-SMX: trimethoprim-sulfamethoxazole. [a]Data not available for all patients.

microorganisms was associated with worse lung function and a greater risk of hospitalization. These findings suggest that TD-SCVs, which are emerging pathogens associated with chronic infections, can influence the course of the disease over time.

During the study period, the prevalence of the TD-SCV phenotype in our sample was 14.2%, similar to that reported by Morelli et al. [19] In our study, the median age at TD-SCV emergence was 14.0 years, comparable to the 14.4 years found by Yagci et al. [20] but considerably lower than the 23.0 years found by Morelli et al. [19] Those differences might be related to the age groups studied.

In the present study, the clinical data on pancreatic insufficiency were not positively associated with bronchiectasis. However, we observed an association between hospitalization rates and TD-SCV isolation. The higher morbidity observed in this group was likely related to greater impairment of lung function, as reported by Wolter et al. [7] Although the number of deaths was higher in the TD-SCV group than in the control group, this difference was not significant. According to the literature, the association between TD-SCV isolation and the risk of death is related to this phenotype and to bacteremia. [5]

In agreement with previous studies, [10,21,22] TMP-SMX use was significantly higher in our TD-SCV group, suggesting that the use of this medication is a risk factor for the emergence of the TD-SCV phenotype. This antimicrobial agent is commonly used to treat infections with *B. cepacia* complex, *S. maltophilia*, and methicillin-resistant *S. aureus*,[13] all of which are commonly isolated from patients with CF.[17] The protein thymidylate synthase is disrupted by *thyA* mutations caused by use of TMP-SMX, and that induces the production of high levels of cyclic di-AMP, which in turn induces activation of the interferon-stimulating protein in the host and increases the number of inflammatory cells in the airways, resulting in severe pulmonary dysfunction.[23]

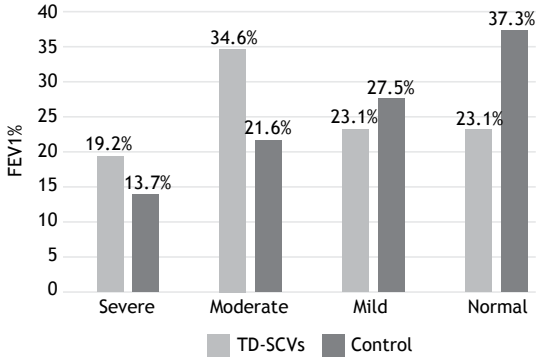

Figure 2. Classification of pulmonary function, by percent of predicted FEV_1 (FEV_1%), in patients with cystic fibrosis, with and without thymidine-dependent small-colony variants (TD- SCVs).

Colonization by different microorganisms was used as a selection criterion for the control group; therefore, the time since TD-SCV isolation (coinfection) was not significantly different between the two groups. However, impaired pulmonary function (low FEV_1%) was associated with the presence of TD-SCVs, which agrees with the results obtained by Wolter et al.[7]

Finally, it is unlikely that our findings were influenced by the CFTR genotype, because most of the patients in both groups had F508del and G542X mutations, the most common genotypes in our sample. However, our study has some limitations, such as the small number of samples and the limited amount of secondary clinical data. However, *S. aureus* infection with the TD-SCV phenotype is still underdiagnosed in patients with CF, and few studies have demonstrated the impact of infections with this phenotype.

In our study sample, TMP-SMX use was found to have affected the emergence of the TD-SCV phenotype. In addition, there was a direct relationship between worse pulmonary function and colonization/infection with TD-SCVs. Successful TD-SCV detection in microbiology laboratories is essential for adequate treatment, which affects morbidity and mortality in patients with CF.

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AUTHOR CONTRIBUTIONS

APOT: conceptualization; investigation; methodology; and writing - original draft. DCS: conceptualization; investigation; methodology; writing - review and editing. LLC: formal analysis; supervision; and writing - review and editing. JKP: formal analysis; and writing - review and editing. KSN: methodology; and writing - review and editing. RRP: statistical analysis. CAR: methodology; and writing - review and editing.

Table 2. Descriptive data analysis of demographic and clinical characteristics of patients with cystic fibrosis, with and without thymidine-dependent small-colony variants of *Staphylococcus aureus*.

Variable	Group	N	Range	Median	SD	*p*-value
Age (years)	TD-SCV	32	1-26	14.0	6.2	0.897
	Control	64	1-25	14.5	6.0	
Spirometry[a]						
FEV_1%	TD-SCV	25	16-132	61.8	24.5	0.04
	Control	47	30-131	78.7	27.6	

TD-SCV: thymidine-dependent small-colony variant. [a]Spirometric data not available for all patients.

NARF: conceptualization; methodology; supervision; writing - review and editing. LMDC: formal analysis; and writing - review and editing.

CONFLICTS OF INTEREST

None declared.

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Translation and cross-cultural adaptation of the Telemedicine Satisfaction Questionnaire for use in Brazil

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Study carried out at the Escola Paulista de Medicina/Universidade Federal de São Paulo, São Paulo (SP) Brasil.

ABSTRACT

Objective: To translate, cross-culturally adapt to Brazilian Portuguese, and evaluate the reliability of the Telemedicine Satisfaction Questionnaire (TSQ). **Methods:** This cross-sectional study involved patients from the Smoking Prevention and Cessation Center (PrevFumo) who participated in at least four of the eight scheduled remote meetings with the PrevFumo psychologist in 2020, 2021, or 2022. Participants were contacted by telephone and asked to answer the 14 questions of the TSQ three times at intervals of 7 or 10 days. **Results:** We assessed 53 patients (73.3% women). The mean age was 49.7 ± 10.2 years. The mean smoking history was 35.32 ± 24.8 pack-years. Of the 53 patients evaluated, 30.2% had completed high school or had some higher education, and 32.1% were classified as socioeconomic class B2 (A being the highest and E being the lowest). Forty-nine (92.5%) of the patients attended all eight meetings. The TSQ with only three answer options showed high reliability, with approximately 90% agreement after three applications. Patients were satisfied with telemedicine. **Conclusions:** The TSQ is rapidly applied, is easy to complete, and showed high reliability in our patient sample. Patients declared that they were satisfied with their telemedicine experience.

Keywords: Telemedicine; Patient satisfaction; Surveys and questionnaires; Cross-cultural comparison; Smoking cessation.

INTRODUCTION

The Pan American Health Organization defines telemedicine as the remote, real-time delivery of health care services by any health professional using information and communication technologies to diagnose, treat, and prevent diseases.[1]

In Brazil, the use of telemedicine began in 1994, first being employed by cardiologists for remote electrocardiogram examinations.[2] On December 27, 2022, law no. 14,510 amended law no. 8,080 (from September 19, 1990), to authorize and regulate the practice of telemedicine throughout the country. Telemedicine, known as *telessaúde* in Brazil, comprises the remote delivery of services related to all health professions regulated by competent agencies of the federal executive branch.

Several questionnaires assess patient satisfaction with telemedicine. The following are the most widely used: the Telehealth Usability Questionnaire, which assesses the feasibility of implementing telemedicine services[3]; the Telemedicine Satisfaction Questionnaire (TSQ)[4]; the Florida Patient Acceptance Survey[5]; the Telemedicine Satisfaction and Usefulness Questionnaire[6]; the Patient Satisfaction Questionnaire Short-Form[7]; the Patient Satisfaction with Physician[8]; the Service User Technology Acceptability Questionnaire,[9] which assesses the beliefs of uses regarding the acceptability of telemedicine; and the Telehealth Satisfaction Scale, developed for patients with memory disorders.[10]

To our knowledge, there have been few studies evaluating patient satisfaction with telemedicine in Brazil, and none have used a translated, cross-culturally adapted questionnaire according to guidelines.[11,12] Although Dias et al.[13] used a questionnaire to evaluate the satisfaction of patients receiving telemedicine for the treatment of headaches, the description encompassed only the domains and possibilities of answers ("yes" and "no"), with no detailing of the questions. Severini et al.[14] assessed the satisfaction of adult patients who used telemedicine, although their study lacked descriptions regarding how the questionnaire was adapted. Brandão et al.[15] reported a satisfaction questionnaire to assess the acceptance and impact of telemedicine at a referral center for special immunobiologicals; however, the questionnaire questions were not described. Macharet et al.[16] assessed the feasibility of telemedicine in urogynecology using only seven questions from a questionnaire originally consisting of 14. Dias et al.[17] investigated the efficiency of real-time telerehabilitation in patients with Parkinson's disease and found good patient satisfaction with telemedicine. However, their study sample comprised only 20 participants.

At the Paulista School of Medicine Smoking Prevention and Cessation Center (aka, PrevFumo), group orientation began remotely immediately after COVID-19 was

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declared a pandemic. However, when the pandemic was declared over, we had to decide whether the group orientation should return to in-person or continue being conducted remotely. To date, the in-person consultations have returned only for the initial visit. In this context, because of a lack of information regarding the satisfaction of our patients with remote group orientation, we felt compelled to assess their level of satisfaction before deciding whether to recommence the in-person group meetings. A literature review about satisfaction with telemedicine resulted in the choice of the TSQ because of its easy application and objective questions to assess the level of satisfaction with telemedicine and the reasons for the satisfaction.[4] Nevertheless, before it could be used in Brazil, the TSQ would have to be translated and adapted to Brazilian culture.

The primary objective of this study was to translate, cross-culturally adapt, and validate the TSQ for use in Brazil. Secondary objectives were to analyze the relationships that satisfaction with telemedicine has with nicotine addiction, smoking history, education level, socioeconomic class, symptoms of anxiety, depressive symptoms, and quality of life.

METHODS

Patients were invited by telephone to participate in this cross-sectional study. The study was approved by the Research Ethics Committee of the Federal University of São Paulo/Hospital São Paulo (Reference no: 64593722.0.0000.5505), in the city of São Paulo, Brazil. All participating patients gave written informed consent, either by e-mail or by text message. We included adult patients treated via the PrevFumo, regardless of sex and level of education, who participated in at least four of the eight scheduled remote group orientations.

Initially, the questionnaire was translated by one of the investigators who was fluent in English and Brazilian Portuguese.[11,12] In the cross-cultural adaptation phase, the initial Brazilian Portuguese-language version was presented to 10 patients from our outpatient clinics, who discussed the words that best expressed what the questionnaire proposed. This version was further discussed by a multidisciplinary team, including a physiotherapist, a psychologist, a nurse, and a physician. The cross-culturally adapted version was then back-translated to English by another person and compared to the original English version to evaluate the similarity.[11,12]

After a given patient had been enrolled, the following data were collected from medical records of the initial consultation at PrevFumo: sociodemographic characteristics including age, gender, education, and socioeconomic class according to the Brazilian economic classification criteria[18]; smoking history; degree of nicotine addiction, determined with the Fagerström test[19]; respiratory symptoms; motivation to stop smoking; degree of anxiety, depression, or both, determined with the Hospital Anxiety and Depression Scale (HADS)[20]; and quality of life, determined with the World Health Organization Quality of Life Instrument, brief version (WHOQOL-BREF).[21] The Brazilian economic classification criteria classify individual socioeconomic status into six classes from A (the highest) to E (the lowest). The Fagerström test comprises six questions with scores ranging from 0 (no addiction) to 10 (high addiction). The HADS has 14 questions that evaluate the probability of a diagnosis of anxiety or depression, with scores ranging from 0 to 21. The WHOQOL-BREF has 26 questions with a maximum total score of 130, higher values being associated with better quality of life.

The TSQ consists of 14 questions about satisfaction with telemedicine,[4] answered on a five-point Likert scale (Table 1): 1 = strongly disagree; 2 = disagree; 3 = indifferent; 4 = agree; and 5 = strongly agree. To assess the reliability of the questionnaire, we recruited a sample of 50 participants to answer the 14 TSQ questions by phone call at three different time points, one-week apart.[22] The same investigator conducted all three interviews, which ensured test-retest reliability.

Statistical analyses were conducted using the R software, version 4.2.2.[23] Data normality was verified with the Shapiro-Wilk test. Values are presented as absolute and relative frequencies (for categorical variables) or as mean and standard deviation (for continuous variables). Intraclass correlation coefficients (ICCs) were calculated in order to compare the reliability of TSQ responses among the three applications, and results were classified as poor (< 0.5), moderate (0.5-0.75), good (> 0.75-0.9), or excellent (> 0.9).[24] For correlation analysis between the TSQ score and the nonparametric variables age, education, socioeconomic class, Fagerström test score, smoking history, anxiety, depression, attendance to the virtual education meetings, and quality of life, Spearman's test was used. For comparison of the nonparametric variable sex, the Mann-Whitney test was used. There is no consensus on the interpretation of correlation values, but it is widely accepted that values under 0.4 should be considered indicative of a weak correlation. Values of $p < 0.05$ were considered statistically significant.

RESULTS

The final sample consisted of 53 participants, 73.3% of whom were female (Table 2). The mean age was 49.7 ± 10.2 years. Of the 53 patients evaluated, 16 (30.2%) had completed high school or had some higher education. The most common socioeconomic class (in 32.1%) was B2 (29-37 points). A total of 92.5% of participants connected to all eight meetings. The mean total score of the WHOQOL-BREF was 12.3 ± 2.49 (51.9% ± 15.5%), and the mean total score of the Fagerström test was 5.81 ± 2.28 (39.6% were highly addicted). The mean smoking history was 35.3 ± 24.8 pack-years. On the HADS, the mean anxiety

Table 1. Telemedicine Satisfaction Questionnaire.

1. I can easily talk to my healthcare professional. *(Eu posso falar facilmente com o meu profissional da saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
2. I can hear my health care provider clearly. *(Eu posso ouvir claramente o meu profissional da saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4-Agree	5- Strongly agree
3 My health care provider is able to understand my health care condition. *(Meu profissional da saúde pode entender minha condição de saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
4. I can see my health care provider as if we met in person. *(Eu consigo ver meu profissional da saúde como se nós estivéssemos pessoalmente)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
5. I do not need assistance while using the system. *(Eu não preciso de ajuda quando estou usando o sistema da telemedicina)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
6. I feel comfortable communicating with my health care provider. *(Eu me sinto à vontade me comunicando com meu profissional da saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
7. I think health care provided via telemedicine is consistent. *(Eu acho que a orientação sobre a saúde através da telemedicina é confiável)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
8. I obtain better access to health-care services by using telemedicine. *(Eu consigo fácil acesso ao serviço de saúde através da telemedicina)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
9. Telemedicine saves me time traveling to hospital or a specialist clinic. *(A telemedicina me economiza tempo em ir ao hospital ou a uma clínica especializada)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
10. I receive adequate attention. *(Eu consigo receber uma atenção adequada)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
11. Telemedicine provides for my health care needs. *(A telemedicina satisfaz a minha necessidade de cuidados da saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
12. I find telemedicine an acceptable way to receive health care services. *(Eu acho a telemedicina um modo aceitável de receber serviços de cuidados à saúde)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
13. I will use telemedicine services again. *(Eu usaria usarei os serviços da telemedicina novamente)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree
14. Overall, I am satisfied with the quality of service being provided via telemedicine. *(No geral, eu estou satisfeito com a qualidade do serviço sendo fornecida através da telemedicina)*				
1- Strongly disagree	2- Disagree	3- Indifferent	4- Agree	5- Strongly agree

score was 10.8 ± 4.4 (45.3% had probable anxiety), whereas the mean depression score was 8.2 ± 3.7 (49.1% had probable depression).

Reliability analysis

Table 3 presents the ICC between the three applications of the TSQ. Reliability was poor for 8 of the 14 questions. In addition, reliability values were better in the second and third interviews than in the first interview, probably because of the poor-to-moderate concordance found.

Descriptive analysis for the grouped score with five answer options

Table 4 shows the frequency of combinations found in the three interviews, from which we considered a total of 742 answers (53 participants times 14 questions). The percentage of concordance for the answers "strongly agree" (number 5) and "agree" (number 4) in the three interviews was 46% and 16.7%, respectively. The following five most frequent combinations included only the answers "strongly agree" and "agree" (numbers 4 and 5).

Descriptive analysis for the grouped score with three answer options

During the interviews, participants repeatedly reported not seeing differences between the answers "strongly disagree" and "disagree" and between "strongly agree" and "agree". In this sense, we reanalyzed data considering "strongly disagree" and "disagree" as one answer and "strongly agree" and

Table 2. Sociodemographic and clinical characteristics of the participants.

Variable	(N = 53)
Age (years), mean ± SD	49.7 ± 10.0
Sex	
Female, n (%)	39 (73.6)
Male, n (%)	14 (26.4)
Weight (kg), mean ± SD	74.5 ± 20.3
Height (cm), mean ± SD	163.5 ± 9.9
Level of education, n (%)	
None or ≤ 9 years of schooling	7 (13.2)
High school graduate ± some college	22 (41.5)
College graduate ± graduate school	33 (45.3)
Socioeconomic class, n (%)	
A (45-100 points)	4 (7.6)
B (29-44 points)	25 (47.2)
C (17-28 points)	23 (43.4)
D-E (0-16 points)	1 (1.9)
Number of meetings attended, n (%)	
4	2 (3.8)
5	1 (1.9)
6	1 (1.9)
8	49 (92.5)
WHOQOL-BREF	
Total score, mean ± SD	12.3 ± 2.5
Percentage, mean ± SD	51.9 ± 15.5
Fagerström test	
Total score, mean ± SD	5.8 ± 2.3
Score of 0-4, n (%)	15 (28.3)
Score of 5-10, n (%)	38 (71.7)
Smoking history (pack-years), mean ± SD	35.3 ± 24.8
HADS anxiety score, mean ± SD	10.8 ± 4.4
0-7, unlikely, n (%)	14 (26.4)
8-21, likely, n (%)	39 (73.6)
HADS depression score, mean ± SD	8.17 ± 3.7
0-7, unlikely, n (%)	20 (37.7)
8-21, likely, n (%)	33 (62.3)

WHOQOL-BREF: World Health Organization Quality of Life Instrument, brief version; and HADS: Hospital Anxiety and Depression Scale.

Table 3. Reliability analysis for the three applications of the Telemedicine Satisfaction Questionnaire.

Question	ICC	95% CI	p-value	Interpretation
1	0.488	0.325-0.640	0.550	Poor
2	0.469	0.306-0.623	0.639	Poor
3	0.599	0.440-0.732	0.103	Moderate
4	0.400	0.233-0.565	0.877	Poor
5	0.490	0.328-0.641	0.538	Poor
6	0.555	0.402-0.693	0.228	Moderate
7	0.416	0.251-0.579	0.835	Poor
8	0.582	0.433-0.714	0.132	Moderate
9	0.490	0.327-0.642	0.538	Poor
10	0.591	0.440-0.721	0.112	Moderate
11	0.591	0.435-0.723	0.118	Moderate
12	0.499	0.333-0.650	0.499	Poor
13	0.432	0.264-0.594	0.784	Poor
14	0.537	0.379-0.679	0.311	Moderate

ICC: intraclass correlation coefficient.

Table 4. Descriptive analysis of grouped scores with five answer options in three interviews (N = 742) and the frequency of answer combinations.

Answers			Frequency of answer combinations
Interview 1	Interview 2	Interview 3	n (%)
5	5	5	343 (46.2)
4	4	4	124 (16.7)
4	5	5	92 (12.4)
4	4	5	35 (4.7)
5	4	4	25 (3.4)
5	4	5	21 (2.8)
4	5	4	17 (2.3)
2	4	4	13 (17.5)
5	5	4	10 (1.3)
4	3	4	7 (0.9)
3	4	4	7 (0.9)
4	4	2	4 (0.5)
3	4	5	4 (0.5)
2	5	5	4 (0.5)
2	4	3	3 (0.4)
3	3	4	3 (0.4)
2	5	4	3 (0.4)
2	4	5	3 (0.4)
3	5	5	3 (0.4)
2	3	3	2 (0.3)
3	3	3	2 (0.3)
4	3	3	2 (0.3)
4	4	3	2 (0.3)
2	2	4	2 (0.3)
5	2	5	2 (0.3)
2	2	2	1 (0.1)
2	4	2	1 (0.1)
4	5	2	1 (0.1)
4	2	3	1 (0.1)
5	3	3	1 (0.1)
3	4	3	1 (0.1)
1	5	3	1 (0.1)
4	5	3	1 (0.1)
2	3	4	1 (0.1)

Option 1: strongly disagree; Option 2: disagree; Option 3: indifferent; Option 4: agree; and Option 5: strongly agree.

"agree" as another answer; thus, resulting in three options: "disagree" (number 1), "indifferent" (number 2), and "agree" (number 3). With this new classification, we observed that 89.9% of participants answered "agree" (number 3) in all three interviews (Table 5).

Correlations between TSQ score and sociodemographic variables

No association was found between the TSQ score and sex on the Mann-Whitney test (W = 320.5, p = 0.332). On Spearman's correlation test, the TSQ score was not found to correlate with age (r = −0.18, p = 0.196), education (r = −0.17, p = 0.21), socioeconomic class (r = 0.21, p = 0.140), attendance to telemedicine educational meetings (r = 0.24, p = 0.080), nicotine addiction (r = 0.17, p = 0.212), smoking history (r = 0.07, p = 0.602), anxiety (r = 0.07, p = 0.602), depression (ρ = 0.07, p = 0.602), and quality of life (ρ = −0.05, p = 0.714).

DISCUSSION

For this study, we translated the TSQ to Brazilian Portuguese, cross-culturally adapted it for use in Brazil, and evaluated its reliability. We found that all of the participants were satisfied with telemedicine and that the TSQ was reliable, rapidly applied, easily completed, and easy to understand.

The translation and cross-cultural adaptation of a questionnaire should follow the guidelines established by Beaton et al.[11] and Wild et al.[12] Depending on the complexity of a questionnaire, more than one translator can perform the translation and back-translation.[12] When translating a questionnaire into the local

Table 5. Descriptive analyses of grouped scores with three answer options in three interviews (N = 742) and the frequency of answer combinations.

Answers			Frequency of answer combinations
Interview 1	Interview 2	Interview 3	n (%)
3	3	3	667 (89.9)
1	3	3	23 (3.1)
2	3	3	14 (1.2)
3	2	3	7 (0.9)
3	3	1	5 (0.7)
1	3	2	4 (0.5)
3	2	2	3 (0.5)
3	3	2	3 (0.4)
2	2	3	3 (0.4)
1	2	2	2 (0.3)
2	2	2	2 (0.3)
1	1	3	2 (0.3)
3	1	3	2 (0.3)
1	1	1	1 (0.1)
1	3	1	1 (0.1)
3	1	2	1 (0.1)
2	3	2	1 (0.1)
1	2	3	1 (0.1)

Option 1: disagree; Option 2: indifferent; Option 3: agree.

language, it is recommended that the senior author of the original questionnaire be consulted to discuss and resolve questions regarding the interpretation of terms or phrases. In the cross-cultural adaptation phase, the version translated into the local language must be presented and discussed with persons with the same status the questionnaire was created, in order to determine which words best express what the questionnaire will assess. For this phase, a multidisciplinary team joined the investigators to discuss with patients which terms would be the best for the Brazilian Portuguese-language version of the TSQ. The translated version should then be back-translated by a different person, compared with the original version to evaluate similarity,[11,12] and presented to the senior author of the original version for acceptance or suggestions.[11,12] The translation and cross-cultural adaption of the TSQ for use in Brazil encompassed all of those phases. However, we were unable to contact the first or the senior authors of the original TSQ, despite sending messages via internet and attempting to contact the university. Nevertheless, we do not believe that the lack of contact limited the translation, given that the statements in the questionnaire were quite clear.

Few questionnaires assessing satisfaction with telemedicine can be found in the Brazilian literature. Studies similar to ours have used different questionnaires without clear descriptions regarding their development or translation. Although Dias et al.[17] assessed satisfaction with telemedicine by questioning sociodemographic parameters, transportation, and travel time to the hospital, no description was presented regarding the number of patients satisfied with the care given by the health care professional. Those authors also did not describe the translation and cross-cultural adaptation. Although the TSQ has been previously used in Brazil for assessing the perspectives of legal guardians regarding consultations with patients under 18 years of age, only 7 of the 14 questions were asked and no information was given concerning the translation.[16] Likewise, Brandão et al.[15] applied a satisfaction survey for the use of immunobiologicals, although the questionnaire used was not specified.

The present study assessed reliability by applying the Brazilian Portuguese-language version of the TSQ at three different time points. Reliability is the repeatability or reproducibility of a measure or variable, and it is commonly assessed by applying a questionnaire at least twice.[25-27] However, reliability increases with sample size and the number of questionnaire applications. For a sample size of 50 participants with three repetitions, the confidence intervals are narrower than, for instance, a sample of 15 participants with four repetitions. Therefore, the number of questionnaire applications is important in a study design to reduce the typical error.[22].

Participants completed the TSQ by choosing one of the five answers on the Likert scale for each question. However, most of them stated that the answers "strongly disagree" and "disagree" and the options "strongly agree" and "agree" were similar and difficult to understand as different options. Considering that the answers "strongly agree" and "agree" expressed the same feeling (i.e., acceptance of what was considered in the question), we merged the two answers into one and found that most (89.9%) of the participants were satisfied with their telemedicine experience. Although Likert scales typically present five answer options, a

different number of options can be considered. For example, in one study that cross-culturally adapted an instrument to investigate the perception of health professionals about teleconsultation, seven options were given.[28] Likewise, five options were presented to patients undergoing treatment for type 2 diabetes,[4] whereas three options were given to evaluate the responsiveness of a system by applying a usability script to three devices[29]: notebooks, tablets, and smartphones. It is possible that the level of education influenced the number of answer options; that is, participants with a high level of education might be more capable of sorting out a more precise answer than are those with no formal education. Nevertheless, we observed no differences among different education levels in terms of the answers chosen.

For questions 12, 13, and 14 of the TSQ, which refer directly to satisfaction with telemedicine, the positive response rate was high (87.7%, 94.3%, and 94.3%, respectively) after three interviews. The reasons why patients were satisfied with telemedicine were assessed through questions 7, 9, 10, and 11, which also presented high reliability (90.1%, 94.3%, 84.9%, and 90.6%, respectively). The ICC analysis was hampered by the large percentage of answers grouped into two responses, considering the five Likert scale options.

The novel finding of this study was the high rate of satisfaction with telemedicine by our patients. Telemedicine has been used for over 30 years,[30] and the COVID-19 pandemic recently led to in its adoption worldwide. With the closure of the outpatient clinic, virtual consultations became an alternative for communication between health care professionals and patients. Our smoking cessation clinic maintained the group orientation through telemedicine, but information on patient satisfaction or whether they would prefer to go back to the previous system (in-person group meetings) was lacking. Despite the high satisfaction rate, our results may apply only to certain consultations. Knowledge about the physical health of patients was optional in the smoking cessation group, because the meetings focused on advice and reinforcement techniques.

One limitation of our study was the initial refusal of participants to respond to calls and questions at three different time points to answer the same questions; they considered the repetition unnecessary. This was mitigated by explaining the reasons for the repetition and emphasizing the need for appropriate guidance to increase the reliability of the study. Another limitation was the application of the TSQ to patients who required only guidance and motivation to stop smoking. Therefore, other specialties should use the Portuguese-language version of the TSQ that has been cross-culturally adapted for use in Brazil to determine whether patients were satisfied with telemedicine. A third possible limitation was the lack of a test-retest reliability analysis.

Despite its development in 2002 and use in various studies, the TSQ is not widely used in Brazil, probably because previous translations were not performed in accordance with the standards.[11] In addition, the use of telemedicine became widespread in Brazil in 2020 (during the COVID-19 pandemic) and was regulated only in 2022.[31] With the increasing development of telemedicine in Brazil, the TSQ is a reliable tool to assess the level of satisfaction of patients regarding health care services.

One of the strengths of the present study was the large sample size and application of the TSQ at three different time points. This design increased the reliability of results. Another strength was the high reliability regarding satisfaction with telemedicine. In addition, no significant difference was observed between the TSQ score and the variables assessed, indicating that it may be applied to any individual, regardless of age, gender, education level, socioeconomic class, symptoms of depression or anxiety, and quality of life.

The Portuguese-language version of the TSQ, cross-culturally adapted for use in Brazil, appears to be easily and quickly applied, and patients considered the use of telemedicine acceptable in the smoking cessation group meetings. This acceptability might have been influenced by the fact that telemedicine is reliable, saves time, provides adequate attention, and meets health care needs. Applying the TSQ at three different time points, with three answer options, showed high test-retest reliability.

AUTHOR CONTRIBUTIONS

MEL: data collection, writing, editing, and descriptive analysis; SSN: writing and editing; ACF: data collection and essay; JRJ: writing, descriptive analysis, and translation.

CONFLICTS OF INTEREST

None declared.

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Tumor spread through air spaces in lung cancer: prospective analysis of the accuracy of intraoperative frozen section examination

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ABSTRACT

Objective: To establish the accuracy of frozen section examination in identifying tumor spread through air spaces (STAS), as well as to propose a reproducible technical methodology for frozen section analysis. We also aim to propose a method to be incorporated into the decision making about the need for conversion to lobectomy during sublobar resection. **Methods:** This was a nonrandomized prospective study of 38 patients with lung cancer who underwent surgical resection. The findings regarding STAS in the frozen section were compared with the definitive histopathological study of paraffin-embedded sections. We calculated a confusion matrix to obtain the positive predictive value (PPV), negative predictive value (NPV), sensitivity, specificity and accuracy. **Results:** The intraoperative frozen section analysis identified 7 STAS-positive cases that were also positive in the histopathological examination, as well as 3 STAS-negative cases that were positive in the in the histopathological examination. Therefore, frozen section analysis was determined to have a sensitivity of 70%, specificity of 100%, PPV of 100%, NPV of 90.3%, and accuracy of 92% for identifying STAS. **Conclusions:** Frozen section analysis is capable of identifying STAS during resection in patients with lung cancer. The PPV, NPV, sensitivity, and specificity showed that the technique proposed could be incorporated at other centers and would allow advances directly linked to prognosis. In addition, given the high accuracy of the technique, it could inform intraoperative decisions regarding sublobar versus lobar resection.

Keywords: Neoplasm invasiveness; Frozen sections; Lung neoplasms/pathology; Lung neoplasms/surgery.

INTRODUCTION

The concept of tumor spread through air spaces (STAS) is defined by the World Health Organization (WHO) Classification of Tumors as "micropapillary clusters, solid nests, or single cells spreading within air spaces beyond the edge of the main tumor."[1] Although the concept of STAS varies across studies, the WHO concept is the most widely accepted and disseminated in the literature. Although Kodama et al.[2] first identified STAS in 1980, a debate began in 2023 when Onozato et al.[3] identified tumor islands as a factor for worse five-year disease-free survival in early-stage lung adenocarcinomas: 44.6% in patients with tumor islands and 74.4% in those without. In 2015, Kadota et al.[4] introduced the concept of STAS to the world by reporting a cumulative five-year recurrence rate of 42.6% in STAS-positive patients who underwent sublobar resection, compared with 12.7% in those undergoing lobectomy. In that same year, Warth et al.[5] evaluated a cohort of 569 patients with lung adenocarcinoma and found that overall survival and five-year disease-free survival were worse among those with STAS, as well as establishing important definitions regarding this pathological entity. Subsequent studies, conducted between 2015 and 2018, presented similar results and pointed out new findings.[6-11] All of these studies identified STAS in the postoperative period, which led to a need to detect this important risk factor in the intraoperative period in order to be able to convert sublobar resections into lobectomies. In 2018, Walts et al.[12] were pioneers in the study of intraoperative frozen pathology for this purpose, despite the fact that they obtained negative results.

A meta-analysis conducted by Chen et al.,[13] involving a collective total of 3,754 patients in 14 studies, suggested that the presence of STAS was associated with worse recurrence-free survival and overall survival in non-small cell lung cancer (NSCLC). Subgroup analysis by histological type indicated that the presence of STAS was significantly associated with worse recurrence-free survival after resection of lung adenocarcinoma, lung squamous cell carcinoma, or pleomorphic lung carcinoma. It was also related to shorter overall and recurrence-free survival, regardless

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of tumor stage.[13,14] The presence of STAS was also more frequently observed in advanced-stage NSCLC, exhibiting prognostic value in all pathological stages. It is also an unfavorable prognostic factor in pulmonary metastases from colorectal cancer, although its role is not yet fully defined.[14] Therefore, given the high risk of locoregional recurrence in patients with STAS, the treatment standard for these patients may be lobectomy instead of sublobar resection, whether the patient meets the criteria for segmentectomy or not.[13,15]

Given the data in the literature demonstrating the negative impact that STAS has on patient survival, the major dilemma is regarding the timing of diagnosis. A finding of STAS in the postoperative analysis of sublobar resection poses a pertinent question: should we proceed with lobectomy, necessitating a return to the operating room, or simply observe the progression? Obviously, if we could decide intraoperatively, through frozen section pathology, this dilemma would be resolved. Intraoperative frozen section is a well-known technique widely used by pathologists. However, there are some obstacles to its use in the setting of lung cancer, especially because of the lack of a defined protocol to serve as a basis. Another important factor is that STAS is also often difficult to distinguish from intra-alveolar macrophages, a distinction that must be made on the basis of the nucleus-cytoplasm ratio and degree of nuclear atypia.[15] Therefore, our aim was to establish the accuracy of intraoperative frozen section pathology in identifying STAS, as well as to propose a technical methodology for frozen section pathology analysis that can be reproduced. In addition, on the basis of our findings, we aim to propose a method to be incorporated into the decision-making process regarding the need for lobectomy in indications for sublobar resection.

METHODS

This was a prospective, nonrandomized study in which patients with a preoperative or intraoperative diagnosis of lung cancer underwent diagnostic or therapeutic resection. During the procedure, the surgical specimen was analyzed through frozen section pathology. If a diagnosis of STAS was confirmed, the surgical team, along with the pathologist, indicated conversion from sublobar resection to lobectomy. Categorically, conversion was not indicated only in cases of metastasis from other sites, of inadequate pulmonary reserve, and of advanced tumors. Subsequent to the procedure, the surgical specimen was sent for definitive histopathological analysis of paraffin-embedded sections, after which the details of the case were entered into a database and the results were compared. The study was approved by the Scientific and Editorial Committee of the *Hospital Geral de Caxias do Sul*, operated by the University of Caxias do Sul, in the city of Caxias do Sul, Brazil. All participating patients gave written informed consent.

We identified 44 patients who underwent lung resection for diagnosis or definitive treatment between April 2020 and October 2022 in the Thoracic Surgery Department of the *Hospital Geral de Caxias do Sul*. It is worth noting that the COVID-19 pandemic imposed certain difficulties during that interval, especially at high-complexity referral hospitals like ours. Of the 44 patients initially selected, 6 were excluded: 1 because the result was inconclusive; and 5 because the frozen section was not screened for STAS by the pathologist who was part of the study, thus maintaining the prospective nature of the study. This resulted in a total of 38 patients: 28 who were negative for STAS (in 22 sublobar resections and 6 lobectomies); and 10 who were positive for STAS (in 6 sublobar resections and 4 lobectomies). We emphasize that, regardless of the STAS status, tumors for which lobectomy was indicated were subjected to such.

Histological analysis

The histological analysis compared the results of the STAS investigation in frozen sections with the definitive histopathological study of paraffin-embedded sections. Using a standardized histological technique based on the previous experience of the team and the international literature, two pathologists interpreted the intraoperative findings. However, in each case, the intraoperative finding and the histopathological result were both evaluated by the same pathologist thereby avoiding case overlap.

For the intraoperative frozen section examination, two randomly selected sections from different areas of the parenchyma immediately adjacent to the lesion were sampled. These sections encompassed a small portion of the lesion, the transition to the adjacent parenchyma, and the adjacent parenchyma up to 1.0 cm away when possible (Figure 1). The distance of 1.0 cm was chosen because STAS is evaluated at the tumor margins, despite the absence of a specific measurement for this evaluation in the current literature. Histological sections of 4-5 µm in thickness were cut in a cryostat and stained with routine hematoxylin and eosin. To increase the sensitivity of the intraoperative assessment without prolonging the examination time, only two sections were selected; ideally, the entire tumor margin should be evaluated, but this is unfeasible due to time constraints. The result was communicated to the surgeon and documented in writing. Figure 2 illustrates the presence of STAS in one of our cases.

For the histopathological examination, the same histological sections used in the intraoperative frozen section examination were embedded in paraffin to prepare histological slides, cut to a thickness of 3 µm, and stained with hematoxylin and eosin. Additional sections were included to represent the tumor, following the sampling recommendations and guidelines for histopathological reports established by the College of American Pathologists.[16] The inclusion of additional paraffin-embedded sections

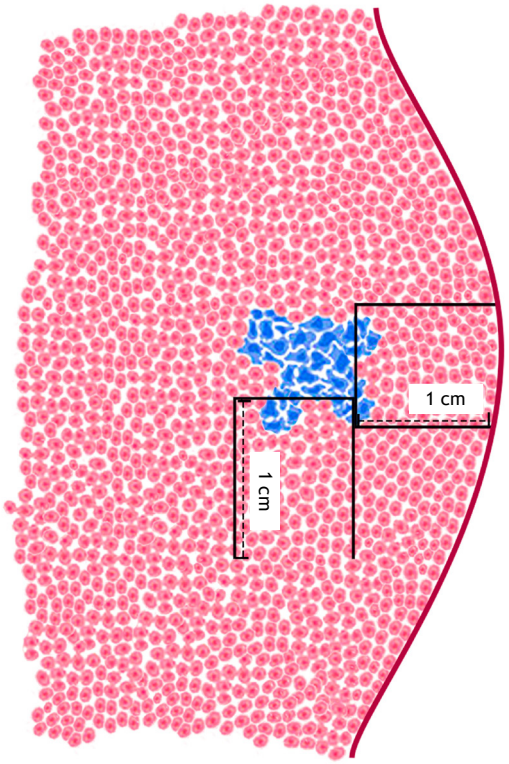

Figure 1. Illustration of material sampling for frozen section examination.

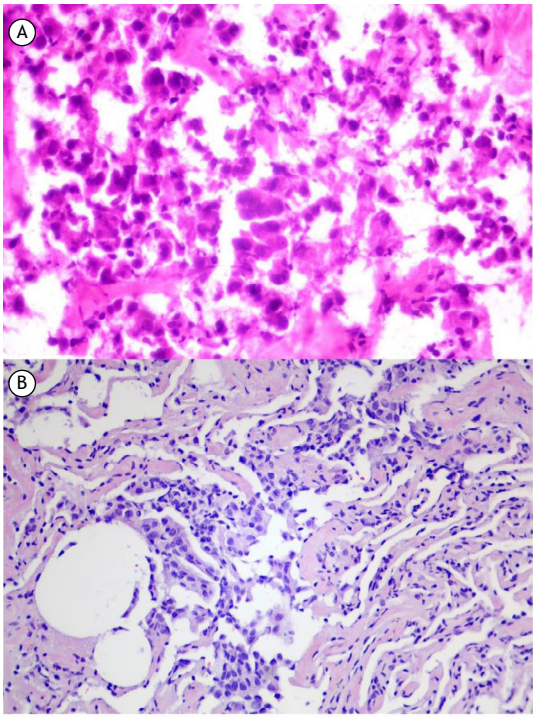

Figure 2. Example case demonstrating tumor spread through air spaces in the intraoperative frozen section (A) and in the paraffin block (B).

may facilitate the identification of STAS in areas not sampled during the frozen section analysis.

Statistical analysis

The database was created with information collected from the electronic medical records of the selected patients. The categorical (dichotomous) diagnosis of STAS (i.e., STAS positivity and STAS negativity) made by the evaluating pathologist from the frozen sections was compared with the results of the evaluation of paraffin-embedded sections by the same pathologist. After finalizing the counts related to the categorizations obtained with the two techniques, we calculated a confusion matrix to determine the positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity of frozen section analysis. Those values were used to determine the accuracy of the method. In addition, a ROC curve was constructed to compare intraoperative frozen section examination with histopathological examination, by determining the AUC. Variables investigated for potential associations with STAS positivity were defined on the basis of previous studies, and chi-square tests were applied to qualitative variables, whereas Student's t-tests were used for quantitative variables. Means and medians were calculated for continuous variables, and standard deviations were computed for subsamples. Categorical variables are presented as counts and percentages. Statistical analysis was performed with the IBM SPSS Statistics software package, version 27.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Comparison between frozen section analysis and definitive histopathological diagnosis

The intraoperative frozen section examination identified 7 patients as STAS positive and 31 as STAS negative, whereas the definitive histopathological examination identified 10 and 28 patients, respectively, as such (Table 1). The frozen section examination identified 7 cases (18.4%) as STAS-positive cases and 3 as STAS-negative cases, those 3 being identified as STAS-positive cases in the histopathological examination of the paraffin-embedded sections, resulting in a sensitivity of 70%, specificity of 100%, PPV of 100%, and NPV of 90.3%. These data are presented in a confusion matrix in Table 1. Five previous studies have also compared intraoperative frozen section examination with definitive paraffin-based histopathology,[12,17-20] as detailed in Table 2.

The frozen section examination identified the majority of positive cases, and all negative cases in the histopathological examination had the same result in the intraoperative examination, translating to a test accuracy of 92% and an AUC of 0.850 (Figure 3).

Characteristics of the STAS-positive and STAS-negative cases in the definitive histopathology

Our study sample comprised 38 patients, with a mean age at the time of the surgical procedure of 69.66 ±

Table 1. Confusion matrix of the results of the intraoperative frozen section examination and the histopathological analysis.

Frozen section	Definitive histopathology		Total
	STAS-positive	STAS-negative	
STAS-positive	7	0	7
STAS-negative	3	28	31
Total	10	28	38

STAS: spread through air spaces.

Table 2. Comparison among previous studies that compared intraoperative frozen section examination and definitive histopathological analysis of paraffin-embedded sections.

Reference	Year	N	AUC	Sensitivity	Specificity	Accuracy
Walts et al.[12]	2018	48	-	48%	100%	-
Eguchi et al.[17]	2019	48	-	71%	92%	-
Villalba et al.[18]	2021	100	0.67	44%	91%	71%
Zhou et al.[19]	2021	163	-	55%	80%	74%
Ding et al.[20]	2023	294	-	55%	85%	74%
This study	2024	38	0.85	70%	100%	92%

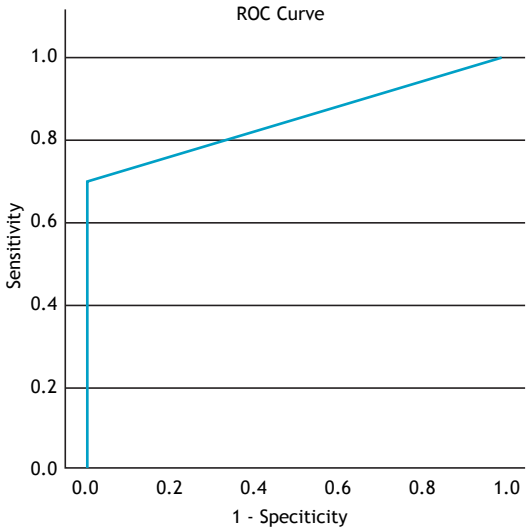

Figure 3. ROC curve of tumor spread through air spaces in the frozen section examination.

12.13 years. Of those 38 patients, 28 (73.7%) had a negative STAS result on histopathological examination and 10 had a positive STAS result (26.3%), with mean ages of 70.39 years (median, 73 years) and 67.6 years (median, 66.5 years), respectively. Sublobar resection was performed in 28 cases (73.7%), and lobectomy was performed in 10 (26.3%).

Among the 28 patients who were negative for STAS, the median age was 73 years (mean, 70.39 ± 10.6 years), compared with a median of 66.5 years (mean, 67.6 ± 16.2 years) among the 10 positive cases (p = 0.041). The mean tumor size was 1.81 ± 1.22 cm in the STAS-negative cases and 2.07 ± 1.02 cm in the STAS-positive cases (p = 0.697). In the STAS-negative subgroup, 79% of the surgical procedures were sublobar resections and 21% were lobectomies, whereas, in the STAS-positive subgroup, 60% were wedge resections or segmentectomies and 40% were lobectomies (p = 0.264). The proportion of cases with Lung CT Screening Reporting and Data System category 4X findings was similar between the two subgroups (p = 0.436). In the STAS-positive subgroup, the predominant tumor type (in 30%) was adenocarcinoma with an acinar pattern, 50% of the tumors showed vascular invasion, 40% of the patients were nonsmokers, and 60% of the patients had a history of cancer other than lung cancer (p = 0.71). There were no significant differences between the two subgroups in terms of tumor necrosis (p = 0.757), involvement of visceral pleura (p = 0.781), or bronchial invasion (p = 0.951), unlike angiolymphatic invasion, which was observed in 32% of the patients in the STAS-negative subgroup and in 50% of those in the STAS-positive subgroup (p = 0.328). The proportion of never-smokers was 40% in the STAS-positive subgroup, compared with 25% in the STAS-negative subgroup (p = 0.16). In addition, 60% of the patients in the STAS-positive subgroup had a history of neoplasia at a site other than the lungs (Table 3), with the vast majority being colorectal (p = 0.475). It should be noted that these findings are not statistically relevant given the small sample size, intergroup heterogeneity, and convenience sampling. However, the chi-square tests for frozen and histopathological sections coincide and are consistent with findings in the international literature. The same was true for the Student's t-tests for patient age and tumor size (see the supplementary material).

DISCUSSION

In recent decades, thoracic surgery has progressively moved toward minimally invasive procedures and non-radical resection. The discussion on sublobar resection necessarily involves identifying STAS in the preoperative or intraoperative assessment. The method proposed for this purpose is intraoperative frozen section examination, for which there are discrepancies in the literature related to its use. In the present study, with technical standardization, STAS

Table 3. Demographic and clinical characteristics of the sample (N = 38), by histopathological subgroup.

Characteristic	STAS-negative (n = 28)	STAS-positive (n = 10)	p-value
Age (years), median (mean ± SD)	73 (70.39 ± 10.6)	66 (67.6 ± 16.2)	0.041
Sex, n (%)			
Female	16 (57.1)	6 (60.0)	0.879
Male	12 (42.8)	4 (40.0)	
Tumor size (cm), mean ± SD	1.81 ± 1.22	2.07 ± 1.02	0.697
Type of resection, n (%)			
Sublobar	22 (78.6)	6 (60.0)	0.264
Lobar	6 (21.4)	4 (40.0)	
Lung-RADS category, n (%)			
4A	4 (14.2)	1 (10.0)	0.436
4B	6 (21.4)	3 (30.0)	
4X	18 (64.4)	6 (60.0)	
Histology, n (%)			
Colorectal metastasis	5 (17.8)	1 (10.0)	0.71
Solid adenocarcinoma	5 (17.8)	1 (10.0)	
Lepidic adenocarcinoma	5 (17.8)	1 (10.0)	
Acinar adenocarcinoma	6 (21.4)	3 (30.0)	
Mucinous adenocarcinoma	3 (10.7)	2 (20.0)	
Papillary adenocarcinoma	1 (3.6)	0	
Micropapillary adenocarcinoma	0	2 (20.0)	
Poorly differentiated adenocarcinoma	1 (3.6)	0	
Carcinosarcoma	1 (3.6)	0	
Atypical carcinoid	1 (3.6)	0	
Tumor necrosis, n (%)			
Yes	7 (25.0)	2 (20.0)	0.757
No	21 (75.0)	8 (80.0)	
Involvement of visceral pleura, n (%)			
Yes	2 (7.1)	1 (10.0)	0.781
No	26 (92.8)	9 (90.0)	
Bronchial invasion, n (%)			
Yes	3 (10.7)	1 (10.0)	0.951
No	25 (89.3)	9 (90.0)	
Angiolymphatic invasion, n (%)			
Yes	9 (32.1)	5 (50.0)	0.328
No	19 (67.8)	5 (50.0)	
Smoking status, n (%)			
Never smoker	7 (25.0)	4 (40.0)	0.16
Current smoker	11 (39.3)	1 (10.0)	
Former smoker (≥ 20 pack-year history)	10 (35.7)	5 (50.0)	
History of lung cancer, n (%)			
Yes	6 (21.4)	1 (10.0)	0.437
No	22 (78.6)	9 (90.0)	
History of other cancer, n (%)			
Yes	13 (46.4)	6 (60.0)	0.475
No	15 (53.6)	4 (40.0)	

STAS: spread through air spaces; and Lung-RADS: (American College of Radiology) Lung CT Screening Reporting and Data System.

was recognized in the frozen section examination, which showed high (70%) sensitivity and robust (100%) specificity, resulting in an accuracy of 92%. These findings are significant and pave the way for intraoperative identification of STAS, with important prognostic value, in pulmonary resection, especially sublobar resection, in Brazil.

Walts et al.[12] were the first to compare intraoperative frozen section examination with definitive paraffin-based histopathology, in 2018. Those authors

evaluated 48 patients with stage T1 or T2 tumors, 46 of whom were positive for STAS. They found that intraoperative frozen section pathology had a sensitivity of 48%, specificity of 100%, PPV of 100%, and NPV of 8%. However, the authors did not clearly describe a standardized protocol for the frozen section pathology technique and obtained limited samples of normal lung parenchyma adjacent to the lesion.[12] The following year, Eguchi et al.[17] analyzed a sample of 48 T1N0 adenocarcinomas, evaluated by 5 different pathologists, who achieved a sensitivity of 71%, specificity of 92%, and 75% agreement among them. The authors did not describe the frozen section methodology, using only the criterion of the resected non-neoplastic adjacent parenchyma being at least one third the size of the main tumor.[17] Villalba et al.,[18] in a sample of 100 patients analyzed by 3 pathologists, obtained an AUC of 0.67, sensitivity of 44%, specificity of 91%, accuracy of 71%, PPV of 79.2%, and NPV of 68.4%. They also reported moderate interobserver agreement among pathologists who made the analyses and intraobserver agreement (because the slides were analyzed more than once) ranging from 77% to 85%. Again, no frozen section methodology was described.[18] In a 2021 study, Zhou et al.[19] evaluated 163 stage I adenocarcinomas and were the first to clearly describe the methodology of intraoperative frozen section examination. Those authors found the technique to have a sensitivity of 55%, specificity of 80%, accuracy of 74%, PPV of 48%, and NPV of 85%. It is noteworthy that they described various artifacts as exclusion factors for the diagnosis of STAS, which could explain the high false-positive rate.[19] In a 2023 study, Ding et al.[20] retrospectively analyzed frozen section examination in a sample of 294 patients with NSCLC, demonstrating that it had an accuracy of 74.14%, sensitivity of 55.14%, and specificity of 85.02%, with discordance between the cases with a consolidation-to-tumor ratio (CTR) ≤ 0.5 and those with a CTR > 0.5, the results being more satisfactory in the latter. Thus, they concluded that intraoperative frozen section examination is applicable in cases of NSCLC with a CTR > 0.5.[20] Bearing these data in mind, we observe that all previous studies have evaluated frozen section examination retrospectively, with ours being the first prospective study of the topic.

A study conducted by Metovic et al.[21] aimed to investigate whether gross specimen handling procedures influence the rate of STAS detection in cases of lung cancer. The study involved a prospective analysis of 51 surgical lung specimens, encompassing various histological types. Each specimen was meticulously handled, with fresh tissue sections cut using a new blade for each incision, followed by separate processing after formalin fixation. The authors identified STAS in 64.7% of the cases, predominantly as clustered formations (in 87.9%). It is noteworthy that they found no significant difference between the rates of STAS detection before and after tumor sectioning, in the upper or lower lung parenchyma and in fresh or fixed tissues.[21] These findings suggest that STAS occurrence is not influenced by gross specimen handling procedures, indicating that it likely represents a biological phenomenon inherent to the tumor rather than an artifact introduced during processing of the surgical sample.

Our study has some limitations. The main limitation was the small size of the patient sample. However, it was a convenience sample, the main objective being to establish a parallel between frozen section examination and histopathological examination, in order to define the former as a valid method for intraoperative diagnosis of STAS. Despite the scarcity of studies on the subject in the literature, we can draw a comparison between out data and what is currently available in the literature. Despite the modest size of our sample, our findings regarding the sensitivity, specificity, PPV, NPV, and accuracy of frozen section examination are comparable to those of previous studies, especially those of Eguchi et al.[17] The literature seems to converge regarding the specificity of the method, although sensitivity varies across studies, which may be explained by the absence of technical standardization or guidelines imposing standardization of slide analysis. To our knowledge, this is the first prospective analysis of the topic, through which we aim primarily to establish a standardized methodology for the detection of STAS in frozen section pathology that does not rely solely on the experience of the pathologist and can be replicated worldwide, thereby expanding the discussion.

We can conclude that intraoperative frozen section pathology with technical standardization is capable of identifying STAS in patients with lung cancer undergoing resection. Despite the small number of patients evaluated, the PPV, NPV, sensitivity, and specificity demonstrated that the technical standardization applied could be incorporated at other centers and allow advancements that are directly associated with prognosis. In addition, given the high accuracy (92%), it is possible to infer that its inclusion would inform intraoperative decisions regarding the choice between lobectomy and sublobar resection. These preliminary results, in view of the scarcity of studies on the subject, bring the topic to the cutting edge of the debate on sublobar resection, given the impact on tumor recurrence in STAS-positive patients undergoing resection smaller than lobectomy, that impact being even more pronounced in patients with good pulmonary reserve.

AUTHOR CONTRIBUTIONS

GLA, BMP, VMP, ACT, RFA, and DRPF contributed to the conception and design of the study; the acquisition, analysis, and interpretation of data; and the writing and critical review of the article. All authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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Expert views on screening for tuberculosis infection in patients commencing treatment with a biologic agent

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ABSTRACT

Objective: Many biologic agents cause some degree of immunosuppression, which can increase the risk of reactivation of tuberculosis infection (TBI). This risk is variable between individual biologics. We aimed to assess current (and recommended) clinical practice of TBI screening and treatment among patients initiating treatment with biologic agents. **Methods:** An online questionnaire was distributed via email to members of the Global Tuberculosis Network and associated professional organisations to seek insights into the screening for and treatment of TBI in patients treated with biologics. **Results:** A total of 163 respondents in 27 countries answered at least one question. For all biologics described in the questionnaire, respondents advised increasing screening relative to current practice. Observed and supported TBI screening rates in patients treated with TNF-α inhibitors were high, especially for older TNF-α inhibitors. Most participants supported TBI screening in patients treated with B- or T-cell inhibitors but not in those treated with interleukin inhibitors. Guideline awareness was higher for TNF-α inhibitors than for other biologic classes (79% vs. 34%). **Conclusions:** Although respondents stated that TBI screening rates are lower than what they consider ideal, there was a tendency to recommend TBI screening in patients treated with biologics not known to be associated with an increased risk of TBI. As a result, there is a potential risk of over-screening and over-treatment of TBI, potentially causing harm, in patients treated with biologics other than TNF-α inhibitors. There is a need to research the risk of TBI associated with biologics and for guidelines to address the spectrum of TBI risk across all types of biologics.

Keywords: Latent tuberculosis; Biological products; Immunosuppression therapy; Recurrence; Mass screening.

INTRODUCTION

Tuberculosis infection (TBI) results from airborne spread of the bacterium *Mycobacterium tuberculosis* from a contagious patient to a susceptible individual. Once infected, the normal host immune response is to confine the TB bacteria within the lung. In most patients, this infection remains confined—a condition previously described as latent TB infection and latterly as TBI. For approximately 5-15% of people with TBI (lifetime risk), the bacteria can escape confinement resulting in active tuberculosis. Although there is not always an identifiable trigger for reactivation, it is significantly more common in immunocompromised individuals.[1]

Biologics, also known as biopharmaceuticals, are drugs containing components from living organisms and typically work by suppressing aspects of the immune system, thus increasing the risk of tuberculosis reactivation. As shown in Table 1, there are four main classes of biologic agents[2-14]: TNF-α inhibitors, interleukin inhibitors, T-cell inhibitors and B-cell inhibitors. The risk of tuberculosis reactivation associated with different medications differs, even within a given class.

The increased risk of active tuberculosis associated with TNF-α inhibitors has been well documented.[14] There is, however, a paucity of meaningful data about the risk of active tuberculosis associated with biologics other than TNF-α inhibitors. Studies

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Table 1. Risk of tuberculosis infection associated with different biologic drugs.

Class	Name	TBI reactivation risk in comparison with the general population RR (95% CI)	Risk in comparison with other drugs or population subgroups RR (95% CI)
TNF-α inhibitors	All classes	17.1 (13.9-21.0)[3]	4.0 (2.4-6.9), compared with patients with RA taking non-biologic disease modifying agents[3]
	Infliximab	18.6 (13.4-25.8), based on the SIR[4]	2.8 (2.1-3.7), compared with etanercept[3]
	Adalimumab	29.3 (20.3-42.4), based on the SIR[4]	3.9 (2.3-6.5), compared with etanercept[3]
	Etanercept	1.8 (0.7-4.3), based on the SIR[4]	
	Golimumab	Insufficient data[5]	Biologic class
	Certolizumab pegol	No comparable data	Similar reactivation risk compared with the other TNF-α inhibitor drugs[6]
T-cell inhibitors	Abatacept	No comparable data[7]; No significant increase[5,8]	Lower compared with TNF-α inhibitors[8]
B-cell inhibitors	Rituximab	No increase; no known cases[5,9,10]	Lower compared with TNF-α inhibitors[8]
Interleukin inhibitors			
IL-6Rα inhibitor	Sarilumab	Insufficient data[8]	
IL-6 inhibitor	Tocilizumab	Low[5,11]	
IL-5 inhibitor	Mepolizumab	No increase[12,13]	
IL-5Rα inhibitor	Benralizumab	No increase[12]	
IL-12/IL-23 inhibitor	Ustekinumab	No increase[8,11,14]	
IL-17 inhibitor	Secukinumab	Slightly elevated[8]	

TBI: tuberculosis infection; RA: rheumatoid arthritis; SIR: standardised incidence ratio.

comparing the risk of active tuberculosis in patients treated with a specific biologic with that determined for the general population (in the same setting) would allow the relative risk of active tuberculosis associated with biologic use to be estimated.[15,16] What evidence is currently available, however, suggests that the risk of tuberculosis reactivation by most non-TNF-α inhibitors is not likely significant (See Table 1).

The risk of TBI reactivation associated with B-cell inhibitor use is thought to be low because the tuberculosis immune response is largely T-cell dominated.[5,9] Rituximab is a widely used and researched B-cell inhibitor, with all available evidence indicating a zero to negligibly elevated risk of TBI reactivation.[5,9,11] As a result, a Rituximab Consensus Expert Committee in rheumatology recently determined TBI screening to be unnecessary prior to its initiation.[5,17]

Although the tuberculosis immune response is largely T-cell driven, use of the T-cell inhibitor abatacept has not been associated with an increased relative risk of TBI reactivation.[5,8] There is scant information available regarding the risk of TBI reactivations associated with T-cell inhibitors other than abatacept.

Where data are available (Table 1), they suggest that the risk of TBI reactivation associated with the use of interleukin inhibitors is either minimally elevated or non-existent.[5,8,11-14,18-20]

Despite reported differences in the risk of TBI reactivation associated with different biologics, it is unclear whether this variability is taken into consideration by physicians determining the need for TBI screening and treatment. There are currently only a few guidelines on TBI screening in patients treated with biologics other than TNF-α inhibitors, with most being generally based on poor quality of evidence (see supplementary material: Table S1). Anecdotal evidence suggests that TBI screening practices fluctuate significantly across different health care facilities and sometimes even between providers within the same facility.

The primary objective of this paper is to describe current clinical practice regarding TBI screening and treatment of patients initiating treatment with biologic agents, on the basis of the results obtained with a survey distributed to members of the Global TB Network. A secondary objective is to identify areas of significant variation in screening practices, which should be addressed with updated clinical practice guidelines.

METHODS

Ethical considerations

Ethics approval for the survey was obtained from the South Western Sydney Local Health District Human Research Ethics Committee (Reference no. 2021/ETH12298).

Survey design

The study survey was designed with Qualtrics software (https://www.qualtrics.com/free-account/).

Questions were organised into several sections exploring different aspects of TBI screening and treatment. We sought to achieve an understanding of current and ideal practice, as considered by experts in the topic of tuberculosis. Demographic data, including age, gender, country of birth and country of practice, were also collected.

The biologic agents listed in the survey were selected to represent indications for various diseases and different lengths of time available on the market. All biologics listed are approved for clinical use by the European Medicine Agency and the U.S. Food and Drug Administration.

Five participants filled out a pilot questionnaire. On the basis of the feedback received at this step, some minor changes were made. Responses to the pilot surveys were included in the final data analysis.

Survey distribution

An email that included a link to the survey, with a participant information sheet attached, was sent to members of the Global TB Network. The Global TB Network is an international group of healthcare practitioners involved in tuberculosis care, including clinicians, epidemiologists and researchers.[21] Members of the Global TB Network also distributed our survey within their own networks, including the Brazilian Thoracic Association, the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR), the Mexican Pulmonary and Thoracic Surgery Society, the French Society of Respiratory Diseases, the Canadian TB Elimination Network and the Australian TB Forum. Participants were informed that their participation in this project was entirely voluntary, and that submission of the survey would imply their informed consent.

Data collection and analysis

The survey was open between 2 May of 2022 and 21 July of 2022. Responses were collected in Qualtrics and exported to Microsoft Excel to facilitate descriptive analyses.

Proportions of responses were calculated for each question, meaning that the denominator could vary between questions. An overall response rate could not be calculated because of the network sampling technique that was employed to distribute surveys. However, rates for fully vs. partially complete surveys were calculated and are described below.

Participants were grouped based on the tuberculosis incidence in their country of practice. Low-incidence settings were distinguished from intermediate-to-high-incidence settings using a cut-off of an annual tuberculosis incidence of 40 per 100,000 population. National tuberculosis incidence rates for 2022 were obtained from the World Health Organization (WHO) website.[22]

RESULTS

A total of 255 surveys were returned to us from participants in a total of 27 countries (Figure 1). Of those, 163 were categorized as complete or partially complete. A survey was considered partially complete if there was a response to at least one question after the demographics section but not all questions were answered.

Of the 163 complete or partially complete surveys, 100 (61.3%) were from European countries (see supplementary material: Figure S1). Grouping country of practice by tuberculosis incidence, 16 countries were included in the low-incidence category, which comprised 114 participants. The remaining 10 countries were categorised as intermediate-to-high-incidence countries and comprised 48 participants. One survey respondent did not provide their country of practice.

Current reported screening practices for TBI as well as screening practices judged as optimal by participants varied among the biologics surveyed (Table 2). There were high rates of observed screening

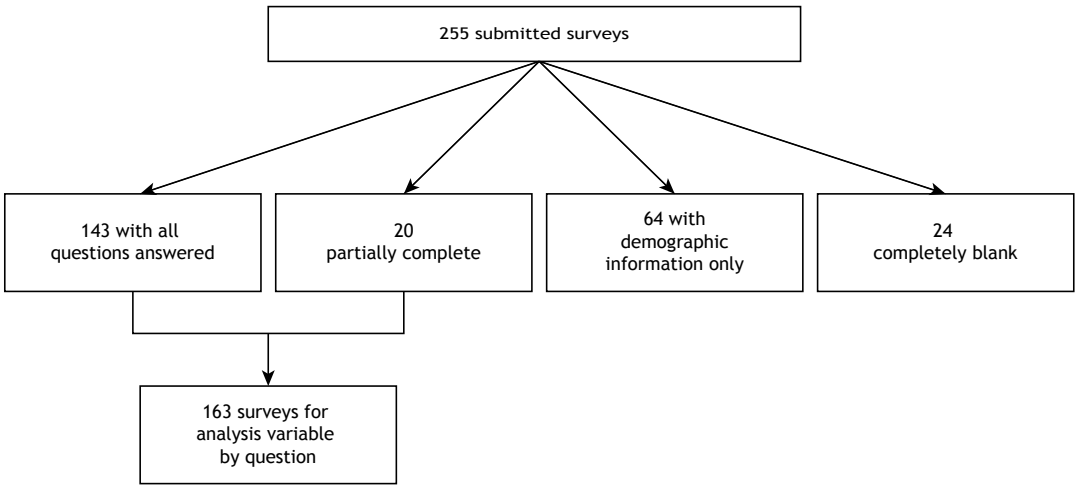

Figure 1. Surveys considered for analysis.

Table 2. Currently observed practices regarding screening for tuberculosis infection and screening practices suggested, for different biologics.

Class/biologic	Participant responses						
	Currently screens for TBI	Supports the use of IGRA and TST for TBI screening	Supports the use of CXR for TBI screening	Thinks that TBI screening is warranted	Thinks there is insufficient evidence for TBI screening	Does not know whether TBI screening is indicated	Thinks any form of TBI screening (IGRA/TST/CXR) is warranted
	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)	% (n/N)
TNF-α inhibitors							
Infliximab	93.2 (151/162)	96.2 (151/157)	61.1 (96/157)	0	0	3.2 (5/157)	96.8 (152/157)
Adalimumab	89.4 (143/160)	96.7 (145/150)	60.0 (90/150)	0	0	2.7 (4/150)	98.0 (147/150)
Etanercept	87.6 (141/161)	96.6 (143/148)	60.8 (90/148)	0	0	2.0 (3/148)	98.0 (145/148)
Certolizumab pegol	66.4 (103/155)	88.2 (127/144)	54.9 (79/144)	0	0.7 (1/144)	11.1 (16/144)	89.6 (129/144)
Golimumab	68.2 (107/157)	89.5 (128/143)	55.2 (79/143)	0	0.7 (1/143)	9.8 (14/143)	90.9 (130/143)
T-cell inhibitor							
Abatacept	59.6 (90/151)	70.7 (99/140)	43.6 (61/140)	2.8 (4/140)	5.0 (7/140)	20.0 (28/140)	72.8 (102/140)
B-cell inhibitor							
Rituximab	59.5 (94/158)	61.3 (87/142)	39.4 (56/142)	14.8 (21/142)	11.3 (16/142)	10.6 (15/142)	64.1 (91/142)
Interleukin inhibitors							
Sarilumab (IL-6)	38.0 (57/150)	52.5 (74/141)	31.2 (44/141)	7.1 (10/141)	17.0 (24/141)	23.4 (33/141)	53.9 (76/141)
Tocilizumab (IL-6)	47.4 (72/152)	58.2 (82/141)	36.2 (51/141)	11.3 (16/141)	17.0 (24/141)	13.5 (19/141)	60.3 (85/141)
Mepolizumab (IL-5)	17.2 (26/151)	29.0 (40/138)	19.6 (27/138)	31.2 (43/138)	18.1 (25/138)	19.6 (27/138)	33.3 (46/138)
Benralizumab (IL-5)	16.0 (24/150)	27.5 (38/138)	18.1 (25/138)	31.2 (43/138)	18.1 (25/138)	20.3 (28/138)	31.9 (44/138)
Ustekinumab (IL-12/IL-23)	47.0 (72/153)	47.8 (67/140)	32.9 (46/140)	10.7 (15/140)	15.7 (22/140)	25.7 (36/140)	50.0 (70/140)
Secukinumab (IL-17)	36.6 (56/153)	43.1 (59/137)	28.1 (43/153)	9.5 (13/137)	18.2 (25/137)	29.2 (40/137)	46.0 (63/137)

TBI: tuberculosis infection; IGRA: interferon-gamma release assay; TST: tuberculin skin test; and CXR: chest X-ray.

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for the TNF-α inhibitor class, especially for the older drugs infliximab (93%), adalimumab (89%) and etanercept (88%). The perceived screening rates for certolizumab pegol and golimumab were lower (67% and 68%, respectively). For TBI screening in patients treated with TNF-α inhibitors, participant recommendations for using an IFN-gamma release assay (IGRA) or tuberculin skin test (TST) ranged from 88% and 97%, and recommendations for using chest X-ray (CXR) in the screening process ranged from 55% to 61%.

Most respondents reported and supported TBI screening in patients treated with B- or T-cell inhibitors but not in patients treated with interleukin inhibitors except those treated with sarilumab or tocilizumab, for which more than 50% recommended TBI screening despite a minority believing that this is current practice at their health care facility. The rates of observed and suggested TBI screening were lowest for the severe asthma drugs benralizumab and mepolizumab (16% and 17%, respectively). Those two drugs also had the highest proportions of respondents advising against screening (31% for both).

For all biologics, overall, the number of participants who considered a CXR to be warranted in the TBI screening process was lower than that of those who recommended the use of an IGRA or TST (Table 2). For all of the biologics listed, the respondents supported more screening than what they currently observed at their respective health care facilities.

Of the 159 participants who answered the relevant question, 126 (79.2%) were aware of at least one clinical guideline for TBI screening in patients initiating treatment with a TNF-α inhibitor, compared with 51 (34.4%) of the 148 participants who answered the question related to guidelines for patients initiating treatment with a non-TNF-α inhibitor.

Of the 84 participants who could name at least one guideline relating to TBI screening prior to TNF-α inhibitor use, 20 named the WHO guidelines and 9 named the SEPAR guidelines. Other named guidelines included those issued by the Centers for Disease Control and Prevention (n = 4), the European Society of Clinical Microbiology and Infectious Disease (ESCMID; n = 3), the British Thoracic Society (n = 3) and the American Thoracic Society (n = 2). Three participants named systematic reviews: two reviews of international guidelines[23,24]; and one that was specific for non-TNF-α biologics.[25] Twenty-four participants (19%) were aware of local hospital guidelines. Multiple participants named national guidelines from their country of practice, including Brazil (n = 8) and France (n = 8).

Of the 25 participants who named at least one guideline for non-TNF-α inhibitors, 5 were aware of the SEPAR guidelines and 2 were aware of the ESCMID guidelines. Ten participants named local or national guidelines from their country of practice. Other named guidelines included those issued by the WHO (n = 3) and the Centers for Disease Control and Prevention (n = 1), as well as those issued by Alimentary Pharmacology and Therapeutics (n = 1). Two participants named vague guidelines, such as "rheumatological guidelines" and "clinical recommendation 2021", and one participant named the systematic review specific for non-TNF-α biologics.[25]

Most respondents were selective when choosing patients for TBI screening (Figure 2). However, a considerable proportion (23.8%) suggested that TBI screening should be conducted in all patients treated with biologics irrespective of the TBI reactivation risk

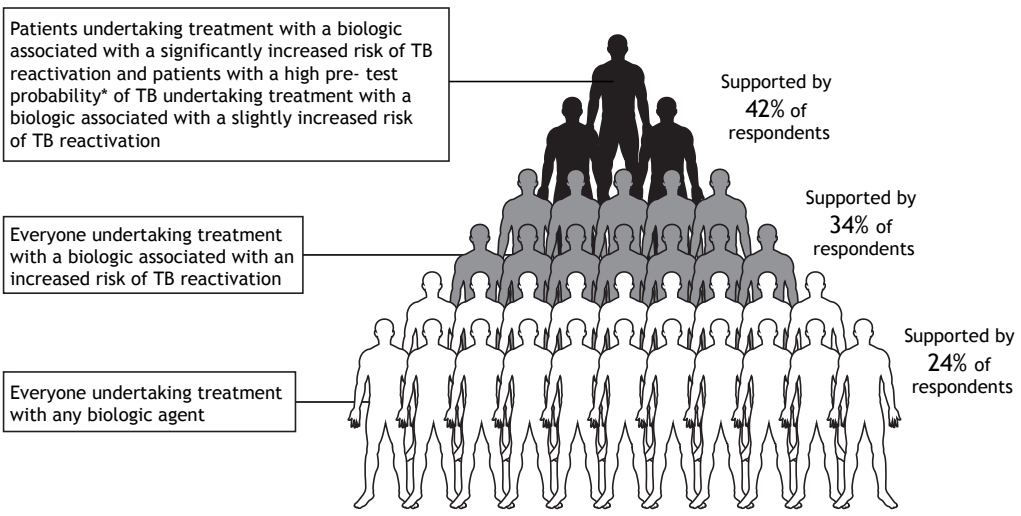

Figure 2. Proportional distribution of participant responses regarding which patients initiating treatment with which biologics should be screened for infection with tuberculosis (TB). *An increased pre-test probability would, for example, be based on a history of close TB contact, birth in a high TB burden country, and previous treatment for active tuberculosis. NOTE: This figure was created by using Servier Medical Art templates, which are licensed under a Creative Commons Attribution 3.0 Unported License; https://smart.servier.com.

associated with the biologic in question. The number of participants who recommended any form of TBI screening for any of the biologics listed was higher than was that of those who recommended no screening (see supplementary material: Table S5).

There were two preferred screening algorithms, with 36.0% of the participants being in favour of IGRA alone and 33.3% favouring IGRA and TST sequentially (in any order) if the first test result is negative. Only a few participants (4%) supported the use of TST alone.

Most (60.1%) of the respondents were in favour of a CXR being performed in all patients undergoing treatment with biologic agents independent of the result of TBI screening or the presence of symptoms (Table 3). A CXR can help to exclude active tuberculosis and detect other diagnoses, such as a neoplasm.

Of the 146 participants who answered the relevant question, 114 (78.0%) indicated that they would repeat TBI screening upon new exposure to an infectious tuberculosis patient, whereas only 63 (43.2%) indicated that they would repeat screening upon travel to a high tuberculosis incidence country and only 52 (35.6%) indicated that they would perform TBI screening at regular intervals. In the free text response, four survey participants emphasised the need to know the baseline screening result before making any decisions about tests (see supplementary material: Tables S2 and S3).

The most commonly used tuberculosis preventive therapy regimen, reported by 43.6% of the respondents, was 6-9 months of isoniazid (Table 4), whereas 45.7% indicated a preference for rifampin-containing regimens, either alone for 4 months (25.0%) or together with isoniazid for 3 months (20.7%). The least commonly used treatment regimen (cited by 9.3% of the respondents) was 12 doses of rifapentine and isoniazid over 3 months.

Of the 102 participants in low tuberculosis incidence countries, 71 (69.6%) preferred patients to undergo 1 month of tuberculosis treatment prior to the start of treatment with a biologic agent (see supplementary material: Table S4). However, only 22 (56.4%) of the 39 respondents in intermediate-to-high tuberculosis incidence countries were in favour of this approach, generally recommending a longer duration of tuberculosis treatment before commencing treatment with a biologic compared with those in low incidence countries. Few participants selected the "Other" option, in which some emphasised that the duration of tuberculosis treatment would be variable depending on the urgency of biologic treatment (n = 4) and some suggested immediate or concurrent commencement of treatment with the biologic (n = 3).

Of the 141 participants who answered the relevant question, 114 (80.8%) supported monitoring of liver function test results during tuberculosis treatment. Support was very low for routine repeat CXR (5.7%) and repeat TBI screening (4.2%), whereas 14.9% preferred to conduct no routine monitoring tests.

For the 10 participants who chose the free text option, recommendations included a complete blood count (n = 4), renal function tests (n = 2) and monitoring clinical symptoms or adverse events (n = 2). The 2 remaining participants emphasised the importance of the baseline TBI screening results.

A comparison of the survey responses from each country and their national guidelines showed that there was some deviation between the two. Although the SEPAR guidelines recommend screening for patients treated with any biologic, 70% of the participants working in Spain would not screen patients treated with rituximab (which aligns with other international guidelines). Most (66%) of those participants follow the guidelines to initiate biologics after 1 month of tuberculosis treatment and an even larger proportion (87%) would repeat TBI screening upon exposure to an infectious tuberculosis patient, although only 57% adhered to the guideline recommendation for using a combination of IGRA and TST during screening for TBI. There was more variation in the chosen treatment regiments for TBI, with 38% following the SEPAR recommendation of 6-9 months of isoniazid and 31% suggesting 3 months of the rifampin-isoniazid combination, which the guidelines recommend in exceptional circumstances only (see supplementary material: Table S1). Many (43%) of the participants in Brazil showed a preference for using either TST or IGRA without preference, as opposed only 14% who stated that they adhere to the Brazilian Thoracic Association recommendation for TST only. The Brazilian guidelines were published in 2009, possibly explaining this discrepancy. Specifically, the guidelines recommend periodic TST testing in patients initiating treatment with TNF-α inhibitors (see supplementary material: Table S1). Most (64%) of the participants in Brazil were aligned with their national guidelines in terms of their tuberculosis treatment of choice, employing the recommended 6-9 months of isoniazid, and in terms of the timing of the initiation of biologic treatment,

Table 3. Survey participant suggestions regarding the role of chest X-ray in screening for tuberculosis infection in patients initiating treatment with a biologic.

Under what condition CXR should be performed	(N = 148)
In all patients, n (%)	89 (60.1)
Only when TBI screening is positive, n (%)	25 (16.9)
Only in patients with symptoms (e.g., cough), n (%)	9 (6.1)
In symptomatic patients or when TBI screening is positive, n (%)	25 (16.9)

CXR: chest X-ray; and TBI: tuberculosis infection.

following the recommendation of waiting until after 1 month of tuberculosis treatment. Participants in Australia and the United Kingdom (8 participants from each) generally followed their national guidelines. From Europe, North America, Asia and Oceania, there was only a limited number of completed surveys, most of which were from Europe. That reflects the profile of the membership of the Global TB Network which has a strong European base.

DISCUSSION

Management of TBI is a core intervention to achieve tuberculosis elimination, with patients treated with TNF-α inhibitors and other biologics representing a vulnerable group deserving specific attention.[26]

The results of this global survey suggest that tuberculosis specialists believe that there is under-screening of patients treated with different biologics at their respective health care facilities. There was strong support for TBI screening in patients treated with TNF-α inhibitors, as well as a high level of awareness of at least one clinical practice guideline for TBI screening in patients initiating treatment with TNF-α inhibitors. Participant awareness of guidelines regarding TBI screening in patients initiating treatment with non-TNF-α inhibitor biologics was much lower. There was also a high degree of variation in current screening practices for the non-TNF-α inhibitors other than mepolizumab and benralizumab. Those two biologics are commonly used for the treatment of severe asthma and were associated with low rates of screening recommendations by the respondents. Most respondents reported and supported TBI screening in patients treated with B- or T-cell inhibitors but not in patients treated with all interleukin inhibitors (the exceptions being sarilumab and tocilizumab). The most popular screening regimen was for IGRA alone or IGRA and TST used sequentially (in any order) if the first result is negative. There were no substantial differences in tuberculosis screening recommendations between low- and intermediate-to-high-incidence countries.

The increased risk of tuberculosis associated with TNF-α inhibitors is well documented, and it seems that many health care professionals extrapolate that risk to other biologic classes.[5,27] In our study, respondents indicated very high perceived levels of TBI screening for TNF-α inhibitors and supported such screening, with no participants recommending against it. This is consistent with current evidence of the significantly elevated TBI reactivation risk associated with these drugs.[3] It is noteworthy that, despite evidence suggesting a low or possibly absent risk of TBI reactivation with non-TNF-α inhibitors, the proportion of participants preferring any form of TBI screening was greater than was that of those preferring no screening for patients treated with any of the biologics listed in this survey.

Table 4. Tuberculosis preventive therapy preferences amongst respondents, by tuberculosis incidence level in the country of practice.

Tuberculosis incidence	Preferred treatment regimen					Total responses	No response	Grand total
	6-9 months of isoniazid % (n/N)	4 months of rifampin % (n/N)	3 months (12 doses) of rifapentine + isoniazid % (n/N)	3 months of isoniazid + rifampin % (n/N)	Other % (n/N)	N	n	N
Low	40.0 (40/100)	29.0 (29/100)	4.0 (4/100)	27.0 (27/100)	0	100	14	114
Intermediate to high	53.8 (21/39)	15.4 (6/39)	20.5 (8/39)	5.1 (2/39)	5.1 (2/39)	39	9	48
Unknown*	0	0	0	0	100.0 (1/1)	1	0	1
Total	43.6 (61/140)	25.0 (35/140)	8.6 (12/140)	20.7 (29/140)	2.1 (3/140)	140	23	163

*Country of practice not indicated.

The guidelines and clinical standards currently available[28] mainly focus on TBI screening in patients treated with TNF-α inhibitors and to a much lesser extent on screening in patients treated with other biologics. Some, such as the SEPAR guidelines,[29] extrapolate the recommendations for TNF-α inhibitors to other biologics. The ESCMID guidelines explicitly refer to different biologics by name,[13,30] with separate risk assessments for specific classes of biologic agents. Local guidelines from the National Health Service Gloucestershire Hospitals and the Drug and Bulletin Board of Navarre, Spain, also give specific recommendations for individual biologics.[31,32] All guidelines are generally based on weak or insufficient evidence.

The general recommendation for TBI screening in our survey seemed to be relatively undifferentiated for different biologic classes and not necessarily aligned with the low TBI reactivation risk for many non-TNF-α inhibitor biologics. However, these recommendations were often aligned with guideline recommendations. Although evidence suggests that ustekinumab is associated with no increased risk of TBI reactivation, multiple guidelines recommend screening in patients treated with this medication.[11,14] The ESCMID guidelines justify this by stating that there is a biologically plausible increase in TBI reactivation risk.[13] Though no cases of TBI reactivation have been associated with the use of sarilumab, the ESCMID guidelines recommend screening because it is an IL-6 inhibitor like tocilizumab, which has been associated with a risk, albeit a low risk, of TBI reactivation.[11,13,20] This clearly demonstrates the need for high quality studies assessing the risk of TBI reactivation associated with different biologics, to inform the development of guidelines.

The only biologics included in this study for which some guidelines (including those at a local level) recommended against TBI screening were rituximab, mepolizumab and benralizumab. Current evidence suggests that these three drugs, along with ustekinumab, are not associated with an increased risk of TBI reactivation.[5,8,9,11-14] The survey results demonstrate considerable variation in screening practices for rituximab (60% current observed screening) and ustekinumab (47% current observed screening). Almost equal proportions of participants indicated they believe any form of TBI screening is indicated for patients treated with mepolizumab or benralizumab (33% and 32%, respectively, vs. 31% who believed that no screening is indicated for either drug), which indicates that there is clinical uncertainty and variation in practice.

Participants supported more frequent screening than what they currently observed for all of the drugs listed in this study. A universal recommendation for TBI screening in patients treated with any biologic can lead to over-screening, an increased risk of false-positive test results if the pre-test tuberculosis risk is low and subsequent over-treatment. This may unnecessarily expose the patient to the potential adverse effects of TBI treatment, mainly hepatotoxicity.[33] Therefore, it is important that the risks and benefits of TBI screening and treatment are assessed on an individual basis when dealing with patients treated with biologics other than TNF-α inhibitors.

We found that current practice did not always align with national guidelines regarding screening for TBI in patients about to receive biologics. In some countries, the national guidelines had not been updated recently, which could explain such divergences.

Our study has some limitations. The smaller number of responses from tuberculosis professionals working in countries with a high tuberculosis incidence likely reflects the different approach to tuberculosis control in those countries. In high-incidence countries, treatment of active tuberculosis rather than tuberculosis preventive therapy is the primary emphasis of tuberculosis control programmes. In addition, at the time of the distribution of the survey, the combination treatment of isoniazid and rifapentine was not widely available in some countries, and it is unclear whether this TBI treatment regimen would be the preferred option for many today. That combination was also not listed in most (older) guidelines as a preferred treatment regimen. The descriptive study analysis provides insights into international practices but does not allow us to establish causality (e.g., between observed practice and local/national guidelines). Furthermore, although the participants were internationally recognised tuberculosis experts, their views may not necessarily be representative of the practices and recommendations related to tuberculosis in their country of practice.

This study has demonstrated participant uncertainty about the need for tuberculosis screening in patients treated with biologics other than TNF-α inhibitors, for which there has been little research and there are fewer available guidelines than for TNF-α inhibitors. Where guidelines exist, they are based on weak or insufficient evidence and are often informed by expert opinion. Therefore, there is a need for further studies of the TBI reactivation risk associated with different biologic agents such as T-cell inhibitors and interleukin inhibitors. In addition, this study illustrates the need for evidence-based clinical guidelines to be developed and disseminated amongst clinicians, along with clear recommendations addressing what to do when there is insufficient information. Recommendations for or against TBI screening should be considered for all immunosuppressive drugs not just biologics.

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AUTHOR CONTRIBUTIONS

AS participated in the study design, questionnaire development; survey design; data analysis; and drafting of manuscript.

GBM, LD'A, J-MG-G, DRS, LAR, LRC, F-XB, ST, CWMO, CH, GS and RC participated in the study design; survey distribution; and writing and critical review of the manuscript.

CCD participated in the study conception and design; ethics approval; questionnaire development; data analysis; writing and critical review of the manuscript; and project supervision.

CONFLICTS OF INTEREST

None declared.

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External validation of the parsimonious EuroLung risk models: analysis of the Brazilian Lung Cancer Registry

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ABSTRACT

Objective: The purpose of this study was to assess performance in the Brazilian Lung Cancer Registry Database by using the parsimonious EuroLung risk models for morbidity and mortality. **Methods:** The EuroLung1 and EuroLung2 models were tested and evaluated through calibration (calibration plot, Brier score, and the Hosmer-Lemeshow test) and discrimination (ROC AUCs), in a national multicenter registry of 1,031 patients undergoing anatomic lung resection. **Results:** The evaluation of performance in Brazilian health care facilities utilizing risk-adjustment models, specifically EuroLung1 and EuroLung2, revealed substantial miscalibration, as evidenced by calibration plots and Hosmer-Lemeshow tests in both models. In terms of calibration, EuroLung1 exhibited a calibration plot with overlapping points, characterized by a slope of 1.11 and a Brier score of 0.15; the Hosmer-Lemeshow test yielded a statistically significant p-value of 0.015; and the corresponding ROC AUC was 0.678 (95% CI: 0.636-0.721). The EuroLung2 model displayed better calibration, featuring fewer overlapping points in the calibration plot, with a slope of 1.22, with acceptable discrimination, as indicated by a ROC AUC of 0.756 (95% CI: 0.670-0.842). Both models failed to accurately predict morbidity and mortality outcomes in this specific health care context. **Conclusions:** Discrepancies between the EuroLung model predictions and outcomes in Brazil underscore the need for model refinement and for a probe into inefficiencies in the Brazilian health care system.

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Keywords: Quality of health care; Models, statistical; Public health; Morbidity; Lung neoplasms.

INTRODUCTION

In a managed care system, the assessment of care quality within surgical units is crucial. Quality is an abstract concept often measured through various indicators.[1] In thoracic surgery, outcome measures are the main quality indicators. Evaluating the performance of health care providers requires adjusting outcomes for different case mixes across institutions.[2]

To facilitate equitable comparative audits, The European Society of Thoracic Surgeons (ESTS) Database Committee developed risk-adjustment models for morbidity and mortality from a dataset of nearly 50,000 patients.[3] These models were simplified into the parsimonious EuroLung1 and EuroLung2 versions in 2019.[4] Those versions offer excellent discrimination capabilities in Europe and are applicable for risk-adjusted performance audits, aiding in quality improvement.

The Brazilian Lung Cancer Registry, a multicenter prospective database, collects data from thoracic procedures at health care facilities in Brazil, supporting quality management. Predictive models like the parsimonious EuroLung risk models facilitate the initial quality assessment and subsequent improvements. Although these models have shown validity in Europe,[4] they have been shown to have limited discrimination capacity when applied to patients in Canada and Japan.[5,6]. To our knowledge, there have been no studies evaluating their applicability in Latin America. This is crucial because of disparities among these populations, including variations in socioeconomic factors and challenges related to diagnosing lung cancer and initiating treatment, often due to barriers to health care access.

The primary objective of this study was to assess the performance of thoracic surgery facilities in Brazil by using the parsimonious EuroLung1 and EuroLung2 risk models within the Brazilian Lung Cancer Registry. A secondary objective was to test the external validity of the parsimonious EuroLung risk models in the Brazilian context.

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METHODS

Ethics statement

This study was approved by the local institutional review board (Registration no. 16424413.2.1001.0065). The requirement for informed consent was waived because only anonymized data were used.

Modeling cohort - parsimonious EuroLung1 and EuroLung2 models

In 2017, the ESTS Database Committee published the first models for the prediction of risk after anatomical lung resection (EuroLung1 for cardiopulmonary morbidity and EuroLung2 for 30-day mortality), based on data from approximately 50,000 patients.[3] A recent update described models that are more parsimonious.[4] The parsimonious EuroLung models contain five variables for morbidity and six variables for mortality. The two models (EuroLung1 and EuroLung2) contain some common variables associated with morbidity and mortality—age, sex, postoperative FEV_1 ($ppoFEV_1$), and thoracotomy—together with some that are specific for either morbidity (extended resection) or mortality (BMI and pneumonectomy).[4]

Cardiopulmonary complications listed in the ESTS database were included as outcome variables.[7] Mortality was defined as any death within 30 days after operation or surgical death occurring at any time during the same hospital stay. Extended resection[3] consisted of chest wall involvement; Pancoast tumors; resection of the atrium, superior vena cava, aorta, diaphragm, or vertebra; bronchial sleeve resection; pleuropneumonectomy; sleeve pneumonectomies; and intrapericardial pneumonectomy.

Aggregate EuroLung2 model

Similar to what was done in the original EuroLung study,[7] we tested the aggregate version of the EuroLung2 model to be used as a simple risk stratification tool. using ROC analysis, we found the best cutoff values associated with mortality to be as follows[8]: age > 70 years; $ppoFEV_1$ < 70%; and BMI < 18.5 kg/m^2.[8] A score of 1 point was assigned to the variables with the smallest odd ratios at logistic regression (age > 70 years and $ppoFEV_1$ < 70%) and proportionally weighting the four other variables[4]: 2.5 points for male sex, BMI < 18.5 kg/m^2, and thoracotomy; and 3 points for pneumonectomy.[4] Patients were grouped into seven risk classes to evaluate incremental risk of mortality.[4]

Performance evaluation

This study evaluates the performance in Brazilian health care facilities utilizing the EuroLung1 and EuroLung2 risk-adjustment models.[4] We used a validation cohort from the nationwide multicenter registry known as the Brazilian Lung Cancer Registry. This registry stands as a forward-looking, comprehensive database including patients who have undergone surgical treatment for lung cancer. It involves 12 institutions across five Brazilian states that have provided data related to patients treated between December of 2009 and December of 2022. Our sample comprised 1,031 lung cancer patients who underwent anatomic lung resection during that timeframe, representing 46.25% of all anatomic lung resections cataloged in the Registry. We excluded patients for whom any values pertaining to pivotal variables were missing.

The definitions of variables were derived from the ESTS standardization document.[9] The goal is to use both risk models as instruments of internal auditing and for quality control in the local context.

Statistical analysis

To test the parsimonious EuroLung1 and EuroLung2 scores, we used the published coefficients for both scores[8] to assess the calibration and discrimination.[9,12,13] The logit of the EuroLung1 model was as follows:

$$-2.852 + 0.021 \times age + 0.472 \times male - 0.015 \times ppoFEV1 + 0.662 \times thoracotomy + 0.324 \times extended\ resection$$

The logit of the EuroLung2 model was as follows:

$$-6.350 + 0.047 \times age + 0.889 \times male - 0.055 \times BMI - 0.010 \times ppoFEV1 + 0.892 \times thoracotomy + 0.983 \times pneumonectomy$$

In our assessment, we employed calibration plots, the Brier score, and the Hosmer-Lemeshow test. The calibration plot displays the relationship between observed frequencies and predicted probabilities.[8,10,11] The Brier score quantifies the overall disparity between the predicted probability of an event (such as winning) and the actual occurrence of that event.[8,10,11] The Hosmer-Lemeshow test divides the study cohort into deciles based on predicted values, comparing the observed rates with the expected rates.[8,10,11] Model discrimination was characterized by the ROC AUC.[8,10,11]

In order to investigate the linear association between the levels of the score for the variable "risk class" and patient mortality (aggregate EuroLung2 model), the Mantel-Haenszel chi-square test (MH χ^2) was applied to the data.

Continuous variables are expressed as median and interquartile range, whereas categorical covariates were described as absolute counts and percentages. The 95% confidence intervals are also presented.

Analyses for model development and validation were performed using the R package, version 3.3.3 (R Core Team, 2017) and Stata software, version 15.0 (Stata Corp., College Station, TX, USA). Values of $p < 0.05$ were considered statistically significant.

RESULTS

Among 1,210 patients who underwent lung resection and were characterized in our database, critical data were missing for 179, and the remaining 1,031 patients were included in further analyses. The characteristics of the included patients are shown in Table 1. Major

cardiopulmonary complications occurred in 196 patients (19.0%), and 46 patients (3.8%) died in the hospital or within the first 30 days after the procedure. The observed morbidity rate was higher than that predicted by the EuroLung1 model (19.0% vs. 13.1%). As for mortality, the observed rate was higher than that predicted by the EuroLung2 model (3.8% vs 1.5%). The observed and predicted outcomes in the validation dataset from the EuroLung1 and EuroLung2 models are shown in Tables 2 and 3, respectively.

For the EuroLung1 model, the calibration plot shows some overlap, indicating a lack of perfect calibration. The slope of 1.11 suggests that the model is slightly overestimating probabilities (Figure 1). The Brier score of 0.15 indicates moderate calibration performance, and the p-value of 0.015 from the Hosmer-Lemeshow test suggests that the model is not well calibrated. In addition, the AUC for the EuroLung1 model was 0.678 (95% CI: 0.636-0.721), indicating weak discrimination performance (Figure 2).

For the EuroLung2 model, the calibration plot shows less overlap, indicating better calibration (i.e., improved alignment between predicted probabilities and observed outcomes) than that of the EuroLung1 model. The slope of 1.22 further supports that finding, suggesting a closer fit between predicted and observed probabilities (Figure 2). The Brier score of 0.03 indicates good calibration performance, although the Hosmer-Lemeshow test suggested that the model is not well calibrated, given the p-value of 0.044. The EuroLung2 model had acceptable discrimination, as demonstrated by an AUC of 0.756 (95% CI: 0.670-0.842).

Patients were grouped into five risk classes showing incremental risk of mortality, as can be seen in Table 4. There is a statistically significant linear association ($p < 0.001$; MH $\chi^2 = 6.530$, therefore, $p < 0.05$) between the levels of the score of the aggregate EuroLung2 model and the percentage of mortality of patients. The patients in the lowest risk class had a 3.4% mortality rate, whereas those in the highest risk class had a 28.2% mortality rate. It is noteworthy that the 9.5-12.0 score category was removed from this analysis because it comprised only five cases, which is not sufficient for a reliable prognosis of death.

DISCUSSION

The external validation assessment of the parsimonious EuroLung1 and EuroLung2 models

Table 1. Characteristics of the Brazilian Lung Cancer Registry and European Society of Thoracic Surgeons databases.[a]

Variable	Database	
	BLCR (N = 1,031)	ESTS (N = 82,383)
Male gender	471 (45.7)	53,780 (65.0)
Age (years)	65.8 (58.5-65.8)	64.6 (57.6-71.2)
BMI (kg/m^2)	26.1 (23.1-29.4)	25.1 (22.4-28.3)
Chronic artery disease	77 (7.5)	6,725 (8.2)
Cerebrovascular disease	41 (4.0)	2,434 (3.0)
Chronic kidney disease	30 (2.9)	4,579 (5.6)
Complications	196 (19.0)	12,955 (15.7)
Thoracotomy	383 (37.1)	61,252 (74.0)
ppoFEV$_1$ (% of predicted)	66.3 (54.5-77.4)	73.0 (59.0-87.0)
Extended resection	55 (5.3)	4,722 (5.7)
Death within 30 days[b]	46 (3.8)	1,851 (2.2)

BLCR: Brazilian Lung Cancer Registry; ESTS: European Society of Thoracic Surgeons; and ppoFEV$_1$: postoperative FEV$_1$. [a]Results are expressed as median and IQR for numeric variables and as count and percentage of the total for categorical variables. [b]Counted from the date of anatomic lung resection.

Table 2. Observed and predicted outcomes from the parsimonious EuroLung1 model in the validation cohort (N = 1,031).

Decile	Probability	Events		No events	
		Observed (n)	Predicted (n)	Observed (n)	Predicted (n)
1st	5.84	6	4.7	97	98.30
2nd	7.29	13	6.7	90	96.30
3rd	8.54	12	8.1	91	94.90
4th	9.8	11	9.4	92	93.60
5th	11.47	15	10.8	88	92.20
6th	13.33	22	12.8	81	90.20
7th	15.35	21	14.7	82	88.30
8th	18.24	18	17.3	85	85.70
9th	23.64	33	21.3	70	81.70
10th	40.06	45	29.4	59	74.60

Table 3. Observed and predicted outcomes from the parsimonious EuroLung2 model in the validation cohort (N = 1,029).

Decile	Probability	Events		No events	
		Observed (n)	Predicted (n)	Observed (n)	Predicted (n)
1st	0.28	0	0.2	103	102.80
2nd	0.4	1	0.4	100	102.60
3rd	0.52	0	0.5	101	102.50
4th	0.69	1	0.6	98	102.40
5th	0.93	3	0.8	93	101.20
6th	1.18	1	1.1	99	101.90
7th	1.6	4	1.4	98	101.60
8th	2.21	3	1.9	97	101.10
9th	3.44	8	2.8	91	100.20
10th	14.06	16	5.7	76	97.30

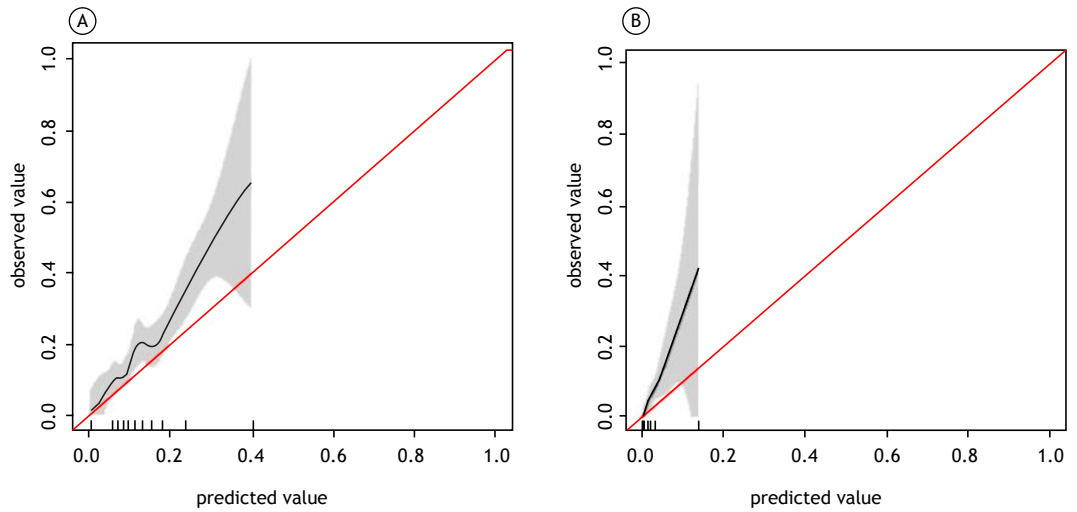

Figure 1. Calibration plot for the EuroLung1 and EuroLung2 models (A and B, respectively). The calibration curves highlighted in gray represent the 95% CIs. EuroLung1 model applied to data from 1,031 patients; EuroLung2 model applied to data from 1,029 patients.

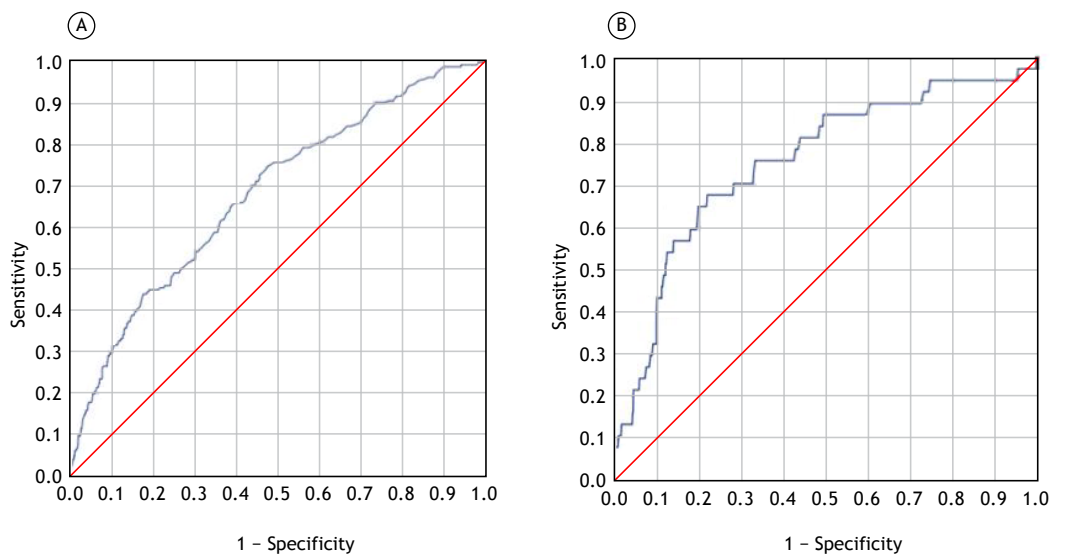

Figure 2. Discrimination. ROC curves for the EuroLung1 and EuroLung2 model analyses (A and B, respectively). AUC for the EuroLung1 model analysis = 0.678 (95% CI: 0.636-0.721). AUC for the EuroLung2 model analysis = 0.756 (95% CI: 0.670-0.842). EuroLung1 model applied to data from 1,031 patients; EuroLung2 model applied to data from 1,029 patients.

Table 4. Analysis of linear association between the variables risk class and mortality from the aggregate EuroLung2 model in the sample as a whole (N = 1,205).

Risk class (score category)	Patients (n)	Deaths (n)	Mortality rate (%)	95% CI
0-2.5	589	20	3.40	(3.13-3.66)
3.0-5.0	407	26	6.39	(5.81-6.97)
5.5-6.5	123	18	14.63	(12.43-16.84)
7.0-7.5	47	9	19.15	(21.85-34.56)
8.0-9.0	39	11	28.21	(5.98-34.02)

Note: $p < 0.001$ (Mantel-Haenszel chi-square = 6.530) between risk class and mortality.

reveals miscalibration in both. In addition, performance assessments of Brazilian health care facilities using risk-adjustment models like EuroLung1 and EuroLung2 indicate a higher observed mortality and morbidity rate in the Brazilian Lung Cancer Registry than those predicted by the EuroLung risk models. The miscalibration observed in both models indicates the limitations of directly applying them to the Brazilian population without appropriate adjustments, and it emphasizes the need for recalibration or development of locally tailored models to enhance accuracy and improve clinical decision-making. These findings also suggest limitations in the direct application of the EuroLung models to the Brazilian population without suitable modifications, which could potentially highlight the underperformance of health care facilities in Brazil.

The EuroLung risk models represent recent advancements in population-based tools for predicting cardiopulmonary morbidity and mortality following anatomic lung resection, necessitating external validation across diverse populations for generalizability.[2,3] However, such validation is often hindered by population-specific discrepancies.[8] In the Brazilian cohort, the EuroLung2 model demonstrated acceptable discrimination, as evidenced by a higher AUC value. However, discrepancies in both models probably stem from the exclusion of critical variables in the ESTS model, which are vital in the Brazilian context, such as racial and social factors, along with caseload variations. This observation is consistent with the findings of a study conducted in Japan,[6] highlighting the predictive limitations of the EuroLung models for morbidity and mortality due to notable baseline differences with the European demographic.[6] Such omissions might significantly impact the observed underperformance of Brazilian health care facilities. Nonetheless, the discrepancy between the observed and predicted morbidity rates can be attributed to patient-specific factors, which encompass pre-existing comorbidities, socioeconomic conditions, and the disease stage at the time of diagnosis.[9,12-14] In Brazil, a middle-income country, the absence of adequate education regarding disease prevention often results in patients presenting to the health care system with advanced, symptomatic disease,[15] in contrast to their counterparts in high-income countries. Notably, Knorst et al.[16] reported a historical cohort study in which the time from the onset of initial symptoms to the diagnosis of lung cancer in a university hospital in the southern region of Brazil exceeded 20 weeks, whereas the Standing Medical Advisory Committee recommendation is that the interval between symptom onset and treatment should be no longer than 6-8 weeks.

The discrepancy in mortality may be linked to systemic factors, including access to health care services for prevention, timely diagnosis, and treatment.[17] In Brazil, over 75% of patients depend exclusively on the Brazilian Unified Health Care System. Despite its goal of providing universal care, the system faces significant challenges related to accessibility, diagnostic delays, treatment availability, and substantial disparities among cancer care facilities concerning diagnostic and treatment technologies.[18,19] For example, Lista et al.[20] discovered that almost 80% of the initial treatments for lung cancer in Brazil did not take the diagnosis into consideration; only 6.8% of patients received a lung cancer diagnosis within 30 days after experiencing symptoms. Another study conducted among the Brazilian population revealed that 10-18% of lung cancer patients, regardless of their disease stage, did not undergo any cancer treatment due to their poor clinical condition,[21] rendering them unable to withstand the risks associated with treatment.

Lung cancer remains a pressing public health concern in Brazil, and as a response to this challenge, the country has implemented a series of public policies aimed at improving surgical treatment outcomes. Over the past decade, Brazil has made significant strides in this area, with initiatives focused on expanding access to early detection, enhancing surgical techniques, and ensuring equitable care for all patients. In addition, strong public health measures in Brazil have led to notable reductions in tobacco consumption in Brazil, setting a valuable precedent for other low- and middle-income countries. National research in Brazil has revealed a nearly 50% reduction in smoking prevalence, aligning with a corresponding decrease in tobacco-related fatalities.[22] These policies, coupled with efforts to reduce health care disparities, have the potential to revolutionize lung cancer surgery in Brazil, ultimately leading to better patient outcomes and a brighter future in the fight against this devastating disease.

Another reason for the underperformance of Brazilian health care facilities may be related to surgical skills. Therefore, we will examine the data in a more

granular manner to gain a deeper understanding of the quality of surgical care at the facilities that could be associated with these outcomes. Subsequently, we will investigate design actions aimed at enhancing improvement factors. Overall, these findings highlight the complex interplay between patient-specific and systemic factors that influence the calibration and performance of risk models in a diverse health care landscape such as that of Brazil. Further research and tailored interventions are essential to bridge these disparities and improve the quality of lung cancer care in the country.

The present study relied on data from the Brazilian Lung Cancer Registry, a prospective multicenter database. The main limitation of the study is the size of the sample, which was small in comparison with the original population from which the models were generated. In addition, the study may simply be underpowered to assess the calibration and discrimination of the risk models. The fact that 46% of the cases were excluded from analysis in both arms because key values were missing raises concerns about the validity of our findings. This significant data gap suggests a potential bias, given that less than half of the facilities contributed meaningful data, limiting the comprehensiveness and reliability of the analysis. Furthermore, the Brazilian Lung Cancer Registry includes 12 institutions in five Brazilian states and does not represent the entire country. However, it is important to note that it stands as the only database related to the surgical treatment of lung cancer in Brazil. Therefore, the findings should be interpreted within the context of the studied population. Moreover, our database initially included mostly patients from the public health care sector, only later including those from the private sector. In the present study, no analyses were carried out separating patients by sector.

The disparities between the EuroLung model predictions and Brazilian patient outcomes highlight the need for model adjustments and signal potential underperformance within the health care system in Brazil, underscoring the importance of investigating contributing factors. The EuroLung2 model showed promising performance in terms of discrimination in the Brazilian cohort, indicating its potential utility. Considering additional variables and exploring machine learning analytics may further enhance the performance of surgical risk prediction models.

MEETING PRESENTATION

This abstract was presented as a poster at the 31st Annual Conference of the ESTS, in Milano, Italy.

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AUTHOR CONTRIBUTIONS

PDD: conceptualization; data curation; formal analysis; methodology; and writing. RMT: conceptualization; methodology; supervision; and writing – review & editing. AB: writing – original draft; and writing – review & editing. LLL: conceptualization; data curation; formal analysis; methodology; and writing. CAC: writing – original draft; and writing – review & editing. JSF: original draft; and writing – review & editing. JLG: original draft; and writing – review & editing. FEGC: original draft; and writing – review & editing. FSM: writing – original draft; and writing – review & editing. PMP-F: conceptualization; methodology; supervision; and writing – review & editing.

CONFLICTS OF INTEREST

None declared.

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Drug-induced lung disease: a narrative review

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ABSTRACT

Drug-induced lung disease (DILD) encompasses a broad, highly heterogeneous group of conditions that may occur as a result of exposure to numerous agents, such as antineoplastic drugs, conventional or biological disease-modifying antirheumatic drugs, antiarrhythmics, and antibiotics. Between 3% and 5% of prevalent cases of interstitial lung diseases are reported as DILDs. The pathogenesis of lung injury in DILD is variable, multifactorial, and often unknown. Acute presentation is the most common, can occur from days to months after the start of treatment, and ranges from asymptomatic to acute respiratory failure. The CT patterns are varied and include ground-glass opacities, organizing pneumonia, and diffuse alveolar damage. Notably, there are no clinical manifestations or CT patterns specific to DILD, which makes the diagnosis quite challenging and necessitates a high index of suspicion, as well as the exclusion of alternative causes such as infection, cardiac-related pulmonary edema, exacerbation of a preexisting ILD, and neoplastic lung involvement. Discontinuation of the offending medication constitutes the cornerstone of treatment, and corticosteroid treatment is usually necessary after the onset of clinical manifestations. The prognosis varies widely, with high mortality rates in severe cases. A history of medications related to pulmonary toxicity in patients with new-onset respiratory symptoms should prompt consideration of DILD as a potential underlying cause.

Keywords: Lung diseases, interstitial/chemically induced; Lung diseases, interstitial/diagnostic imaging; Immunotherapy/adverse effects.

Drug-induced lung disease (DILD) constitutes a significant, heterogeneous group of adverse drug reactions that occur after exposure to various medications. To date, more than 500 drugs have been associated with the emergence of DILD, a number that rises every year, particularly with the increasing use of antineoplastic drugs, immune checkpoint inhibitors (ICIs), antiarrhythmics, antibiotics, and disease-modifying antirheumatic drugs (DMARDs).[1,2]

Making a diagnosis of DILD can be challenging if there are preexisting lung conditions such as those induced by radiotherapy, as well as COPD, inflammatory lung disease, and interstitial lung disease (ILD). The clinical and radiological manifestations of DILD are nonspecific, often exhibit an association with the initiation of treatment of a given drug, typically emerging within the first three months of treatment, and may range from mild to severe and life-threatening.[2,3] The present article aims to comprehensively review the spectrum of drug-induced diseases of the lung parenchyma, as well as presenting updated approaches to their diagnosis and management.

EPIDEMIOLOGY

Estimating the incidence of DILD is challenging, because it can vary depending on the population demographics and the treatments available within regional healthcare systems. In studies of patients with non-small cell lung cancer (NSCLC), the overall incidence of DILD across all grades ranges from 1.4% to 5.8%.[3,4] Among patients with autoimmune diseases, especially rheumatoid arthritis (RA), the prevalence of DILD is 0.3-11.0% in those treated with methotrexate and 0.5-3.0% in those treated with anti-TNF agents.[5] Severe (grade 5) pneumonitis occurs in 2-9% of patients, with higher incidences in individuals who have preexisting lung conditions and are using more than one drug simultaneously, often resulting in mortality rates as high as 36%,[2,6] as shown in Chart 1.

In recent cohorts of ILD patients, between 3% and 5% of prevalent cases are reported as drug-induced, translating to an annual incidence of DILD ranging from 4.1 to 12.4 cases per million population. This incidence may be underestimated given the challenges in diagnostic confirmation as well as the emergence of new drugs and treatment combinations.[2]

PATHOGENESIS

The mechanisms of lung injury in DILD are variable and usually multifactorial, depending on the particular drug involved. Key mechanisms include cytotoxic effects on

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alveolar capillary endothelial cells, immune-mediated lung injury, pulmonary drug deposition, oxidative stress, and immune system dysregulation. Unfortunately, the precise pathogenesis is unknown for many drugs.[2]

Although DILD generally affects the lung parenchyma, it can also involve the airways, giving rise to a variety of clinical and histological patterns, including hypersensitivity reaction, pulmonary fibrosis, bronchospasm, pneumonitis, and noncardiogenic pulmonary edema.[7] The interaction between individual factors, such as genetics and previous or current exposures, may predispose individuals to pulmonary toxicity. In Japanese patients, for instance, the presence of HLA-DRB1*04:05 and HLA-B*15:01 alleles has been linked to pulmonary toxicity.[2,8] In contrast, the presence of the HLA-A*3101 allele has been associated with drug-induced hypersensitivity reactions in individuals of European descent.[9]

RISK FACTORS

The likelihood of pulmonary adverse events is influenced by factors such as the agents/dosages administered, exposure duration, and intrinsic (patient) risk factors.[10] Therefore, although the development of DILD is often unpredictable, some individual factors are associated with a higher risk of pulmonary toxicity (Chart 2). For instance, cumulative dose, renal dysfunction, advanced age, and stage IV disease at presentation confer an increased risk of pulmonary toxicity in patients treated with bleomycin.[11] Similarly, genetic factors, preexisting ILD, male sex, smoking, and poor performance status are more associated with adverse events in patients treated with EGFR tyrosine kinase inhibitors (TKIs) or chemotherapeutic agents.[12,13]

CLINICAL, FUNCTIONAL, AND RADIOLOGICAL MANIFESTATIONS

Symptoms of DILD are nonspecific and can manifest within days or years after exposure to the offending drug(s). Acute pneumonitis typically results in shortness of breath, cough, fever, and peripheral eosinophilia, with some patients evolving to acute respiratory failure.

In cases of subacute or chronic disease, particularly those with prolonged exposure, signs of pulmonary fibrosis are common and the main symptoms are worsening dyspnea and reduced exercise capacity. Physical examination may reveal fine or "velcro-like" crackles, whereas digital clubbing is uncommon. In advanced fibrotic disease, there can be signs of pulmonary hypertension (PH) and right ventricular dysfunction.[2,5] In the majority of DILD cases, pulmonary function tests reveal a pattern of restrictive abnormality, although an obstructive pattern may also be seen.[14]

Radiological patterns reflect the generally inflammatory nature of DILD. The most common disease patterns include diffuse alveolar damage (DAD), organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), eosinophilic pneumonia, and sarcoid-like reaction.[2] Details regarding the manifestations of the main drugs that may determine DILD are provided below (Chart 3).

BIOLOGIC AGENTS

In clinical practice, the utilization of biologic agents for the treatment of autoimmune diseases has expanded significantly in recent years. That has resulted in an increase in the occurrence of pulmonary toxicity. Anti-TNF agents have been mostly associated with DILD or exacerbation of a preexisting ILD, as well

Chart 1. Grades of pneumonitis severity.

Grade	Description
1 (mild)	Asymptomatic, radiographic findings only
2 (moderate)	Symptomatic, not interfering with activities of daily living
3 (severe)	Severe symptoms, involving > 50% of lung, and requiring hospitalization
4 (life-threatening)	Life-threatening respiratory involvement, ventilator support required
5 (fatal)	Fatal outcome attributed to drug-induced pulmonary toxicity

Adapted from Delaunay et al.[6]

Chart 2. Main risk factors for drug-induced lung disease.

Advanced age (> 40 years of age)
Renal dysfunction (GFR < 80 mL/min)
Dose-dependent toxicity
Genetic predisposition (familial pulmonary fibrosis, Japanese descent)
Previous radiotherapy
Preexisting ILD
Exposure to high FiO_2
Concurrent administration of pneumotoxic drugs
Poor performance status or advanced lung cancer
Smoking
COPD

Chart 3. Main patterns of pulmonary toxicity and the potential treatments involved.

Acute or subacute ILD	TNF-α antagonists, ICIs, conjugated antibodies, chemotherapy, TKIs, amiodarone, nitrofurantoin, mTOR inhibitors, rituximab, abatacept, methotrexate, leflunomide, azathioprine
Organizing pneumonia	Amiodarone, antineoplastics (including ICIs), TNF-α antagonists, rituximab, sulfasalazine, mTOR inhibitors, minocycline, anticonvulsants, radiation therapy
Pulmonary fibrosis	Chemotherapy (bleomycin, cyclophosphamide, carmustine, busulfan, gemcitabine, amiodarone, nitrofurantoin, and methotrexate)
Eosinophilic pneumonia	Antibiotics (minocycline and nitrofurantoin), anticonvulsant, amiodarone, antidepressants, aspirin, chloroquine, mesalazine, nitrofurantoin, tryptophan, dupilumab, imatinib
Sarcoid-like reaction	BCG therapy, TNF-α antagonists, interferon, breast implant, HAART, pirfenidone, ustekinumab, ICIs, vemurafenib
Noncardiogenic pulmonary edema	Nitrofurantoin, TMP-SMX, all-trans-retinoic acid, aspirin, chemotherapy, cocaine, heroin, hydrochlorothiazide, i.v. epoprostenol, opioids
Pleuroparenchymal fibroelastosis	Cyclophosphamide, alkylating agents (including carmustine), daptomycin, statins
Hypersensitivity pneumonitis	Methotrexate, isocyanates, cannabis, irinotecan
Airway disease	ICIs (durvalumab, pembrolizumab), rituximab, cocaine, vaping, chlorine gas, penicillamine
Alveolar proteinosis	Chemotherapy, cyclosporine, mTOR inhibitors, imatinib, leflunomide

ICIs: immune checkpoint inhibitors; TKIs: tyrosine kinase inhibitors; mTOR: mechanistic target of rapamycin; BCG: bacillus Calmette-Guérin; HAART: highly active antiretroviral therapy; TMP-SMX: trimethoprim-sulfamethoxazole; and i.v.: intravenous. Adapted from Spagnolo et al.[2]

as being frequently associated with infectious and noninfectious granulomatous lung disease, DAD, and, less often, pulmonary fibrosis and OP.[15,16] In addition, other diseases, such as lupus, vasculitis, autoimmune hepatitis, sarcoidosis, uveitis, and demyelinating neurologic diseases, may be triggered by biologic agents.[17] Positivity for antinuclear antibodies (ANA) may also occur during or after the use of such drugs, with the majority of patients remaining asymptomatic.[18]

Infliximab

Infliximab, a chimeric monoclonal antibody, inhibits TNF-α and has been approved for the treatment of inflammatory bowel diseases, psoriasis, psoriatic arthritis, ankylosing spondylitis, RA, and severe sarcoidosis.[19] The incidence of anti-TNF-induced ILD ranges from 0.5% to 3.0%, and pulmonary radiological features attributed to the use of infliximab include aseptic granulomatous pulmonary nodules, interstitial lung infiltrates, eosinophilic pneumonia, and acute respiratory distress syndrome (ARDS).[1,20,21]

Adalimumab

Adalimumab-induced ILD is rarely described. Predictors of a poor prognosis for such complications include age > 65 years, late onset of symptoms, concomitant use of other immunosuppressants, especially methotrexate, and a previous diagnosis of ILD. The mean time to symptom onset is 26 weeks, and the disease may evolve to acute respiratory failure. In the largest sample of patients using adalimumab, imaging modalities like HRCT revealed ground-glass opacities (GGO, Figure 1A) in 83%, honeycombing in 22%, and reticulonodular, sometimes diffuse, opacities in 38%.[15,17]

Etanercept

Etanercept was the first specific anti-cytokine therapy approved for the treatment of RA. It can also be used to treat psoriatic arthritis and ankylosing spondylitis. Among patients with RA, sarcoidosis-like disease is more common in those receiving etanercept. On CT, the features are similar to the typical findings of sarcoidosis, including perilymphatic micronodules and lymphadenopathy.[22] In addition, in etanercept-treated patients with RA (Figures 1B and 1C), it has been shown that 11.0-36.3% of such patients develop ANA positivity and 5.0-15.0% develop positivity for anti-double-stranded DNA antibodies.[16-18, 23]

Rituximab

The anti-CD20 antibody rituximab is widely used for the treatment of malignant lymphoma and various autoimmune disorders, including RA. Acute lung injury with bilateral opacities has been reported to occur at any time during treatment, mostly in patients with neoplastic/hematologic disorders, and may be fatal. Although the mechanism of rituximab-induced lung damage is unknown, it has been suggested that it is related to lysis of neoplastic cells and release of cytokines.[2,24] Most cases of rituximab-induced ILD occur on average 3 months after the first infusion but may occur within the first 24 h after the first injection. Organizing pneumonia and alveolar hemorrhage, as shown in Figure 1D, have also been described.[2]

Abatacept

Abatacept is a biologic DMARD characterized by a fusion protein comprising CTLA-4. It appears to be an effective treatment for patients with RA-associated ILD and can be used in patients with a history of previous pulmonary infection. Although few cases of pulmonary

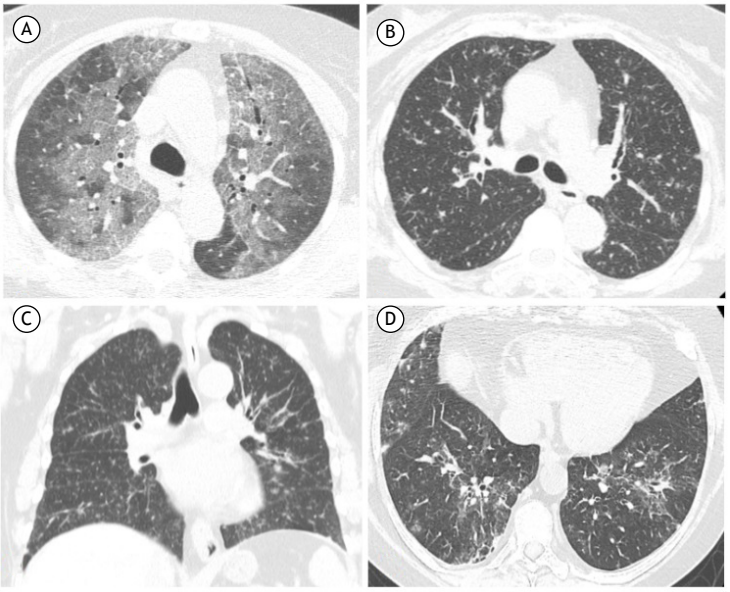

Figure 1. In A, axial CT scan showing pulmonary ground-glass opacities, predominantly in the upper lobes, in a 62-year-old female patient with RA after receiving the second dose of adalimumab. In B and C, CT scans showing diffuse, predominantly perilymphatic, micronodules in a patient with RA and sarcoid-like reaction associated with the use of etanercept. In D, axial reconstruction of a CT scan showing ground-glass opacities and organizing pneumonia patterns in the lower lobes of a patient with systemic lupus erythematosus after rituximab use.

toxicity have been attributed to abatacept compared with other therapeutic agents, such cases have shown a rapid progression to respiratory failure.[25]

Tocilizumab

Tocilizumab is an anti-IL-6 receptor antibody indicated for the treatment of patients with RA, systemic or polyarticular juvenile idiopathic arthritis, or giant cell arteritis. It has also been shown to have the effect of slowing the FVC decline in patients with ILD associated with systemic sclerosis.[26] Pulmonary toxicity is uncommon, with the primary complications being the occurrence of pneumonia and opportunistic infections. However, pneumonitis, OP, and sarcoid-like reactions have been described.[27,28]

ANTINEOPLASTIC THERAPY

Pulmonary toxicity has been reported to occur in 10-20% of all patients treated with antineoplastic drugs, typically within weeks or a few months after treatment initiation. Identifying specific causative agents is challenging, especially due to the combination of drugs and radiotherapy, which increases the risk of pulmonary toxicity in patients with lung cancer. Radiological abnormalities include patchy or diffuse GGO, consolidation, centrilobular nodules, interlobular septal thickening, and reticular changes. The prognosis is uncertain and typically worse in patients who have a high burden of previous lung disease.[2]

Platinum analogues

Platinum-based chemotherapy is frequently used in the treatment of various cancers, such as colorectal, lung, and genitourinary cancer. Various cases of oxaliplatin-induced interstitial pneumonia have been reported over the past few decades.[29] Shimura et al.[30] reported that smoking, pulmonary metastasis, and the presence of a preexisting lung disease were linked to a higher risk of developing platinum-induced pulmonary toxicity. Lung lesions typically develop after 5 or 6 cycles of treatment, often presenting as interstitial pneumonia and GGO. The use of carboplatin and cisplatin can also lead to ARDS and eosinophilic pneumonia.[1]

Taxanes

Taxanes, which include paclitaxel and docetaxel, are a class of mitotic inhibitors. The combination of platinum and taxane therapy is widely employed in the treatment of lung cancer.[31] Retrospective studies have reported an overall incidence of pulmonary toxicity as high as 4.6% in NSCLC patients receiving docetaxel therapy, with the median onset of symptoms being 18 days after the last administration.[32] In patients with preexisting pulmonary fibrosis treated with a taxane (Figure 2A), the reported rate of grade 3 or higher pneumonitis is 27%.[33]

Antifolates

Pemetrexed is a multitargeted antifolate used in the treatment of malignant pleural mesothelioma and NSCLC. In Japanese cohorts, pemetrexed toxicity was reported to occur in approximately 3.6-4.0% of cases, with the main patterns being GGO and acute interstitial pneumonia. Methotrexate, a similar antifolate, is known to induce steroid-responsive ILD in rheumatic

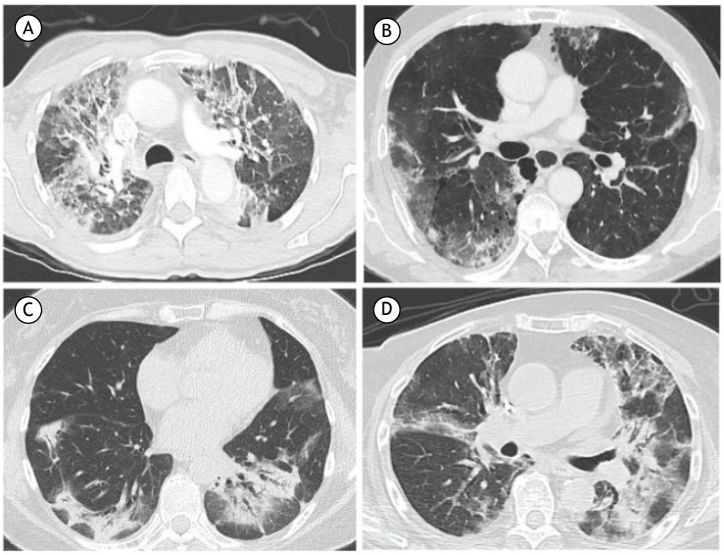

Figure 2. In A, axial CT scan showing pulmonary ground-glass opacities and organizing pneumonia, predominantly in the upper lobes, in a female patient with squamous non-small cell lung cancer using docetaxel. In B, CT showing ground-glass opacities overlapping with areas of emphysema, particularly in the right lower lobe, in an elderly patient with lung cancer using pembrolizumab. In C, CT scan showing bilateral areas of consolidation in the lower lobes, consistent with organizing pneumonia, in a 62-year-old female patient with melanoma under treatment with nivolumab plus ipilimumab. In D, axial CT scan shows ground-glass opacities and consolidations suggestive of organizing pneumonia in middle and upper lobes in a patient with breast cancer treated with trastuzumab-deruxtecan.

patients (see below), and similar occurrences have been reported in cases of pemetrexed toxicity.[34]

EGFR-TKIs

Pneumonitis is noted as a feature of class-effect toxicity of EGFR-TKIs, including gefitinib, erlotinib, afatinib, cetuximab, and osimertinib. The overall incidence of all-grade DILD in patients treated with an EGFR-TKI reportedly ranges from 0% to 5.3%, with a low risk of recurrence in patients retreated after the initial exposure.[12,35] Risk factors include a significant smoking history, advanced age, preexisting ILD, poor performance status, recent NSCLC diagnosis, and involvement of > 50% of lung areas.[12] The HRCT patterns are similar to those seen with cytotoxic agents, which most commonly manifest as diffuse GGO, OP, or a fibrotic pattern.[1,2]

Anaplastic lymphoma kinase-TKIs

The incidence of pulmonary toxicity in patients with advanced NSCLC using the anaplastic lymphoma kinase-TKIs crizotinib and alectinib is estimated to be approximately 1.8% and 2.6%, respectively. In Japanese patients, the incidence may be higher (up to 5.77%), especially in smokers and the elderly, and symptoms begin approximately 4-8 weeks after treatment initiation. The most commonly reported patterns are OP and DAD.[36]

Antineoplastic antibiotics

Bleomycin is a polypeptide antineoplastic antibiotic that is commonly used in the treatment of lymphoma and germ-cell tumors. Bleomycin-induced pulmonary toxicity has been recognized since the early clinical trials in the 1960s, and it is one of the drugs with the greatest potential for pulmonary toxicity. Such toxicity is predominantly fibrotic and appears to be immune-mediated by macrophages and lymphocytes secreting TNF, together with hypersensitivity reactions, the production of reactive oxygen radicals, and cellular toxicity. Major risk factors for bleomycin-induced pulmonary toxicity include age > 40 years, chronic kidney disease, cumulative dose > 300,000 IU, and stage IV disease at presentation. Several distinct pulmonary syndromes are associated with bleomycin use, including OP, eosinophilic pneumonia, and, most commonly, a diffuse GGO pattern related to DAD,[11,37,38] as depicted in Figure 4D.

Doxorubicin is an anthracycline antibiotic used in the treatment of solid tumors such as breast cancer, as well as leukemia and lymphoma. Treatment with doxorubicin is limited by its cardiac toxicity, dose dependent congestive heart failure, and cardiomyopathy. Rare cases of pneumonitis and progression to fibrotic ILD have been described.[39]

Antineoplastic drugs

Capecitabine is an oral prodrug of 5-fluorouracil. The clinical efficacy of capecitabine has been demonstrated in the treatment of gastric, colorectal, and breast cancer. Only a few adverse pulmonary events have attributed to the drug, most commonly a sarcoid-like reaction, mediastinal/hilar lymphadenopathy, and airway involvement.[40]

Irinotecan is a chemotherapeutic agent that is widely used for the treatment of colorectal, gastric,

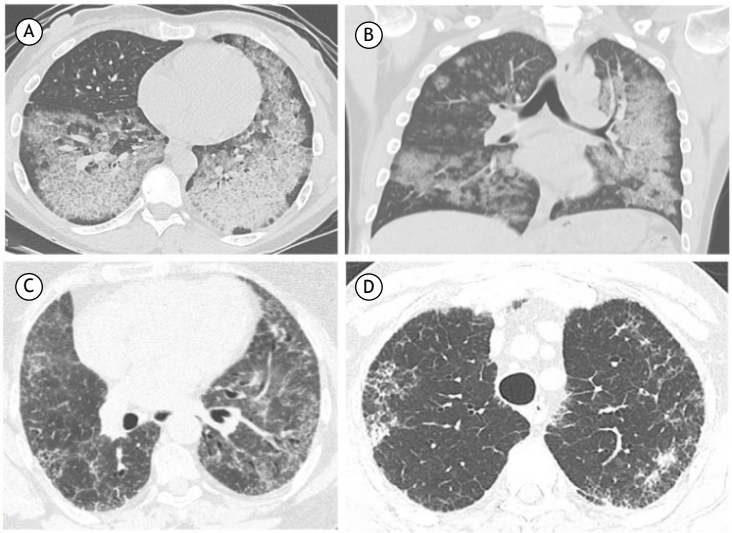

Figure 3. In A and B, chest CT showing ground-glass opacities and thickened interlobular septa, consistent with pulmonary alveolar proteinosis, in a patient using everolimus after kidney transplantation. In C, CT scan showing pulmonary ground-glass opacities, predominantly in the lower lobes, with traction bronchiolectasis in a 65-year-old female patient with RA after receiving methotrexate. In D, axial CT scan showing reticulated infiltrate and bilateral consolidations, predominantly in the upper lobes, in a male patient who received nitrofurantoin.

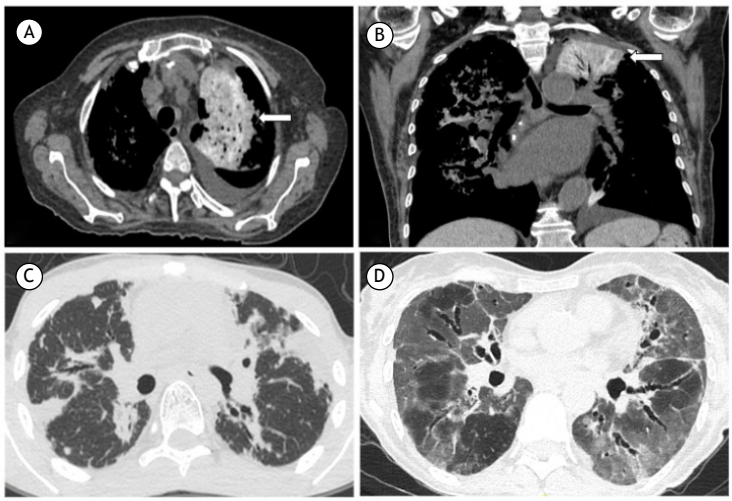

Figure 4. In A and B, axial and coronal CT scans, respectively, showing hyperattenuating lung parenchyma in the upper lobes (arrows) in a 77-year-old female patient with heart failure using amiodarone. In C, CT scan showing bilateral pleural thickening, predominantly in the upper lobes, in a male patient with lymphoma who underwent treatment with cyclophosphamide and developed pleuroparenchymal fibroelastosis. In D, CT scan showing diffuse pulmonary ground-glass opacities in a male patient after use of bleomycin for lymphoma treatment.

lung, and breast cancer. The incidence of DILD after irinotecan use is low (approximately 1%). The most common patterns are DAD, OP, and hypersensitivity pneumonitis.[41]

Fludarabine is a nucleoside analog that is widely used in the treatment of low-grade lymphoproliferative malignancies including chronic lymphocytic leukemia and low-grade non-Hodgkin lymphoma. In such cases, the incidence of pulmonary toxicity is approximately 8.6%. Acute interstitial pneumonia, OP, eosinophilic pneumonia, and pulmonary nodules are the most common abnormalities described.[42,43]

Chlorambucil is an alkylating agent also used for the treatment of indolent lymphoproliferative disorders such as chronic lymphocytic leukemia. Pulmonary toxicity has been reported as a dose-independent adverse effect occurring during or after treatment with chlorambucil. Events may range from acute interstitial pneumonitis, OP, and bronchiolar disorders to signs of pulmonary fibrosis after prolonged exposure.[44]

Proteasome inhibitors

Bortezomib is a proteasome inhibitor, currently used as the primary treatment for multiple myeloma

(MM) and lymphoma worldwide. Severe pulmonary complications have been reported, the most common findings being acute pneumonitis, OP, and ARDS. The incidence rate is approximately 4.5%, with a mortality of 0.5%, mostly in the Japanese population.[1,45]

Immunomodulators

The immunomodulatory drugs thalidomide and lenalidomide are also indicated for the treatment of MM. Lenalidomide is a less toxic, more powerful immunomodulator than is thalidomide and is typically used in combination with dexamethasone in refractory cases. The mechanism of lung injury remains unclear; acute pneumonitis, OP, and eosinophilic pneumonia are the most common lesions described.[1,46]

Alkylating agents

Busulfan is an alkylating agent that was initially used in the treatment of chronic myelogenous leukemia but is currently used exclusively as a component of different conditioning regimens preceding allogeneic hematopoietic stem cell transplantation. Pulmonary toxicity is estimated to occur in up to 8% of patients using busulfan. Risk factors for DILD after busulfan use include a cumulative dose of more than 500 mg, concomitant administration of additional drugs associated with pulmonary toxicity, and lung irradiation. The most common patterns of pulmonary toxicity are DAD and OP, although pulmonary alveolar proteinosis may also occur.[1,47]

Carmustine is a nitrosourea that is widely used to treat malignant brain tumors, Hodgkin/non-Hodgkin lymphoma, and MM. Pulmonary toxicity can present as DAD, ARDS, radiation recall pneumonitis with acute symptoms, and pleuroparenchymal fibroelastosis (PPFE).[48]

Pyrimidine analogues

Gemcitabine is a pyrimidine analog that is widely used to treat solid tumors such as breast, colon, ovarian, and pancreatic cancer, as well as NSCLC. The frequency of gemcitabine-related pulmonary toxicity is estimated to range from 2.7% to 24.0%, with few severe cases. The most common patterns are NSIP, hypersensitivity pneumonitis-like lesions, alveolar hemorrhage and radiation recall pneumonitis. The combination of gemcitabine and carboplatin also induces a significant decrease in diffusion capacity.[49,50] However, the mechanisms of pulmonary toxicity remain unclear.

IMMUNOTHERAPY

Immunotherapy revolutionized the treatment of cancer with the development of ICIs, which have a broad range of indications, including lung cancer, melanoma, bladder cancer, and head and neck tumors.[2] However, ICIs can also induce specific hyperactivation of the immune response, leading to systemic tissue damage. Immune-related adverse events, such as rash, colitis, hepatitis, myocarditis, endocrine disorders, and pneumonitis, are commonly reported. The incidence of pneumonitis varies from 3% to 6%, including 1-2% of grade 3-4 adverse events.[2,51] Immunotherapies may initially provoke an increase in tumor size or the development of new lesions as pseudoprogression. Immunotherapy-mediated pseudoprogression is defined as a ≥ 25% increase in tumor burden that is not seen on repeated imaging performed ≥ 4 weeks after the initial study.[52]

PD-1 inhibitors

Pembrolizumab is an antibody against programmed cell death 1 (PD-1) that increases anti-tumor T-cell responses by blocking the interaction between PD-1 on T cells and its ligand (PD-L1) on cancer cells. The main risk factors for pembrolizumab-induced pulmonary toxicity include age > 70 years, prior thoracic radiation, previous lung disease (COPD, asthma, or ILD), combination therapy (chemotherapeutic drugs or ICI followed by osimertinib), smoking status, and histological type of NSCLC (squamous NSCLC).[53] The most common patterns are diffuse GGO and OP, followed by fibrotic NSIP and centrilobular ground-glass nodule patterns (Figure 2B).[37]

Nivolumab, another antibody that targets PD-1, is currently used for the treatment of patients with malignant melanoma, NSCLC, renal cell carcinoma, Hodgkin lymphoma, and head and neck cancer. The onset of pulmonary toxicity varies from within a few days to more than a year after initiation, with a median of 3 months after use of the drug.[2] Studies have shown that the prevalence of pneumonitis caused by nivolumab (Figure 2C) is low (2.9%), although it increases significantly (to 11.8%) when nivolumab is combined with another ICI.[54] Up to 10% of patients with advanced NSCLC have a preexisting ILD, and nivolumab seems to be safe in this population.[55]

PD-L1 inhibitors

Atezolizumab is a humanized IgG1 monoclonal antibody against PD-L1, used in tumors such as NSCLC, melanoma, and urothelial bladder cancer. The incidence of atezolizumab-induced interstitial pneumonitis is less than 1%, with grades 3 and 4 accounting for 1.1-2.6% of cases, considered to be one of the lowest pneumonitis rates among ICIs. The most common CT changes suggestive of toxicity are the NSIP pattern and sarcoid reaction/lymphadenopathy.[56]

Durvalumab is a selective, human IgG1 monoclonal antibody that also blocks PD-L1. This drug is clinically active in urothelial carcinoma, hepatocellular carcinoma, head and neck squamous cell carcinoma, gastroesophageal cancer, and lung cancer.[57] The overall incidence of DILD secondary to durvalumab is less than 5% but reaches 38% when the drug is combined with osimertinib, showing subclinical pulmonary infiltrates with diffuse GGO, bronchospasm, and bronchiectasis.[1,51]

CTLA-4 inhibitors

Ipilimumab, a monoclonal antibody that blocks CTLA-4, is widely used in the treatment of melanoma, usually in combination with nivolumab (Figure 2C). The reported incidence of DILD is higher (10%) in cases of combined anti-PD1/PDL1 and anti-CTLA 4 treatment.[2] Airway disease can occur, and COPD exacerbations following CTLA-4-based therapies have been reported, although such occurrences appear to be rare complications of ipilimumab use. Intrathoracic lymphadenopathy and a pattern suggestive of sarcoidosis are seen in 5-7% of patients treated with the combination of ipilimumab and nivolumab.[56]

Conjugated antibodies

Trastuzumab-deruxtecan (T-DXd) is a novel antibody drug conjugate that consists of the anti-ERBB2 (HER2) monoclonal antibody trastuzumab and the topoisomerase I inhibitor deruxtecan. It is most commonly used in advanced breast cancer but also in the treatment of gastric and lung cancer. The most significant result of T-DXd-related toxicity is ILD, the incidence of which varies depending on the location of the tumor. A variety of radiological findings can be observed, such as OP, NSIP, hypersensitivity pneumonitis-like patterns, and ARDS. Up to 25% of patients with lung cancer treated with T-DXd develop pneumonitis. Because of the high toxicity rates, if the patient develops symptomatic ILD/pneumonitis (grade ≥ 2; Figure 2D), T-DXd treatment must be permanently discontinued, and corticosteroid treatment should be promptly initiated.[1,58]

MISCELLANEOUS

Antiarrhythmics, antimicrobials, and immunosuppressants can also result in DILD, as described below. The pathogenesis is variable in these scenarios, including pulmonary drug deposition, hypersensitivity reactions, immune dysregulation, and endothelial injury.

Mechanistic target of rapamycin inhibitors

The mechanistic target of rapamycin inhibitors sirolimus and everolimus are potent immunosuppressive drugs used after organ transplantation and for the treatment of lymphangioleiomyomatosis. Estimates of the incidence of pneumonitis vary between 5% and 15%.[59] These inhibitors are significant inducers of DILD, which manifests mainly as lymphocytic interstitial pneumonia, OP, or alveolar hemorrhage (Figures 3A and 3B).[2] In patients with lymphangioleiomyomatosis, sirolimus therapy has been proven to be safe, and although pneumonitis has also been reported, it seems to be reversible and not to have an impact on long-term tolerability.[60]

Methotrexate

Methotrexate is commonly used in RA, other rheumatic diseases, psoriasis, and some malignancies.[2] Methotrexate-induced lung disease is the archetype of drug-induced pulmonary toxicity in patients with RA, usually occurring early in the course of therapy. Historically, methotrexate has been associated with RA-ILD; however, although it can induce subacute pneumonitis, a potentially lethal condition, its use does not seem to be associated with an increased risk of chronic fibrosing ILD; in fact, it might even be protective.[61]

The most common CT and histological findings of methotrexate-induced lung disease are similar to those of hypersensitivity pneumonitis. Other patterns include OP and DAD.[22] The incidence of methotrexate-induced lung disease (Figure 3C) is estimated to be less than 1%.[62]

Leflunomide

Leflunomide is a DMARD used in the treatment of RA that can lead to ILD exacerbation, accelerated formation of pulmonary rheumatoid nodules, and diffuse alveolar hemorrhage.[22] Most patients present DILD within three months after starting leflunomide, with acute symptoms for a week or less. Bilateral GGO and DAD are the most common radiological and histopathological findings, respectively. Patients with preexisting ILD are particularly vulnerable to this complication, and leflunomide should therefore be used with caution in this population.[63]

Amiodarone

Amiodarone is an antiarrhythmic widely used for supraventricular and ventricular arrhythmias, with a reported incidence of DILD of 1.2-8.8%[37] and a mortality rate of 3-37%.[2,62] A high cumulative dose is an important risk factor for amiodarone-related DILD. The combination of high doses (> 400 mg/day) and long-term use is more strongly associated with DILD than are dose or duration alone. The HRCT features include diffuse GGO, thickened interlobular septa, OP, ARDS, eosinophilic pneumonia, and diffuse alveolar hemorrhage. Lung nodules and masses may be seen, particularly in cases of subacute progression.[37,64]

In patients receiving amiodarone, hyperattenuating lung parenchyma is commonly seen in areas of atelectasis on chest CT. This likely represents tissue deposition of iodine, analogous to what may be seen in the liver and thyroid,[37] as depicted in Figures 4 A and 4B.

Nitrofurantoin

Nitrofurantoin (a 5-nitrofuran derivative) is commonly used for the treatment and prophylaxis of urinary tract infections. In registry studies, DILD accounts for 16-48% of the nitrofurantoin-related adverse events reported.[64] Nitrofurantoin-induced pulmonary toxicity occurs almost exclusively in women, mainly middle-aged or elderly women, because of their increased susceptibility to recurrent urinary tract infections and more frequent use of the drug. Acute presentations are more frequent, occurring within the first weeks of

treatment, and may induce autoimmunity with ANA or antineutrophil cytoplasmic antibody positivity.[2]

Radiologically, nitrofurantoin-induced acute pulmonary toxicity manifests as diffuse GGO and consolidation with or without reticular changes, and traction bronchiectasis in patients with chronic disease. Histopathological findings may vary; acute disease is characterized by mild (and often eosinophilic) interstitial inflammation, whereas diffuse interstitial pneumonia with an NSIP pattern is predominant in chronic reactions,[2] as illustrated in Figure 3D.

Cyclophosphamide

Cyclophosphamide is an alkylating agent that is widely used in the treatment of autoimmune diseases and in hematological malignancies as part of a chemotherapy regimen.[65] One potential late complication of treatment with alkylating agents is PPFE, which is characterized by fibrosis involving the pleura and subpleural lung parenchyma, predominantly in the upper lobes. The onset of PPFE after the administration of these treatments presents wide variability among the reported cases, ranging from 6 months to 16 years.[66] Early onset pneumonitis and late onset pneumonitis with fibrosis (Figure 4C) have also been described as potential impacts of toxicity associated with the use of cyclophosphamide.[67]

Bacillus Calmette-Guérin therapy

The intravesical or intrapelvic administration of bacillus Calmette-Guérin (BCG) is effective against urothelial cancer. Pneumonitis is a rare complication of this form of immunotherapy, seen in less than 0.7% of patients following the repeated administration of BCG. Micronodules with a miliary pattern, bilateral pulmonary opacities, and a reticulonodular pattern have been described. A hypersensitivity reaction rather than a disseminated BCG infection is suspected to be the pathogenesis of this disorder. Epithelioid noncaseating granulomas of the lung have been identified in several cases.[68]

Sulfasalazine

Sulfasalazine is used worldwide for the treatment of ulcerative colitis and RA. The CT findings of DILD secondary to sulfasalazine use include GGO and consolidations with air bronchograms, consistent with OP, as well as interstitial opacities with pleural thickening in the upper lungs. Hypersensitivity pneumonitis occurs in some cases.[69]

RADIATION RECALL PNEUMONITIS

Radiation recall is an inflammatory reaction within previously treated radiation fields precipitated by chemotherapy (taxanes, anthracyclines, alkylating agents, or pyrimidine analogs) or other medications (tamoxifen, simvastatin, levofloxacin, or isoniazid) and can occur in several different systems.[70] The precise pathophysiological mechanism of radiation recall pneumonitis remains unclear. One hypothesis is that radiotherapy sensitizes immune cells and local vasculature, resulting in greater toxicity in previously irradiated areas than in non-irradiated areas after exposure to certain agents.

The classical radiologic manifestations of radiation recall pneumonitis include GGO, diffuse opacities, and patchy consolidation, which corresponds to the shape and size of the radiotherapy field. Radiation pneumonitis commonly occurs in patients treated with radiotherapy to the lung. Radiation recall pneumonitis may occur in the previously irradiated lungs of patients after the administration of inciting agents.[71] Histological features include interstitial edema, hemorrhage, and a fibrinous exudate in the early stages of the disease with later distortion and fibrosis.[72] However, a lung biopsy is very rarely needed to establish the diagnosis of radiation recall pneumonitis.

DIAGNOSIS

The symptoms of DILD are nonspecific, and clinicians should beware of late respiratory symptoms in patients treated with any drug that may cause pulmonary toxicity. When there is a possibility of DILD, the website *www.pneumotox.com* may be useful to check potential toxicities of the drug involved. Disease onset varies from days to even years and is usually unpredictable. Symptoms of DILD include dyspnea, cough, and fever, evolving to respiratory failure with hypoxemia in some cases.[2] Chest CT has high sensitivity for detecting ILD features and is the imaging modality of choice. However, there is no specific pattern for DILD, given that the various forms of interstitial involvement are commonly seen in other ILDs.[62]

The diagnosis of DILD is therefore based on the exclusion of other causes, including infections, heart failure, lymphangitic carcinomatosis, connective tissue disease (e.g., RA or systemic sclerosis), and inflammatory bowel disease. Bronchoscopy is useful for investigating differential diagnosis, such as infections or malignancies, and BAL may show lymphocytosis, eosinophilia, or alveolar hemorrhage, thus usually precluding the need for lung biopsy.[56] Improvement in symptoms following discontinuation of the offending drug favors the diagnosis of DILD, as does recurrence after reexposure.

TREATMENT

Discontinuation of the culprit drug is the mainstay of treatment. Few studies have evaluated the treatment of DILD, and the current guidelines, which are based on observational reports and clinical experience, have not been standardized or validated in prospective clinical trials.[2,56] Pharmacological treatment of DILD is currently based on systemic steroids, and the dosing varies according to severity and the CT pattern.

Severity grades are well-established guidance in the management of toxicity by ICIs (Chart 1). In grade

1 pneumonitis (asymptomatic with only radiographic changes), close follow-up or treatment with low-dose steroids (0.5-1.0 mg·kg^{-1}) can be employed, with drug maintenance (Figure 5). For grade 2 pneumonitis (symptomatic with CT changes), treatment with steroids at 1-2 mg·kg^{-1} per day seems to be adequate and reexposure to the drug can be considered. For grade 3 or higher pneumonitis (severe symptoms and limiting self-care activities of daily living requiring supplemental oxygen), a higher dose of steroids (2-4 mg·kg^{-}1) is recommended, together with drug withholding. Corticosteroid pulse therapy may also be considered in severe cases. Steroid tapering should be conducted very slowly and carefully over the course of at least 6 weeks, given that relapses of pneumonitis have been reported during the weaning period. Persistent changes on chest CT can be useful to guide steroid tapering over time.[6,56,73]

Although the use of immunosuppressive drugs for DILD, such as infliximab, mycophenolate mofetil, and cyclophosphamide, is not completely established, treatment with such drugs may be considered in severe and refractory cases, or when steroids are needed for long periods.

FINAL CONSIDERATIONS

Pulmonary drug toxicity is an adverse event that is common and relevant. The incidence of such toxicity is rising because of the increasing number of new medications included in the list of drugs that can cause DILD, especially in the treatment of autoimmune diseases and cancer. Given the large number of drugs that potentially cause pulmonary toxicity, various patterns of DILD on CT have been described and the prognosis is highly variable. The diagnosis of DILD requires the exclusion of alternative causes and can be a challenge, especially in patients with preexisting ILDs and using several drugs concomitantly. However, lung biopsy is rarely needed in order to confirm the diagnosis. Discontinuation of the offending drug is essential in the treatment, and corticosteroids are frequently used in acute conditions. The decision on whether to rechallenge a patient with the same drug after a prior episode of drug-induced pulmonary toxicity should be made on a case-by-case basis, preferably in the setting of a multidisciplinary discussion.

AUTHOR CONTRIBUTIONS

GPD contributed to the study design; to the acquisition, analysis, and interpretation of data; and to the writing and critical review of the manuscript. EKUNF contributed to the acquisition, analysis, and interpretation of data; and to the writing and critical review of the manuscript. RAK contributed to the acquisition, analysis, and interpretation of data; and to the writing and critical review of the manuscript. AFA contributed to the study design; to the analysis and interpretation of data; and to the critical review of the manuscript. BGB contributed to the study design; to the analysis and interpretation of data; and to the writing and critical review of the manuscript. All authors approved the final version of the article.

CONFLICTS OF INTEREST

None declared.

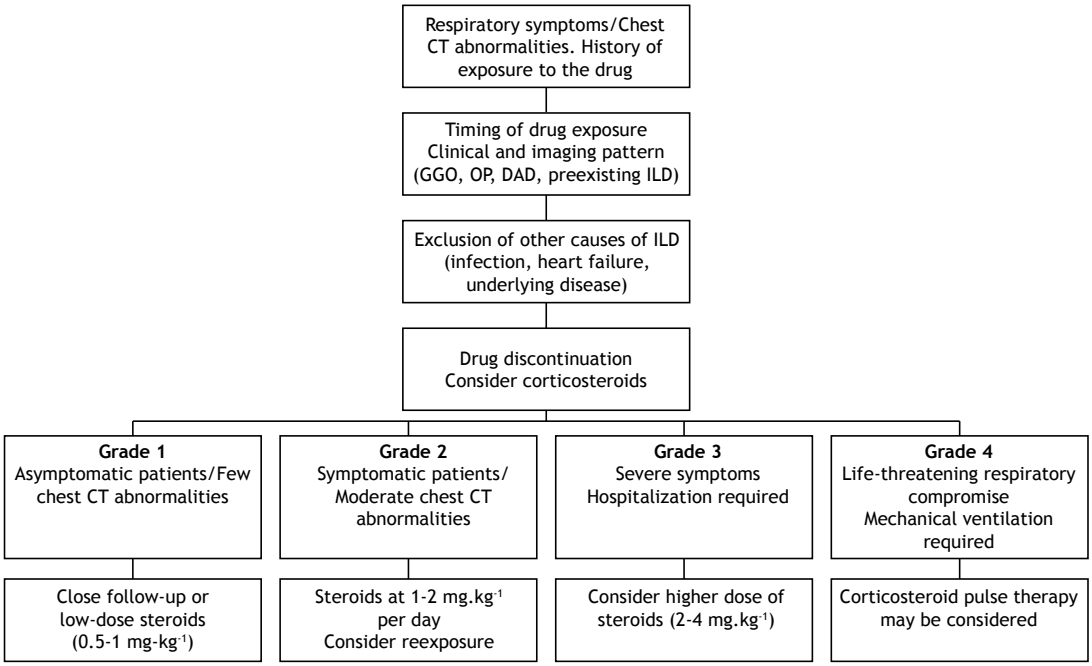

Figure 5. Management of patients with drug-induced lung disease. GGO: ground glass opacities; OP: organizing pneumonia; DAD: diffuse alveolar damage; ILD: interstitial lung disease.

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Thoracic ultrasound: a review of the state-of-the-art

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ABSTRACT

Thoracic ultrasound (TUS) is a tool that has become increasingly essential in the daily practice of thoracic medicine. Driven by the need to assess patients during the COVID-19 pandemic, there has been an increase in the use of point-of-care TUS, which has demonstrated several benefits, either as a complement to clinical decision-making for diagnosis or as a real-time guide for procedures, whether as a predictor or measure of treatment response. Here, we present a review of TUS, based on the most recent scientific evidence, from equipment and techniques to the fundamentals of pulmonary ultrasound, describing normal and pathological findings, as well as focusing on the management of lung disease and guidance for invasive thoracic procedures at the bedside. Finally, we highlight areas of perspective and potential lines of research to maintain interest in this valuable tool, in order to improve the diagnostic process and expand the treatment arsenal.

Keywords: Thorax/diagnostic imaging; Ultrasonography/methods; Point-of-care testing; Lung/diagnostic imaging.

INTRODUCTION

Thoracic ultrasound (TUS) has become increasingly essential in the daily practice of pulmonologists and thoracic surgeons.[1-3] For many years, the use of ultrasound was seen as insufficient for the evaluation of pulmonary diseases, being practically restricted to the ICU and emergency department (ED).[1] Recently, prompted by the need to assess patients during the COVID-19 pandemic, point-of-care TUS has gained ground in clinical practice and has demonstrated several benefits, either as a complement to clinical decision-making for diagnosis or as a real-time guide for procedures, whether as a predictor or measure of treatment response.[1-4]

Faced with the growing demand, we prepared a review of TUS, from equipment and techniques to the fundamentals of pulmonary ultrasound, based on the most recent scientific evidence, describing normal and pathological findings, focusing on patient management with pulmonary pathologies, as well as on guidance for invasive thoracic procedures at the bedside. Finally, we highlight areas of perspective and potential lines of research to maintain interest in this valuable tool in order to improve our diagnostic capability and expand our treatment arsenal.

EQUIPMENT AND TECHNIQUES

Various protocols,[1-5] techniques, and types of equipment have been described and validated for use in TUS, which can be performed with practically any ultrasound system capable of two-dimensional scanning, with conventional brightness (B)-mode, although options such as motion (M)-mode and color flow Doppler can also be utilized.

The ideal probe will depend on the clinical setting and suspected diagnosis.[1-3] A low-frequency (5-2 MHz) curvilinear probe allows visualization of deeper structures and acceptable visualization of the pleural line, ideal for evaluating deeper pathologies, such as pleural effusion (PE) and diseases of the lung parenchyma.[3] High-frequency (14-6 MHz) linear probes generate highly detailed images of superficial structures, which include the intercostal musculature, rib margins, and pleural anatomy.[3]

The patient can be examined in the supine position or in a sitting position (from the back), and the probe can be positioned in the longitudinal or transverse (intercostal) orientation, although it should be nearly perpendicular to the skin surface or pleural line.[1-3]

NORMAL FINDINGS ON TUS

Because of the principles of ultrasound propagation in aerated structures, TUS relies mainly on the

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interpretation of artifacts.[1-4] Recognizing the role of artifacts, especially the A-lines and B-lines, in normal and abnormal pathologies is critical to understanding TUS.[4,5]

The A-lines are reverberation artifacts that appear as parallel echogenic lines arranged below the pleural line and repeated at regular intervals, equidistant from the skin to the pleural surface.[4] In turn, the B-lines emanate perpendicularly from the pleural surface, extend to the depth of the image without decreasing in intensity, and move synchronously with lung sliding (Chart 1). Their characteristic feature is that they obscure A-lines and, in isolation, can also be seen in the aerated lung.[4]

Normal TUS findings include visualization of the intercostal musculature, rib shadows, and the pleural line, together with the presence of A-lines, giving rise to the batwing sign.[1-4] The natural motion of the visceral and parietal pleura results in a phenomenon known as lung sliding, seen in M-mode as the seashore sign (Figure 1). Finally, at the costophrenic recess, the overlap of the aerated lung onto the abdomen creates a demarcated leading edge of the lung air artifact, giving the impression of a lung curtain, known as the curtain sign.

ALVEOLAR-INTERSTITIAL SYNDROME

Alveolar-Interstitial syndrome (AIS) describes several conditions characterized by diffuse interstitial involvement and impaired gas exchange across the alveolar-capillary membrane, potentially leading to respiratory failure.[5,6] Causes can be acute or chronic, including interstitial lung disease, ARDS, and acute pulmonary edema. Pulmonary ultrasound has emerged as a noninvasive tool with the potential to detect AIS at the bedside, with a sensitivity of 85.7% and specificity of 97.7%.[6]

The sonographic diagnosis of AIS is based on the presence and quantification of B-lines (Figure 2), also known as comet tail artifacts.[7] The most widely used definition of AIS is the presence of at least three or more B-lines in the longitudinal plane in two or more anterior or lateral bilateral thoracic regions.[1] While

Chart 1. Thoracic ultrasound profiles.

Syndrome	Ultrasound signs
Aerated lung (normal findings)	Predominant anterior bilateral A-lines (batwing sign), associated with lung sliding (seashore sign), and the curtain sign, at the costophrenic recess.
Interstitial syndrome	Diffuse bilateral anterior B-lines (at least three or more B-lines in 2 or more thoracic regions) associated with lung sliding.
Pleural effusion	Anechoic fluid or homogeneously echogenic fluid between the pleural leaflets, with or without floating debris, septations, or other structures within the effusion.
Pneumothorax	Absent anterior lung sliding (barcode or stratosphere sign), absent anterior B-lines and present lung point.
Pneumonia	Predominant anterior B-lines on one side or in one thoracic region, with predominant anterior A-lines on the other; or presence of alveolar (tissue-like) consolidation

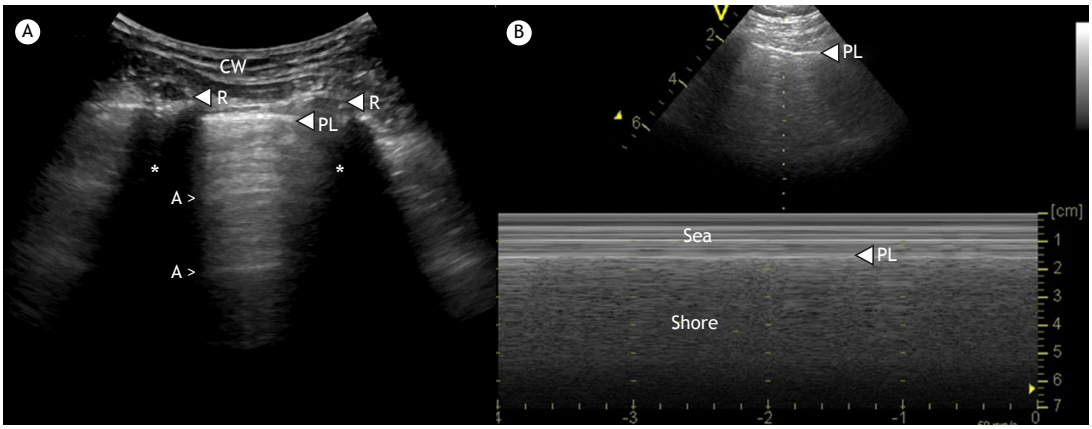


Figure 1. Aerated lung in two-dimensional (2D) mode and corresponding motion (M)-mode image. a) Normal findings: the muscles, fascia, and other soft tissues of the chest wall (CW) are in the upper part of the image. The surfaces of the ribs (R) can be seen as two horizontal hyperechoic, white lines with posterior acoustic shadowing (*). The pleural line (PL) is located just below the ribs. The lung tissue is filled with air and therefore cannot be seen. Consequently, the area that can be seen below the PL is not the lung tissue but artifacts, represented by the A-lines (A). The ribs resemble the wings of a bat, whereas the PL mimics the body of the bat, a pattern known as the batwing sign. b) Normal M-mode findings: the M-mode line can be seen running vertically through the PL at the top of the image. In the corresponding M-mode image, the PL is seen as a hyperechoic line placed at the same distance from the transducer as can be seen in the 2D image. Note the seashore sign, which is so named because, in M-mode, the static structures of the CW can appear as horizontal lines above the PL (representing the sea) and, in the presence of lung sliding, the area below the PL will have a grainy appearance (representing the shore).

three to four B-lines correlate better with interlobular septal thickening, five or more correlate with areas of ground-glass opacity and indicate a more severe interstitial syndrome.[7]

The quantification of B-lines demonstrates a positive linear correlation with extravascular lung water assessed by radiological scores, transpulmonary thermodilution methods, and Wedge pressure by right heart catheterization.[7,8] Loss of aeration can be quantified by using validated scores like the Lung Ultrasound Score, which evaluates six lung regions on each side, assigning a score of 0-3 to each region based on aeration (Chart 2). The global lung ultrasound score is the sum of the regional scores and therefore ranges from 0 to 36.[9]

Pulmonary ultrasound stands out in diagnosing interstitial syndromes within and outside the ICU and ED settings. It is a highly accurate, noninvasive tool for diagnosing acute decompensated heart failure in the ED.[10,11] In cases of interstitial lung disease, it has the potential to serve as a screening tool, demonstrating sensitivity comparable to that of HRCT, especially in patients with systemic sclerosis.[12,13] In addition, for patients with ARDS, the identification of bilateral lung opacities by ultrasound has been incorporated into the new diagnostic criteria.[14] Despite the presumed capability of ultrasound to assess focal and diffuse lung aeration loss and its potential to predict the response to recruitment maneuvers, that capability has yet to be definitively confirmed.[15]

CHEST WALL

The evaluation of the chest wall by TUS includes the analysis of subcutaneous tissue, muscle groups, and ribs. Because those are superficial structures, a high-frequency (14-6 MHz) linear transducer is typically used.

The main indications for the use of this method are for the investigation of localized pain, palpable alterations on physical examination, liquid collections in the chest wall (bruises, postoperative seromas, and abscesses), and solid lesions (nodulations and tumors), as well as for clarifying findings from other imaging modalities. Chest wall TUS can also be used in order to guide punctures and biopsies.[16]

Yet another use is in the evaluation of lytic or blastic bone lesions and rib fractures, in which a loss of linearity of the cortical layer can be observed.[17]

VISCERAL AND PARIETAL PLEURA

Differentiating between the parietal and visceral pleura can be challenging because each leaflet typically measures only approximately 0.2 mm, which may exceed the detection power of ultrasonography. Given that the pleura is a relatively superficial structure, it can be examined by TUS, usually through the intercostal window, visualized as a hyperechoic line below the ribs.

In healthy individuals, in addition to identifying the pleural line, we can also see the leaflets sliding, either in the two-dimensional ultrasound mode (lung sliding) or confirmed by the seashore sign in M-mode. When there is no sliding, the M-mode generates the so-called barcode sign, also known as the stratosphere sign (Figure 3).[18]

SOLID PLEURAL LESIONS

The pleural tissue can be involved in various malignant and benign processes. Diffuse pleural thickening is commonly associated with exudative

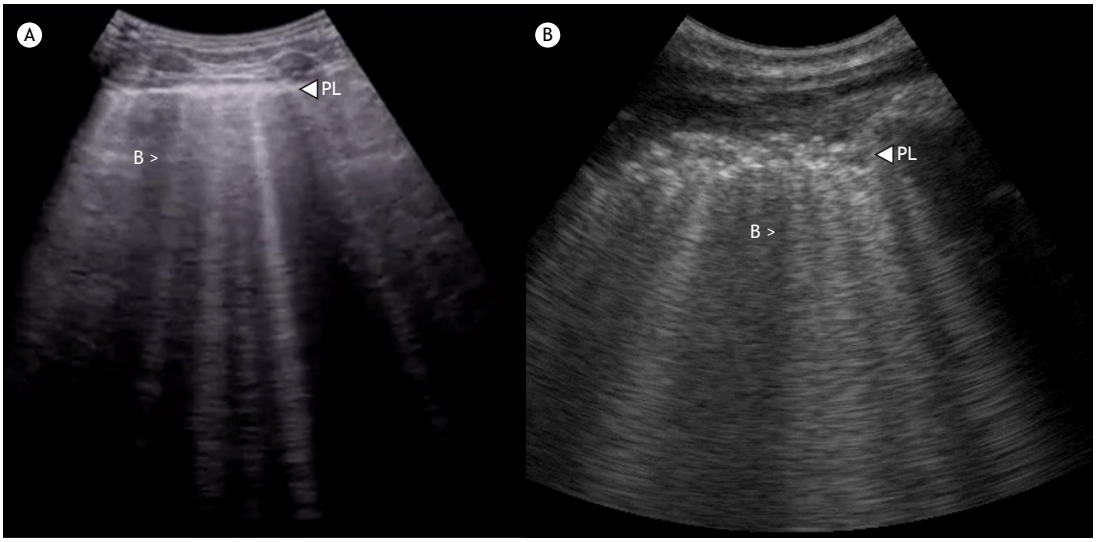
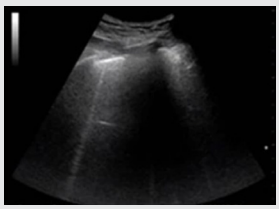
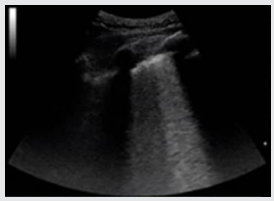
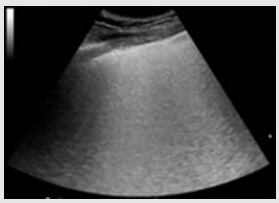
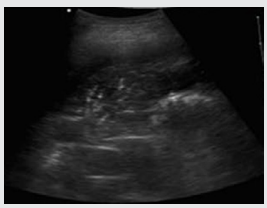


Figure 2. a) Multiple B-lines (B) can be seen as vertical, hyperechoic lines originating from the pleural line (PL) and stretching all the way to the bottom of the two-dimensional brightness (B)-mode image. b) Idiopathic pulmonary fibrosis: thoracic ultrasound image of the lower lobe of a patient diagnosed with idiopathic pulmonary fibrosis. Multiple B-lines are present, and the PL appears severely thickened and fragmented.

Chart 2. Lung ultrasound score.

Ultrasound pattern	Score	Image
Normal aeration: lung sliding with A-lines or fewer than two isolated B-lines	0	
Moderate loss of aeration: multiple, well-defined B-lines	1	
Severe loss of aeration: multiple coalescent B-lines ("White lung")	2	
Complete loss of lung aeration: lung consolidation, presence of a tissue-like pattern	3	

Lung ultrasound score assessment. Six lung zones of interest are examined on each side, delineated by a parasternal line, anterior axillary line, posterior axillary line, and paravertebral line. Each lung region is carefully examined in the longitudinal plane, and each intercostal space present in the region is reviewed in the transverse plane. A semiquantitative score ranging from 0 to 3 is performed according to the lung ultrasound findings in each zone, graded as follows: 0 = normal aeration; 1 = moderate loss of aeration (interstitial syndrome, defined by multiple spaced B-lines, localized pulmonary edema, characterized by coalescent B-lines in less than 50% of the intercostal space examined in the transverse plane, or subpleural consolidations); 2 = severe loss of aeration (alveolar edema, defined by diffuse coalescent B-lines occupying the entire intercostal space); and 3 = complete loss of lung aeration (lung consolidation defined as a tissue pattern, with or without air bronchogram). The global lung ultrasound score is calculated as the sum of the 12 regional scores (ranging from 0 to 36).

PE, hemothorax, or empyema. Focal or circumscribed pleural thickening may correspond to inflammation (pleuritis) or malignant infiltration.[19,20] These findings can help determine the need for a pleural procedure and the most appropriate site for such.

Pleural plaques associated with asbestosis can be identified by their elliptical hypoechoic aspect. Benign tumors (lipomas, fibromas, chondromas, neurinomas, and mixed forms) account for only 5% of neoplastic lesions in the pleura. On ultrasound, these tumors are typically round or oval and encapsulated, with a well-defined outline, and are hypoechoic or moderately echogenic. In general, lung mobility is preserved, and the tumors might be vascularized, which can be confirmed in Doppler mode.[19]

However, malignant pleural tumors (metastases, lung tumor with extension, and malignant mesothelioma) are more common. Signs of malignancy include irregular thickening or nodularity of the pleura, with a heterogeneous ultrasound pattern, associated with PE and infiltration of adjacent structures. In malignant mesothelioma, pleural thickening usually exceeds 10 mm and can be focal or diffuse. Pleural metastases typically have a hypoechoic, homogeneous appearance with an oval or irregular outline. In lung tumors with transpleural extension, pleural sliding tends to be compromised, with invasion of the chest wall and the ribs occasionally being observed, which represents a reliable sign of lung injury from direct tumor extension.[20]

PLEURAL EFFUSION

Given the current evidence, TUS may be considered the imaging method of choice for the initial assessment of PE, being employed to assess pleural fluid volume and character, as an auxiliary method in the search for the etiology, and as a method for guiding thoracentesis or chest drainage.[21]

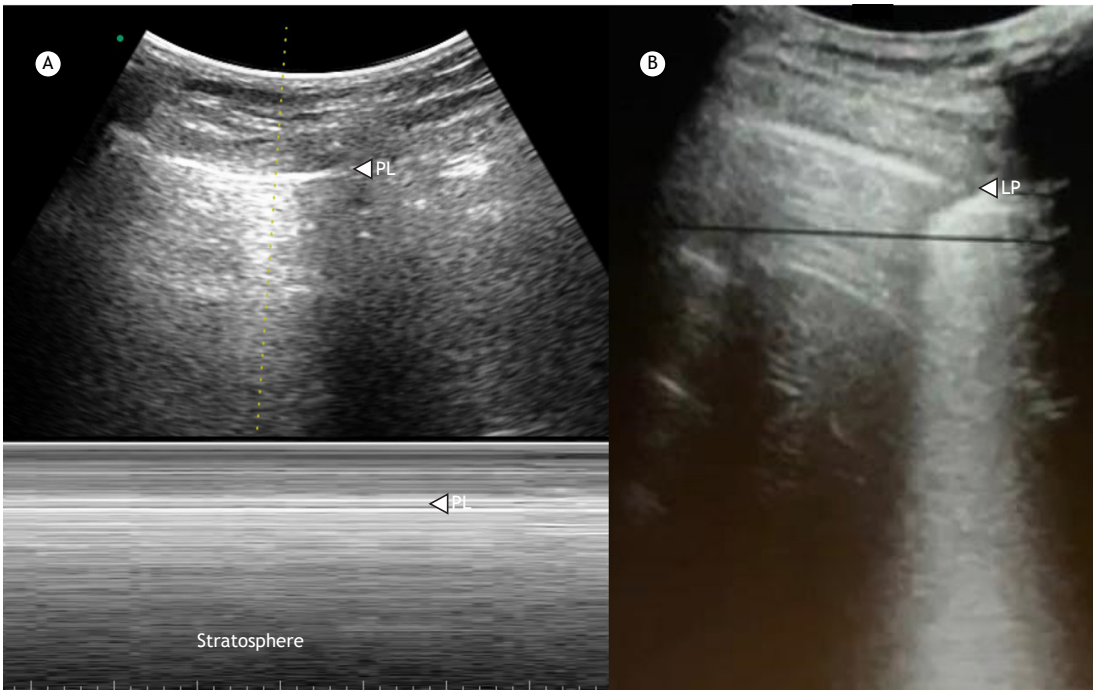


Figure 3. Pneumothorax. a) Motion (M)-mode findings in pneumothorax: if lung sliding and the lung pulse are absent, there will be no change in the area below the pleural line in the two-dimensional (2D)/brightness (B)-mode image. In M-mode, horizontal lines will be seen above and below the pleural line (PL), and the seashore sign can no longer be identified. The M-mode pattern has been described as resembling a barcode or a stratosphere and is therefore known as the barcode sign or stratosphere sign, which can be seen when a pneumothorax is present, as well as in conditions in which lung sliding and the lung pulse are absent (e.g., pleural adhesions). b) 2D-mode showing the lung point (LP). The LP is an ultrasonographic sign that is used in order to locate the junction between the pneumothorax and the area with no air between the visceral and parietal pleural and refers to a pattern of repeated transitions between no lung sliding or B-lines (pneumothorax) into a demonstrable area of lung sliding.

With TUS, we can identify much smaller fluid volumes (even as small as 20 mL) than with other modalities, particularly chest X-ray, and avoid many of the negative aspects of CT, because TUS can be performed in real time at the bedside, with very high spatial resolution.[2,22] Although an accurate quantitative assessment of pleural fluid volume may be possible with TUS, the qualitative assessment is adequate for most clinical decision-making by categorizing the fluid volume as minimal, small, moderate, or large.

The addition of color Doppler may improve the assessment and the differentiation between fluid and pleural thickening. Solid pleural and peripheral lung lesions are generally hypoechoic and show no flow on color Doppler ultrasound, whereas pleural fluid may generate a colored flow pattern during respiratory or cardiac cycles, known as the fluid color sign.[22]

According to its appearance on ultrasound (Figure 4), PE can be classified into four categories[19]:

- Simple PE—anechoic effusion, with no echo between the pleural leaflets; represents free fluid without the presence of septations or other structures within the fluid
- Complex nonseptated PE—anechoic fluid with multiple hyperechoic punctuate foci (swirling echoes) representing floating debris within the effusion, also known as the plankton sign; denotes greater liquid density, by the presence of cells, fibrin, or proteins, but without septa
- Complex septated PE—anechoic fluid with the presence of several septa, forming pockets (loculations) between the pleural leaflets
- Homogeneously echogenic PE—a homogeneous area with a hypoechoic structure; denotes a high-density liquid, such as pus or blood

This classification can help differentiate between exudates and transudates. Transudative PE, as a rule, will appear as a simple PE, although it is not a specific finding. Conversely, exudative PE will almost always appear as echogenicity or complexity. Although there is a strong correlation between the swirling echoes sign and exudative processes, that is also not a specific sign.

Other pleural changes that suggest exudates include pleural thickening and the presence of nodules (or tumors). Alterations in the lung parenchyma consistent with an infectious process (such as consolidation), when accompanied by PE, also suggest exudates.[19,20]

There are sonographic changes that also point to specific causes of PE. The presence of septations, loculations, or homogeneously echogenic fluid, in the clinical suspicion of infection, supports the possibility of complicated parapneumonic effusion or empyema and generally requires pleural drainage. The presence

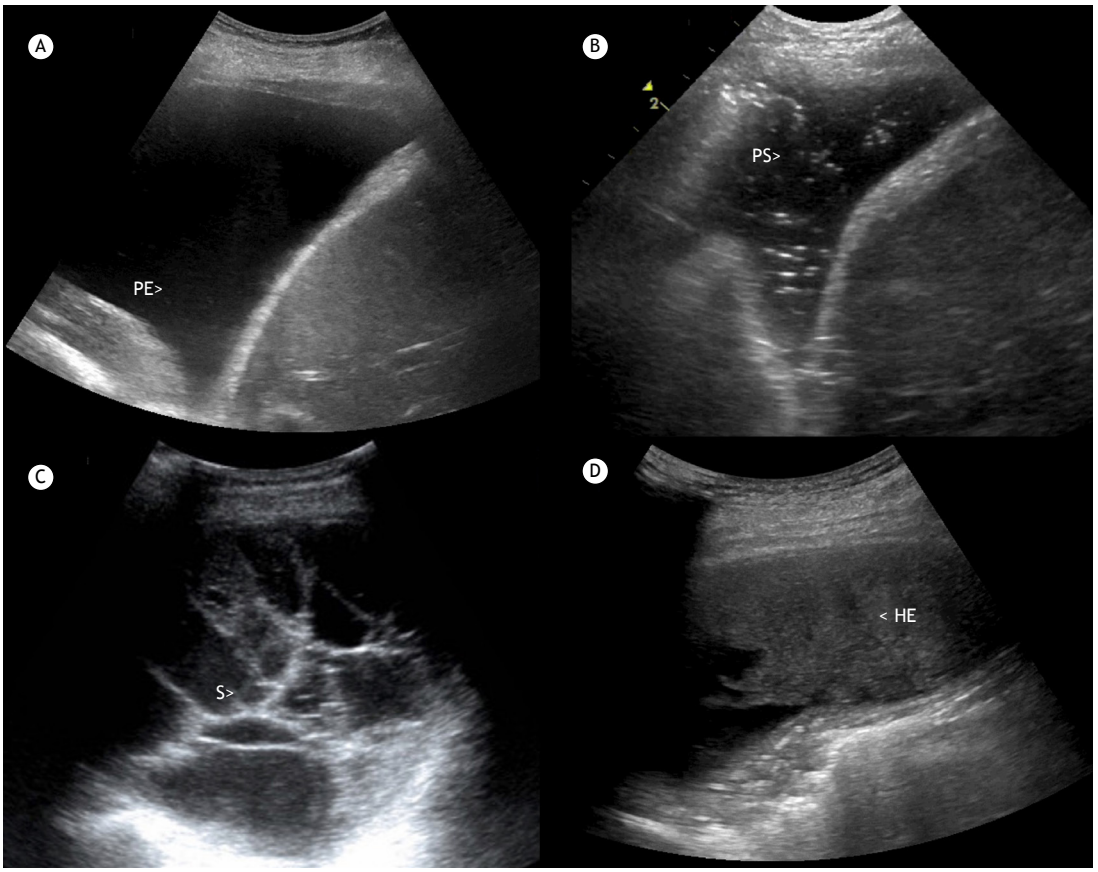


Figure 4. Pleural effusion and its varied presentations. a) Simple pleural effusion: a simple, anechoic, pleural effusion (PE) is present. There are no septations or visible structures floating within the effusion. b) Complex nonseptated PE: anechoic fluid with the presence of multiple hyperechoic punctuate foci representing floating debris within the effusion, also known as the plankton sign (PS). c) Complex septated PE: a complex septated PE is present, containing areas of anechoic fluid as well as several septa (S)/loculations. d) Homogeneously echogenic (HE) fluid: a combination of HE fluid with a stratification effect in the costophrenic recesses (the hematocrit sign) may suggest the presence of hemothorax.

of bubbles in the pleural fluid, described as the suspended microbubble sign, is highly sensitive and specific for empyema.[2,22]

Homogenously echogenic effusions are most often due to hemothorax or empyema. The high cell count of a hemothorax creates a layering effect in the costophrenic recesses, known as the hematocrit sign. In the appropriate clinical context, a combination of the hematocrit sign and the plankton sign is suggestive of hemothorax.[2,22]

When there is pleural or diaphragmatic nodularity and thickening (mainly greater than 10 mm), we should consider the possibility of tumor involvement, which typically presents with the swirling echoes sign. The use of TUS also allows the evaluation of adjacent structures such as the diaphragm, soft tissues, bones, abdominal organs, and mediastinum, which can be helpful in diagnostic clarification.[23]

PNEUMOTHORAX

For evaluating pneumothorax, TUS is useful because it is a noninvasive test that can be performed at the bedside, with good sensitivity and excellent specificity for rapid detection of this pathology.[24] Four important sonographic signs indicate the presence of pneumothorax[25,26]:

- Absence of pleural sliding—The presence of air between the two pleural surfaces leads to the disappearance of pleural sliding. M-mode can be used to confirm the suspicion, on the basis of the characteristic barcode or stratosphere sign (Figure 3). It is noteworthy that pleural sliding may be absent in other conditions, such as pleurodesis, extensive pulmonary fibrosis, and reduced lung compliance.
- Presence of A-lines—These artifacts are present in normally aerated lungs but also in pneumothorax, in which case A-lines are visible but B-lines are not, a finding that has 100% sensitivity for diagnosing pneumothorax. Combining this sign with the absence of lung sliding also has high specificity.
- Absence of the lung pulse—The lung pulse consists of a vertical movement of the pleural line synchronous with the heartbeat (observed in M-mode). In pneumothorax, intrapleural air prevents the transmission of the lung pulse

to the parietal pleura, with the consequent absence of lung sliding and of the lung pulse. In contrast, the presence of the lung pulse rules out pneumothorax.

- Presence of the lung point—The lung point is defined as the transition between the area of normality and that of a pneumothorax. After the absence of pleural sliding and the presence of A-lines have been confirmed, the point where the sliding begins should be identified. That will be the edge of the pneumothorax. The lung point can also be identified in M-mode, in which the barcode sign is followed by the seashore sign. This sign only occurs in pneumothorax, having 100% specificity.

The presence of the lung point can also correlate with the pneumothorax volume. When located medial to the midaxillary line, it indicates 15% pulmonary collapse, suggesting conservative management, whereas when it is lateral to the midaxillary line it represents significant collapse and indicates a need for drainage. However, this quantification strategy has been validated only in trauma patients, and caution should therefore be exercised when extrapolating to other populations.[27]

PNEUMONIA

In the initial assessment and follow-up of patients with a suspected respiratory infection, TUS has increasingly been used as an imaging method, with better sensitivity and accuracy than chest X-ray.[28] One limitation of the use of TUS in this context, however, is that it cannot assess parenchymal changes that are not in the subpleural region. Nevertheless, most infections that affect the lung parenchyma also affect the subpleural region and decrease lung aeration. Therefore, it is possible to identify specific artifacts that correlate with pathological changes caused by pneumonia.[18]

The pattern most often encountered in pneumonia is focal B-lines, which correlate with ground-glass areas and incomplete filling of the alveoli. An asymmetrical pattern typically occurs, with B-lines in each region and A-lines in other regions (including the other hemithorax). With TUS, subpleural consolidation can be identified with excellent sensitivity. Other potential alterations include pleural irregularity and the absence of pleural sliding. In addition, TUS is quite useful for identifying associated PE and possible complications such as empyema and lung abscess.[29]

The recent COVID-19 pandemic has shown the great utility of TUS in patient evaluation, either as an auxiliary method in screening for respiratory symptoms or in the monitoring of hospitalized patients. Several studies have shown that the ultrasonographic alterations observed in the parenchyma and the pleural surface on TUS correlate with those observed on chest CT. In addition, the degree of parenchymal involvement, characterized by decreased lung aeration, seen on TUS has been shown to be associated with symptom worsening and mortality.[30]

The portability of TUS was another great advantage during the pandemic, allowing its use in diverse scenarios. In addition, in intensive care settings, it proved to be an excellent tool for monitoring patients, including those on mechanical ventilation, allowing the assessment of various parameters, such as lung aeration after alveolar recruitment maneuvers.[31]

DIAPHRAGM

Another use for TUS is in the direct evaluation of the mobility and contraction of the diaphragm. During the assessment of diaphragmatic mobility, a low-frequency convex transducer is used and the image is usually obtained through the hepatic window in the right subcostal region. On the left side, the splenic window can be used, although visualization of the diaphragm is usually more complex and measurements tend to be less reproducible.

Mobility is best assessed in M-mode, and measurements can be made in tidal volume, maximal inspiration, maximal expiration, and during the sniff test. The transducer must be positioned between the anterior axillary and midclavicular lines in the cranial-dorsal direction. The measurements are usually more straightforward and more reproducible when the patient is in the supine position.

Mobility of less than 10 mm is considered indicative of severe diaphragmatic dysfunction. Another marker of dysfunction is paradoxical movement of the muscle, usually seen in the sniff maneuver when the diaphragm insinuates into the thoracic cavity during rapid inspiration.[32] Studies evaluating normality values for diaphragmatic mobility have produced discrepant results. In a recent study of 757 healthy individuals, the following results were obtained for diaphragmatic mobility[33]:

- Men during tidal volume: 2.37 ± 0.53 cm
- Men during deep breathing: 5.74 ± 1.26 cm
- Women during tidal volume: 2.22 ± 0.54 cm
- Women during deep breathing: 5.20 ± 1.19 cm

Muscle contraction can be evaluated in the apposition zone, an anatomical region located at the transition between the thorax and abdomen, in which the diaphragm is covered by the pleura (in its portion closest to the thoracic wall) and by the peritoneum (in its portion closest to the abdominal cavity). For this evaluation, a high-frequency linear transducer is used, making it possible to visualize muscle contraction and to determine the thickening fraction, which is calculated with the following formula:

$$Tins - Tex / Tex \times 100$$

where *Tins* is the maximum thickness during inspiration and *Tex* is the maximum thickness during expiration. Muscle contraction is considered adequate when the thickening fraction exceeds 20% (or 30%, according to some authors.[32,33]

Measurements of diaphragmatic mobility and the thickening fraction have both been used in various

settings and inform clinical reasoning in outpatient and intensive care settings. The findings in the evaluation of the diaphragm even correlate with successful weaning from mechanical ventilation. Some data show a correlation between the degree of hyperinflation and diaphragmatic impairment in patients with COPD. Another area that has gained ground is the evaluation of diaphragmatic paresis and paralysis in neuromuscular diseases. In such cases, the TUS findings, in addition to the clinical data, provide predictive information about the progression to respiratory failure.[32,34]

ULTRASOUND-GUIDED PROCEDURES

Endotracheal intubation

Ultrasound is a powerful adjunct in endotracheal intubation and can be used to exclude esophageal intubation and to check tube selectivity. These evaluations can be performed with low- or high-frequency transducers. The latter should provide more detailed images given that both of the sonographic applications discussed target superficial tissues.

Classic methods to detect endotracheal intubation are based on ventilation, with capnography being the gold standard. However, capnography is not available in all EDs and ICUs. In practice, confirmation of a successful procedure is traditionally performed by lung auscultation during ventilation. Thus, if the intubation was inadvertently esophageal, there is a risk of gastric distention and bronchial aspiration during confirmation of the endotracheal tube placement.

When compared with the gold standard (capnography), ultrasound has been shown to display high accuracy in rapidly identifying esophageal intubation, with no risk of insufflation. Two meta-analyses confirmed these findings by showing ultrasound to have a sensitivity of 93-98% and a specificity of 97-98% for that purpose.[35,36]

The physician can use ultrasound in real time or after the intubation (Figure 5). Real-time ultrasound evaluations require two sonographers. One will execute the intubation itself while the other positions the ultrasound probe on the neck of the patient (dynamic evaluation). A rapid ultrasound examination of the trachea during the procedure excludes esophageal intubation in real time.[37] However, the same sonographer can evaluate the position of the tube shortly after the procedure (static evaluation).

While selectivity can be appreciated with lung auscultation, this method has lower diagnostic accuracy. Ultrasound can detect orotracheal tube selectivity by identifying the position of the endotracheal balloon or, more often, by visualizing bilateral lung sliding. A prospective study compared ultrasound and auscultation in terms of their accuracy in excluding tube selectivity. By comparing both methods with the gold standard (fiberoptic bronchoscopy), the study demonstrated that the accuracy of ultrasound and lung auscultation was 95% and 62%, respectively, confirming the superiority of the sonographic evaluation.[38]

Percutaneous tracheostomy

Percutaneous tracheostomy is currently the technique of choice for facilitating mechanical ventilation in critically ill patients. Studies have shown that percutaneous tracheostomy has lower costs and lower complication rates than does conventional tracheostomy.[39]

Although percutaneous tracheostomy is most often performed with the aid of bronchoscopy, ultrasound guidance has been increasingly used. In comparison with the technique guided by anatomical landmarks, ultrasound-guided percutaneous tracheostomy results in a better choice of puncture site, shorter procedure time, fewer punctures, and fewer complications.[40] In comparison with the technique guided by bronchoscopy, the ultrasound-guided procedure has the advantage of evaluating anterior cervical structures, although it is limited by not providing visualization of the posterior wall of the trachea. However, recent studies have shown that both techniques have a similar safety profile.[41,42]

To undergo ultrasound-guided percutaneous tracheostomy, patients should ideally be positioned with cervical hyperextension. The high-frequency linear probe is the best choice for the procedure because it yields detailed images of the superficial structures. The most common techniques to perform percutaneous tracheostomy were described by Ciagla et al.[43] and Griggs et al.[44]

Although some authors have described various preparatory and technical steps associated with increased safety of the procedure,[45] such technical details were beyond the scope of this review. In summary, after identifying a safe site for puncture, the endotracheal tube is pulled, under ultrasound guidance, to a point that allows insertion of the needle into the trachea without accidental puncture of the tube. Tracheal puncture is performed in the midline with ultrasound guidance (Figure 6). The protocol then proceeds to dilation and placement of the tracheal tube, followed by confirmation of adequate ventilation. Ultrasound allows visualization of cervical structures, identification of blood vessels in the path of the puncture, guided traction of the tube, centralization of the tracheal puncture, and identification of immediate complications of the procedure.

Thoracentesis and tube thoracostomy

Ultrasound-guided percutaneous drainage of intrathoracic and pleural collections has several advantages over blind (i.e., unguided) procedures. First, as previously reported, ultrasound can help differentiate between simple and complicated PE, which can facilitate the choice between thoracentesis and tube thoracostomy.

For determining the optimal puncture site in the chest wall, ultrasound enables the sonographer to identify relevant structures, such as the diaphragm, vessels, and nerves, that might be in the drainage

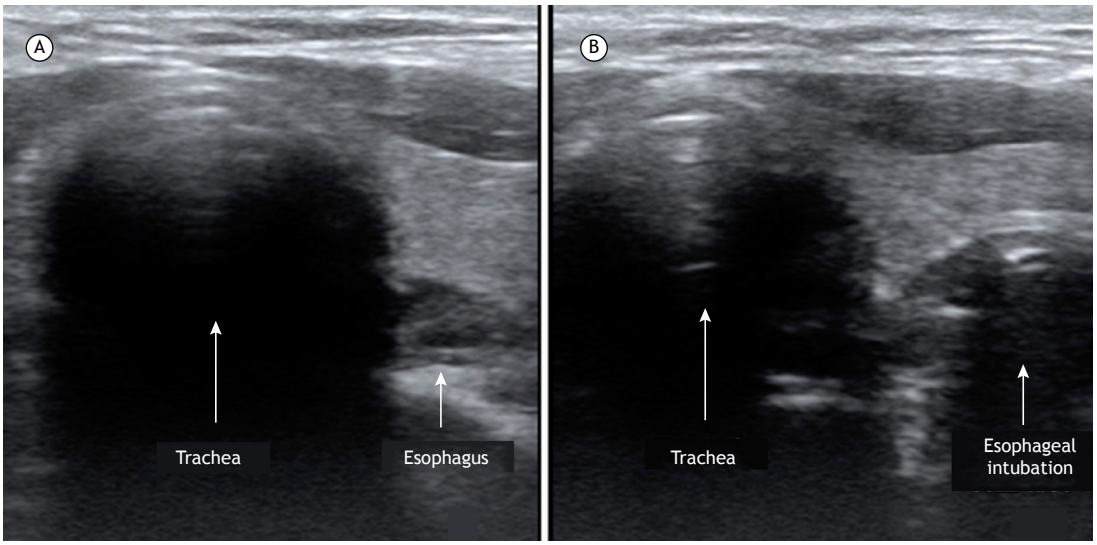


Figure 5. Endotracheal intubation. a) Axial image of the cervical region obtained with a linear transducer identifying the trachea and esophagus. b) The same ultrasound window shows the appearance of the esophagus with an orotracheal tube inside, illustrating esophageal intubation (double tract sign).

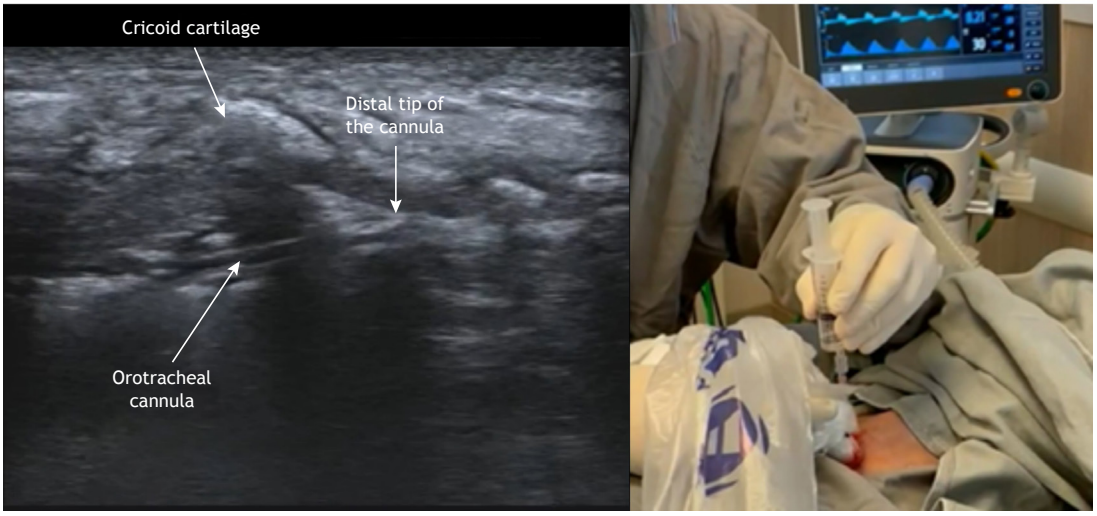


Figure 6. Percutaneous tracheostomy. a) Sagittal view of the trachea showing the orotracheal cannula represented by a double hyperechoic line with acoustic shadowing. The tip of the endotracheal tube is ideally positioned under the first tracheal ring to ensure a clear path for the tracheal puncture while reducing the risk of accidental extubation. b) Repositioning of the endotracheal tube prior to midline perpendicular tracheal puncture is performed under ultrasound guidance, thus reducing the risk of complications. The patient should be placed in the supine position.

tract. It also allows real-time visualization of the collection and the needle tip during its progression, improving the accuracy of the procedure and reducing the risk of complications such as pneumothorax and organ injury.[46,47] In addition, ultrasound guidance can help to optimize drainage by identifying loculations or septations within the collection that may require specific needle positioning or redirection.[48] With TUS, we can also monitor the drainage process by detecting changes in the size and location of the collection in real time, making adjustments to the needle position as needed. This real-time monitoring and adjustment can increase the efficiency of the procedure and minimize the need for repeated attempts or multiple punctures.

Image guidance is particularly useful in cases in which the collection is very small or is in a complex or challenging area, such as near the diaphragm. Guidance with TUS can increase the success rate of percutaneous drainage of such collections, although their localization often requires guidance by other imaging modalities for safety reasons.[49]

Thoracentesis guided by TUS can be performed through site marking or direct needle guidance.[50] In the site marking method, the sonographer identifies the ideal puncture site under TUS guidance and marks it on the skin, then performs the thoracentesis without guidance. In this case, a change in patient position can cause fluid redistribution; therefore,

the procedure should be performed immediately after marking the site. In the direct needle guidance method, the correct needle position is visualized and monitored in real time.

Albeit a common procedure, tube thoracostomy still has a reported complication rate of 14-25%, with complications ranging from those caused by incorrect drain placement to lethal iatrogenic injuries.[51] The routine use of TUS can diminish these risks. Menegozzo et al.[52] described a standardized protocol for ultrasound-guided pleural drainage in which the use of ultrasound is primarily aimed at reducing complications related to drain insertion, identifying a poorly positioned drain (in the subcutaneous tissue) early on and ruling out the presence of a vulnerable neurovascular bundle in the intercostal space. That protocol may be used with trocars (i.e., pigtail catheters) or with blunt dissection.

With TUS, which allows visualization of the diaphragm, some cases of diaphragmatic hernia can be identified, potentially reducing subdiaphragmatic insertions and organ injury during pleural drain insertion. Excluding subcutaneous placement at the end of the procedure allows quicker repositioning, reducing the potential negative implications of a malfunctioning drain, and identifying a vulnerable intercostal artery may reduce the incidence of vascular injuries and their complications.[51,52]

After routine patient preparation, the ultrasound sonographer assesses the regional anatomy to define the drain insertion site. This is done by observing diaphragmatic excursion and the intercostal space, excluding a vulnerable intercostal artery. The intercostal space that does not demonstrate diaphragmatic excursion is preferably used, in order to avoid diaphragmatic injuries. Local anesthesia can then be administered with the aid of ultrasound. The actual drain insertion follows the traditional technique.

If the procedure is a thoracentesis, ultrasound should be used after the fluid drainage to check for residual collections, to verify lung expansion, and to identify complications such as hemothorax or pneumothorax. If the procedure is the placement of a chest tube or an indwelling catheter, ultrasound can be used after drain insertion in order to identify the drain trajectory, excluding subcutaneous positioning (Figure 7). It is essential to highlight the fact that, because of air interposition, the intrapleural trajectory of the drain is seldom visible. However, there have been few studies assessing the results of standardized ultrasound-guided pleural drainage. In addition, to our knowledge, there have been no prospective studies comparing the complication rate of ultrasound-guided pleural drainage with that of conventional pleural drainage. Nevertheless, it is reasonable to assume that the use of ultrasound, by allowing a more detailed analysis of anatomy and offering a rapid means of identifying cases of subcutaneous positioning of the drain, would provide results that are more satisfactory than those provided by the conventional technique.[53]

Ultrasound-guided thoracic biopsies

The technique of closed pleural biopsy to obtain diagnostic tissue has remained prevalent because of its ease of access and high level of acceptance among patients and medical professionals, particularly as an alternative to thoracoscopy and especially in regions with limited health care resources. There are no robust data to allow a distinction between a traditional (i.e., Cope or Abrams) reverse bevel and a core-cutting needle, in terms of specimen quality or diagnostic yield.[54,55]

Ultrasound can be a valuable tool for diagnosing undetermined thoracic lesions because it facilitates the collection of tissue from various structures such as the lung, chest wall, parietal pleura, and (anterior and upper) mediastinum.[54] Ultrasound-guided biopsies can be performed whenever the use of ultrasound would allow a lesion to be visualized, which is not possible in many cases, such as in those of central lung tumors. Ultrasound-guided transthoracic needle biopsy is considered to have an acceptable diagnostic yield and is a cost-effective alternative to CT-guided biopsy,[55] with a complication rate that is generally lower.[56]

Vascular access

Vascular puncture is commonplace in ICUs. For over three decades, ultrasound has repeatedly been cited as an imaging method that can assist in vascular puncture. Currently, ultrasound-guided vascular puncture is part of the best practices for quality improvement and patient safety protocols.

The use of ultrasound guidance for vascular access is associated with a 60% reduction in complications such as pneumothorax and arterial punctures, as well as with a higher catheterization success rate.[57] Ultrasound guidance provides several safety checkpoints. Ultrasound-guided vascular access uses a high-frequency linear probe, which provides detailed images of the superficial structures. The sonographer should identify the relevant structures, differentiate the vein from the artery, and exclude the presence of thrombi in the selected vessel before proceeding to venous puncture under real-time ultrasound guidance. Ultrasound can identify the guidewire position inside the venous structure, providing further safety before the dilation.

After the placement of an indwelling catheter, the sonographer can use ultrasound to evaluate the catheter position, mainly by one of two methods: by visualizing the tip of the catheter in the right atrium or vena cava, typically through a subcostal or right flank window,[58] or by performing the bubble test, which is considered positive when a turbulent flow of intravenous fluid injected through the catheter is visualized in the right atrium or ventricle.[59] Notably, the bubble test will ensure that the catheter is in the vascular system, even if the tip is not in the vena cava or the right atrium. Ultrasound confirmation of the catheter position reduces the need for X-rays and shortens the duration of catheter use for intravenous infusion.

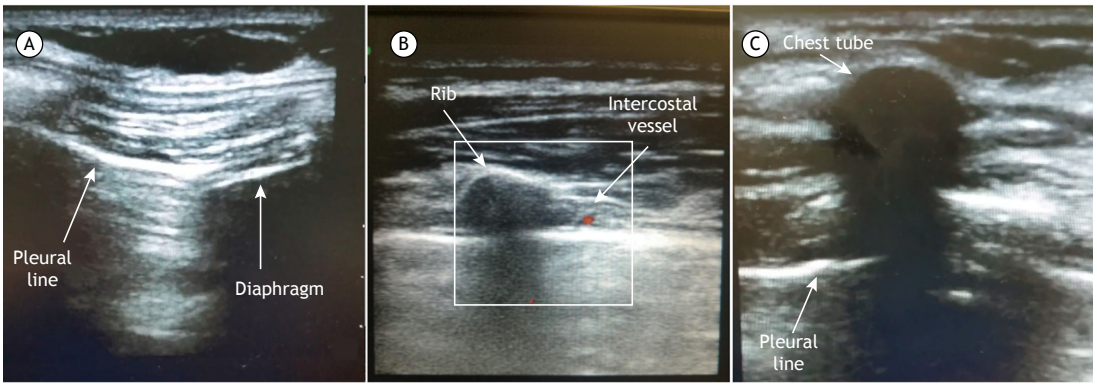


Figure 7. Tube thoracostomy. a) Brightness (B)-mode image, obtained with a linear probe, showing diaphragmatic excursion and a normal lung. The examiner evaluates the range of diaphragmatic excursion during a full cycle of ventilation. This enables the examiner to choose the lowest site for tube insertion while avoiding injury to the diaphragm. If the previously selected site exhibits diaphragmatic movement, a more cranial intercostal space must be scanned. b) Visualization of intercostal vessels using Doppler ultrasound. Once the examiner finds a suitable intercostal space, the insertion site should be scanned with Color Doppler. The intercostal artery most commonly lies on the upper third of the intercostal space. The entire intercostal space should be scanned in order to make sure that there is no blood flow along the insertion path. c) Confirmation of correct positioning of the drain. Axial view of a large-bore chest tube, showing the characteristic hyperechoic arc over a black circle with posterior acoustic shadowing, seen along the subcutaneous plane. Following that image along the drainage site, one should see the drain deepening toward the pleural line.

PERSPECTIVES

Medical utilization and ongoing research have solidified ultrasound as an essential, proficient tool for use in the modern clinic. Technological advances are enhancing the portability, accessibility, and cost-efficiency of ultrasound equipment. These characteristics allow the use of point-of-care ultrasound (POCUS) to extend beyond traditional hospital settings, reaching remote or resource-poor areas, ambulances, and clinics. In addition, the incorporation of artificial intelligence and machine learning algorithms has the potential to aid in interpreting images and recognizing patterns, potentially enhancing the capabilities of health care professionals. However, the increasing use of POCUS leads to ongoing deliberations about regulations and ethical considerations. Ensuring adequate training, standardization, patient confidentiality, data protection, and compliance with guidelines is crucial for its optimal, safe use. Therefore, specialized training programs are needed in order to equip health care professionals with the skills required for effective, accurate use of the technology. This training is pivotal to interpreting images accurately and maximizing the benefits of POCUS.

A well-designed, evidence-based curriculum for ultrasound training is imperative, akin to the requisites for clinical practice. Challenges such as a diverse caseload, inadequate specialized supervision, and different learning paces pose significant hurdles to education within a clinical setting. To ensure proficiency at each stage, appropriate and objective assessments, supported by robust validity evidence, are necessary before transitioning to independent practice. Overall, the future of POCUS appears promising as it continues to progress and integrate into diverse medical practices, providing real-time diagnostics and procedural support across a broad spectrum of health care settings.

FINAL CONSIDERATIONS

Despite the initial low adoption rate, TUS is rapidly gaining traction as a diagnostic tool and a safety measure for interventional procedures in thoracic medicine. It is imperative to consider the TUS findings together with the clinical data for the correct interpretation of a diagnostic examination. It is not a question of TUS superiority over other diagnostic exams, such as X-ray and CT of the chest, but rather of the benefit of complementing the findings of other examinations and permitting point-of-care imaging.

AUTHOR CONTRIBUTIONS

PFBC: conception and design of the study; search of the literature; and writing and critical review of the article. TTM, and AWM: conception and design of the study; search of the literature; and writing the manuscript. FMS, LBM and CAMM: literature search and writing the manuscript. All authors have approved the final version to be published.

CONFLICTS OF INTEREST

None declared.

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Clarifying the face of cannabis lung

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TO THE EDITOR:

Cannabis, also known as marijuana, is the most abused illicit psychoactive substance worldwide. Because it has been legalized in some countries, its use is expected to increase. Cannabis can be consumed by smoking, by vaping, by infusion, by ingestion, or as a tincture. When inhaled, it can induce lung injury. We evaluated six young male cannabis smokers who presented with lung involvement between September 2022 and December 2023. All of the patients gave written informed consent. The mean age was 31.6 years, and the mean BMI was 21.3 kg/m^2. Collectively, the patients had been cannabis users for 5-20 years, smoking 1-10 cannabis cigarettes ("joints") per day. None was a tobacco smoker or had any chronic lung disease. All tested negative for HIV and alpha-1 anti-trypsin deficiency. General blood examinations were unremarkable. All patients underwent unenhanced thin-slice HRCT of the chest. One of the patients, a 25-year-old, reported a six-month history of exertional dyspnea. He had smoked 4-5 joints/day for five years. Representative chest CT images of that patient are shown in Figures 1A and 1B. Four of the other patients (age range, 23-45 years) had smoked 2-5 joints per day for 5-20 years and presented to the emergency room with acute chest pain and dyspnea due to spontaneous pneumothorax requiring drainage (Figure 1, C-F). The remaining patient was a 32-year-old heavy smoker of cannabis with long-standing exertional dyspnea (Figures 1G and 1H). The chest CT findings are summarized in Table 1. In two patients without pneumothorax, a mild restrictive ventilatory pattern was detected, together with a mild reduction in single-breath DL_{CO}. None of the patients had respiratory failure. Because lung damage from cannabis use is still poorly recognized, it is underdiagnosed. The clinical presentation can be insidious, with pneumothorax occurring as an apparently idiopathic spontaneous entity. The definition of cannabis lung is imaging-based, including the presence of large bullae with predominant apical involvement in individuals with a history suggestive of cannabis smoking.[1] However, these features are nonspecific because they have been most widely associated with concomitant tobacco use in anecdotal case reports. Therefore, there is still a lack of studies characterizing radiological findings attributed exclusively to cannabis use. In the first attempt to do so in a systematic manner, Murtha et al. recently described the chest CT findings of 56 cannabis smokers.[2] However, even in that setting, 50 of the individuals analyzed were also tobacco smokers. The authors found that paraseptal emphysema and blebs were the most distinctive features. Those alterations, together with the involvement of chemical and physical factors related to cannabis use, are thought to lead to bullae formation. The mechanism of bullae formation seems to involve cannabis-induced lung toxicity in combination with pleural pressure swings and airway barotrauma, of which the last two are caused by the high inspiratory pressures resulting from cannabis smoking. In comparison with tobacco smokers, cannabis smokers take larger puffs, inhale more deeply, and hold their inhalations longer.[3] Unlike cigarettes, joints are typically unfiltered, which increases tar deposition and carboxyhemoglobin formation by 4-5 times.[3] Cannabis-induced lung injury can go beyond the mere formation of bullae. Short-term exposure to cannabis can lead to bronchodilation, due to the effect of delta-9-tetrahydrocannabinol (the main psychoactive component of cannabis). Long-term exposure is associated with respiratory symptoms (cough, phlegm production, and wheezing) but not necessarily with bronchial obstruction.[4,5] There is evidence that airway inflammation, increased secretions, and bronchial remodeling occur in cannabis smokers.[6,7] Murtha et al.[2] also stated that chest HRCT evidence of bronchial thickening, mucoid impaction, and bronchiectasis can be expected to be found in cannabis smokers. Inspired by these observations and in an attempt to provide data that enable precise interpretation, we exclusively evaluated cannabis smokers who were not tobacco users. With the exception of gynecomastia, all of the radiological findings described by Murtha et al.[2] were represented in our patients, suggesting that they had an exclusively cannabis-related origin. Another element that characterized our study sample was the low mean age (31.6 years), which further underscores the need to focus on this entity whose evolution can be insidious and potentially disabling over time. Spontaneous pneumothorax was the mode of disease presentation in four of the cases presented here. Although this complication is already known in cannabis smokers, the causal association often goes uninvestigated because the evolution of spontaneous pneumothorax can be subtle. This insidious aspect is partly attributable to the young age and the long-line phenotype of subjects with idiopathic spontaneous pneumothorax, which can be confused with that of undeclared cannabis users with lung involvement, suggesting that such a clinical scenario is more common than expected. In our case series, the combination of young age with the extent and type of radiological damage was immediately suspicious for a potential association with cannabis use, which was initially denied by all of the patients. Related clinical aspects should also not be neglected in

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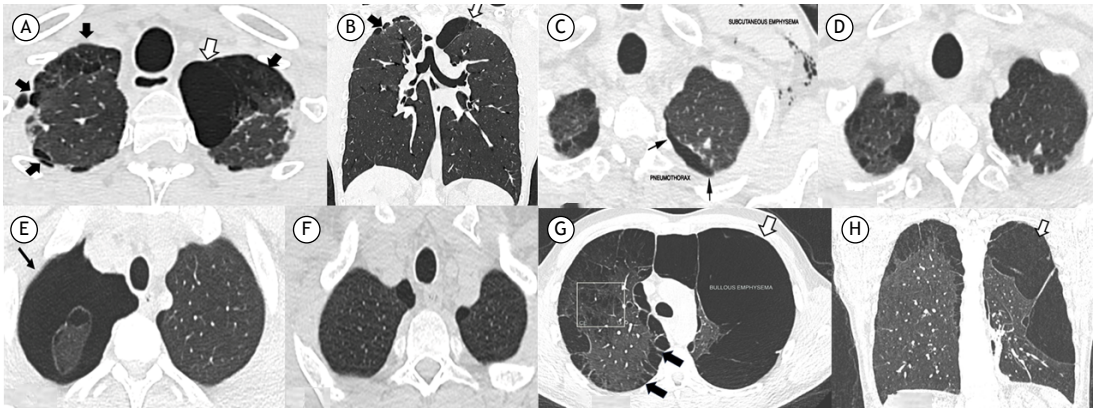

Figure 1. Axial and coronal unenhanced thin-slice chest HRCT scans (A and B, respectively) in a 25-year-old male cannabis smoker, showing a large (5 cm) bulla (white arrows), sharply demarcated by a thin wall in the left lung apex, together with multiple small blebs adjacent to the pleura and small areas of paraseptal and centrilobular emphysema in both lung apices (black arrows). Axial unenhanced thin-slice chest HRCT scans (C and D, respectively) in a 45-year-old male cannabis smoker, showing left pneumothorax (arrows in C) with marked bilateral apical subcutaneous emphysema and sparse areas of paraseptal emphysema along with small blebs and rare bullae that resolved after drainage. Axial unenhanced thin-slice chest HRCT scans (E and F, respectively) in a 23-year-old male cannabis smoker, showing extensive pneumothorax on the right side (black arrow in E) with some blebs adjacent to the visceral anterior pleura and small areas of paraseptal emphysema on the same side, with complete resorption of pneumothorax after chest drainage. Axial unenhanced thin-slice chest HRCT scan (G) in a 32-year-old male cannabis smoker, showing extensive alterations due to destruction of lung tissue on both sides with a coarse bullous formation on the left (white arrow). Coronal multiplanar reconstruction (H) of the same patient showing the bullous formation occupying the upper and middle thirds of the left hemithorax, with subtle septation. In the right lung (visible in G), there were marked changes from paraseptal and centrilobular emphysematous damage (black arrows and square outline, respectively).

Table 1. Synopsis of cannabis-related chest HRCT findings.

Finding	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Emphysema	x	x	x	x	x	x
Paraseptal emphysema	x	x	x	x	x	x
Blebs/bullae	x	x	x	x	x	x
Bronchial thickening	x	x	x	-	x	x
Bronchiectasis	-	x	-	-	-	-
Mucoid impaction	x	x	x	x	x	-
Gynecomastia	-	-	-	-	-	-
Coronary artery calcification	-	-	-	-	-	x

such patients, especially because they can be used in order to exclude other forms of tobacco-induced disorders with which cannabis lung is confused. In addition, some considerations on the potential for disease evolution merit greater attention. Although the current data are inconclusive, the risk of developing lung cancer in the long term should not be ignored.[6,8] There is no doubt that our report is limited by the small size of our sample. A further limitation is the lack of complete lung function data, mainly due to the caution imposed by the extensive lung damage or to the need for pleural drainage positioning. However, our effort might help shed light on an intriguing topic that merits further exploration in larger series through the same systematic approach. In that sense, our contribution aims to sensitize the scientific and medical community to be more suspicious when faced with an entity whose clinical-radiological presentation and course can be even more insidious if the habits of the patient are not properly investigated.

AUTHOR CONTRIBUTIONS

All of the authors contributed to the study conception/design, material preparation, data collection, and data analysis. MB created the first draft of the manuscript, and all of the authors contributed to subsequent versions. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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Acute exacerbation of interstitial lung disease after transthoracic biopsy

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TO THE EDITOR,

We report the case of an 80-year-old male with a recent diagnosis of advanced-stage lung adenocarcinoma, confirmed through transthoracic biopsy (TTB) in the right upper lobe, metastatic to bones and subcutaneous tissue. The patient had a 10-year history of rheumatoid arthritis, treated with adalimumab. He also had fibrotic rheumatoid arthritis-associated interstitial lung disease (RA-ILD) with combined pulmonary fibrosis and emphysema (CPFE) and fibrosis with a typical usual interstitial pneumonia (UIP) pattern; coronary artery disease requiring stent placement; symptomatic bradycardia requiring a pacemaker; and chronic kidney disease of undefined cause. He had a 20-pack-year smoking history and had ceased smoking 10 years prior. The patient was admitted to undergo a repeat TTB to collect material for a mutation panel and programmed death ligand 1 testing, given that the initial biopsy yielded insufficient material. Before the procedure, the patient had not undergone any oncological treatments. One week before this hospitalization, the patient experienced a small-volume hemoptysis episode, leading to a short (48-h) admission for bronchoscopy investigation. Signs of active bleeding from the right upper lobe were observed. Epinephrine was administered locally, and bronchial artery arteriography with selective embolization was performed, resulting in no further episodes of hemoptysis. No BAL or TTB was performed at that time.

On physical examination before the new lung biopsy, the RR was 16 breaths/min, the HR was 70 bpm, the SpO_2 was 94% on room air, and there were basal crackles. Laboratory tests at admission showed abnormal renal function abnormalities (consistent with the preexisting condition of the patient) and findings consistent with anemia of chronic disease. An initial HRCT revealed a neoplastic mass in the right lung, together with CPFE (Figure 1, A-E). Ground-glass opacities surrounding the mass and other nodular lesions corresponded to perilesional hemorrhage identified within the context of hemoptysis. The patient underwent TTB, during which there were no complications and mechanical ventilation was not required. He was discharged the following day. The TTB confirmed a pattern of interstitial fibrosis with the spatial heterogeneity typically found in UIP, along with other areas of tumor infiltration into the lung parenchyma.

Ten days after the procedure, the patient returned to the emergency department with complaints of increased exertional dyspnea, a drop in SpO_2 to 86% on room air, without fever, cough, sputum production, or upper airway symptoms. The RR was 28 breaths/min, the HR was 98 bpm, and pulmonary auscultation revealed worsening crackles up to the middle third of the lung. A repeat chest HRCT showed new diffuse bilateral ground-glass opacities (Figure 1, F-J). Initial diagnostic hypotheses included an infectious process or an acute exacerbation of ILD (AE-ILD).

At this point, empirical antibiotic therapy with piperacillin-tazobactam and azithromycin was initiated, and infectious causes were investigated. The results of blood cultures, urine culture, PCR for cytomegalovirus, an extended molecular panel for viruses and bacteria, and urine antigen tests for *Legionella* sp. and *Streptococcus* sp. were all unremarkable, as were those of tests for procalcitonin, galactomannan, B-type natriuretic peptide, and troponin. There was no new organ dysfunction.

Given the exclusion of infectious processes and the daily worsening of hypoxemia, the most probable diagnosis was determined to be an AE-ILD. Therapy with methylprednisolone (1 mg/kg/day), as well as oral morphine for dyspnea, was initiated on post-admission day 4. Progressively, the patient experienced worsening gas exchange and the need for increased oxygen flow. On post-admission day 7, the use of a high-flow nasal cannula was required, at a flow rate of 60 L/min and an FiO_2 of 80%, achieving an SpO_2 of 85%. The patient developed mental confusion and respiratory discomfort, prompting the initiation of palliative sedation in accordance with the patient's advance care directive. On post-admission day 15, the patient died.

The ILD category encompasses a diverse group of pulmonary disorders, characterized by varying degrees of inflammation and fibrosis, whose prognosis varies widely depending on the specific pathology.[1] Although the diagnostic approach to ILDs and their potential comorbidities, such as lung cancer, often necessitates histopathological examination, the potential risks associated with invasive procedures like transthoracic biopsies are not negligible.[2]

Recognized as the predominant pulmonary manifestation in patients with RA, ILD affects approximately 20% of this patient population. Among these, UIP is the most commonly observed pattern.[3,4] Notably, the risk of lung cancer is higher in individuals with RA than in those without.[5]

A rapidly progressing, life-threatening respiratory condition, AE-ILD is characterized by the emergence of new, extensive alveolar abnormalities superimposed on preexisting pulmonary fibrosis. The diagnostic criteria for

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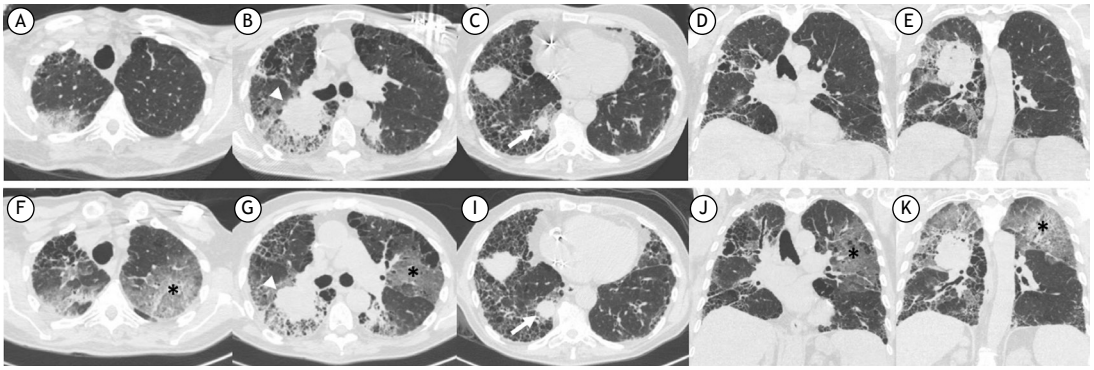

Figure 1. An initial chest CT (A-C: axial plane; D,E: coronal plane) showing a cavitary mass in the right lung (arrowhead), measuring 62 mm in diameter on its longest axis, centered in the posterior segment of the upper lobe and extending to the middle lobe and superior segment of the lower lobe. Note the other nodular lesions scattered throughout both lungs, as well as the ground-glass opacities surrounding those and the mass, which may correspond to perilesional hemorrhage. The images also show extensive (centrilobular and paraseptal) pulmonary emphysema, together with interstitial abnormalities characterized by reticular opacities, traction bronchiectasis/bronchiolectasis, and honeycombing, predominantly in the periphery of the lower lung fields (a typical UIP pattern on CT). Prominent lymph nodes are present in the mediastinum and pulmonary hila, as is a lytic lesion in the right scapula (not shown in the images). (F-J) A follow-up chest CT (F-H: axial plane; I,J: coronal plane), performed 12 days after the biopsy, revealing new ground-glass opacities scattered throughout both lungs, more extensively in the left upper lobe (asterisk), accompanied by sparse small consolidative foci, which may represent an acute exacerbation of the underlying interstitial lung disease. In addition, at least one nodular lesion in the right lower lobe (arrow) had increased in size in relation to what was seen on the initial CT.

AE-ILD include the presence of fibrosing ILD evident on HRCT; an acute onset or worsening of dyspnea, typically within one month; the appearance of a new bilateral ground-glass opacity or consolidation on HRCT; and clinical deterioration that cannot be fully attributed to cardiac failure or fluid overload.[6] The 90-day mortality rate associated with AE-ILD is approximately 50% in patients with RA.[7]

A multitude of factors, including infections, air pollution, aspiration events, transfusions, medications, and pulmonary sample collection, can trigger AE-ILD.[2,8] Procedures associated with AE-ILD include open surgical biopsy, video-assisted thoracoscopic biopsy, BAL, TTB, lung cryobiopsy, and even surgical procedures not directly involving the lungs. However, the risk factors for AE-ILD in patients with RA-ILD are not well understood.[2]

In the case presented here, we believe the most likely explanation for the respiratory deterioration and bilateral ground-glass opacities observed on the HRCT scan was that they were secondary to the TTB. That belief is based on the temporal correlation with the biopsy and the absence of infectious findings, new hemoptysis events, oncological treatments, or other invasive procedures (given that the prior bronchoscopy involved only local hemostatic measures without BAL). Although two other cases of AE-ILD secondary to TTB were reported in a retrospective study,[9] the underlying lung disease in those cases was idiopathic pulmonary fibrosis. For the treatment of AE-ILD, the recommendation in the literature is to use a high dose of methylprednisolone (500-1000 mg per day) for three days.[8] However, we opted for a lower dose of corticosteroid therapy because of the advanced oncologic disease.[8] We initiated treatment only after all infectious causes had been excluded, and that delay could have had a negative impact on the outcome.

In summary, the indication for invasive procedures in patients with ILD should be approached cautiously, because various complications may arise, including acute pulmonary exacerbations.[9] Early recognition of AE-ILD, followed by the initiation of treatment with systemic corticosteroids, is crucial given that this condition has a remarkably high 90-day mortality rate.

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AUTHOR CONTRIBUTIONS

FMC, MTC, BLM, AKM, BLM, and CS: conception, planning and design of the report; and data collection. FMC, MTC, BLM, AKM, BLM, and CS: drafting of the article; and critical revision of the manuscript.

MTC and AKM: critical revision of the manuscript.

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

CONFLICTS OF INTEREST

The authors declare that they have no conflicts of interest.

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Tracheal laceration following rapid sequence intubation

Filipa Jesus[1], Élin Almeida[1], Alcina Tavares[1,2]

A 64-year-old female with major depressive disorder was admitted to the ER after voluntary intoxication with amitriptyline, venlafaxine, and lamotrigine. Upon admission, a Glasgow Coma Scale of 3 was documented, and rapid sequence intubation was promptly performed, initiating the patient on invasive mechanical ventilation. After being transferred to the ICU, subcutaneous emphysema was noted (Figure 1A). Chest CT showed exuberant pneumomediastinum and bilateral pneumothorax (Figure 1B). After chest tube placement, flexible bronchoscopy was performed (Olympus® BF-H190, Olympus, Japan) showing a laceration on the lower third of the posterior tracheal wall (Figure 1C). A double-lumen tube was used to replace the previous single-lumen endotracheal tube, allowing adequate ventilation while bypassing the damaged area and allowing cicatrization. Twelve days after the procedure, endoscopic reassessment (Olympus® BF-H190) showed complete reepithelization of that injury (Figure 1D).

Post-intubation tracheal laceration is a rare but a potentially life-threatening condition, with an overall incidence of 1 per 20.000, increasing up to 15% following emergency intubation.[1] Intubation injuries are more common in females, probably due to a shorter average tracheal length and weaker *pars membranosa.* Subcutaneous emphysema is the most common symptom and also a protective factor, as it favors early diagnosis and rapid initiation of appropriate treatment.[2]

AUTHOR CONTRIBUTIONS

All the authors equally contributed to this work

CONFLICTS OF INTEREST

None declared.

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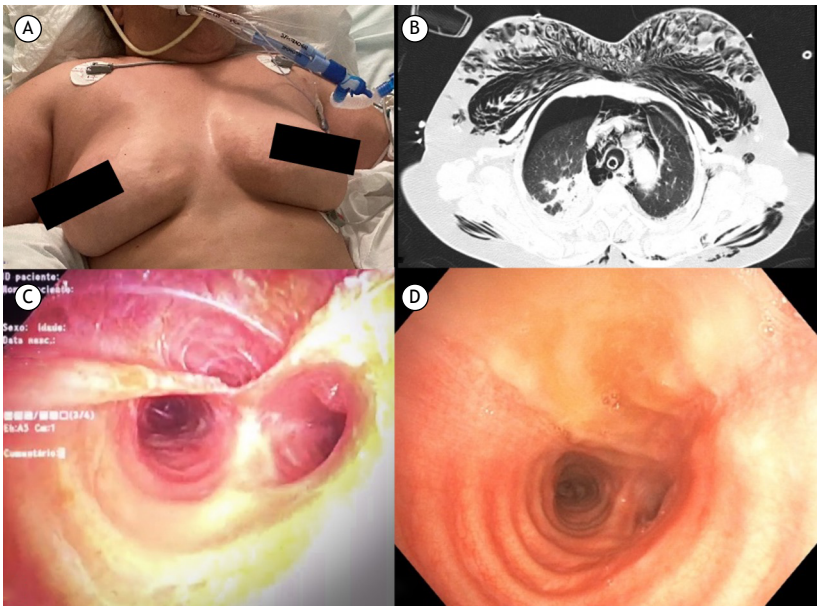

Figure 1. In A, a patient with significant subcutaneous emphysema after being initiated on invasive mechanical ventilation. In B, a chest CT scan revealed exuberant subcutaneous emphysema, pneumomediastinum, and bilateral pneumothorax. In C, a flexible bronchoscopy was performed after intubation, and the image shows a laceration on the lower third of the posterior tracheal wall (anterior view). In D, a repeat flexible bronchoscopy was performed 12 days after the initial endoscopic evaluation, and the image shows complete reepithelization of the posterior tracheal wall (anterior view).

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Diaphragmatic hernia as an infrequent complication of left pneumonectomy

María Emilia Cano[1], Fabiola Adélia Perin[1], Stephan Soder[1]

Pneumonectomy is a complex procedure, associated with significant morbidity and mortality.[1] The most frequent complications involve the cardiovascular and respiratory systems.[2] A 51-year-old patient underwent left pneumonectomy for lung cancer. Adhesions between the visceral and parietal pleura were found intraoperatively and dissected with monopolar electrocautery. The patient presented a successful recovery after the surgery and was discharged from hospital after nine days.

In the second month after surgery, the patient experienced a sudden onset of abdominal and thoracic pain accompanied by vomiting. The CT showed a left diaphragmatic hernia, with the presence of the stomach in the left pleural cavity. After initial measures, such as insertion of a nasogastric tube, a supra-umbilical laparotomy was performed, with satisfactory reduction of the stomach into the abdominal cavity and closure of the diaphragmatic defect with non-absorbable suture reinforced with polypropylene mesh.

Diaphragmatic hernia is a rare complication after pneumonectomy and can occur during hospital recovery or as a late postoperative complication.[3] The iatrogenic cause is considered in this case due to the time it took for the complication to occur. The mechanism of the hernia could be a result of unintentional thinning of the diaphragm during the dissection of adhesions, which makes it more prone to rupture. The abdominal approach is recommended for the management of herniated abdominal structures, allowing correction of the diaphragmatic defect.

AUTHOR CONTRIBUTIONS

MEC: conceptualization (Lead). SD: reviewing & editing of the manuscript (Lead). All of the authors equally contributed with formal analysis, investigation, methodology, visualization, supervision, and drafting of the manuscript, and they approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

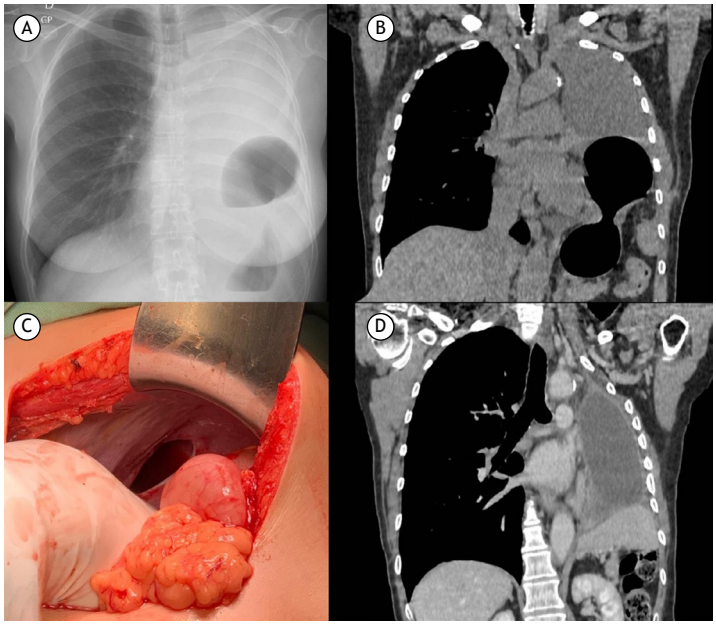

Figure 1. In A, a chest x-ray (frontal) performed on admission. In B., chest CT showing diaphragmatic hernia with gastric contents and pleural fluid filling the post-pneumonectomy cavity. In C, intraoperative image with identification of the diaphragmatic defect. In D, a control chest CT scan two years after diaphragmatic correction showing no herniation.

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Mediastinal fat necrosis—an overlooked cause of chest pain

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

A 55-year-old man was admitted with a three-day history of left anterior chest pain. No fever or another relevant symptom was identified. Physical examination findings were unremarkable. Laboratory tests showed an elevated C-reactive protein level and mild leukocytosis without deviation. Pulmonary thromboembolism was suspected. Chest CT angiography revealed an ovoid mediastinal fatty lesion in the left cardiophrenic region, demarcated by a soft-tissue attenuation ring (Figure 1). In view of these imaging findings, the diagnosis of mediastinal fat necrosis (MFN) was made. A conservative approach was adopted, and the patient's pain was relieved by nonsteroidal anti-inflammatory drugs.

MFN, also known as epipericardial fat necrosis, is a self-limited cause of chest pain that represents an inflammatory process, usually occurring in the juxtapericardial mediastinal fat and leading to encapsulated fat necrosis. MFN usually manifests with acute pleuritic chest pain in previously healthy individuals and can mimic acute cardiopulmonary processes, such as myocardial infarction, pericarditis, and pulmonary embolism. CT can demonstrate an ovoid or round fatty lesion demarcated by a soft-tissue attenuation rim in the mediastinum. Conservative treatment, such as nonsteroidal anti-inflammatory drug administration, is usually sufficient to relieve symptoms.[1-3]

In conclusion, a confident diagnosis of MFN based on imaging findings may help to preclude unnecessary invasive procedures, and conservative symptomatic treatment is the recommended practice.

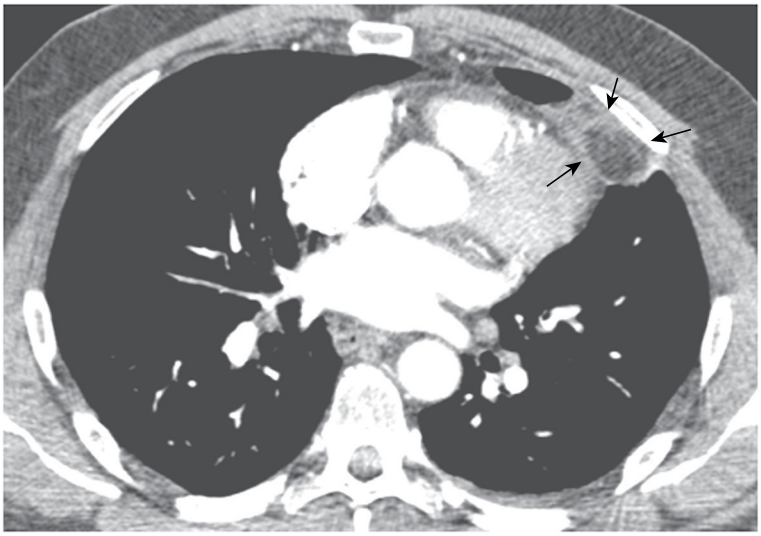

Figure 1. Contrast-enhanced CT image (soft-tissue window) showing an ovoid mediastinal fatty lesion (arrowheads) in the left cardiophrenic region, demarcated by a soft-tissue attenuation ring.

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◄ Voltar ao sumário

A critical analysis of the decreasing trends in tuberculosis cure indicators in Brazil

Hinpetch Daungsupawong[1], Viroj Wiwanitki[2]

DEAR EDITOR:

"A critical analysis of the decreasing trends in tuberculosis cure indicators in Brazil, 2001-2022"[1] is an interesting article. In brief, the study examined the longitudinal development of tuberculosis cure indicators between 2001 and 2022 in Brazil. The data show that, throughout most of the country, there was a considerable decline in the cure indicators for patients with pulmonary tuberculosis or tuberculosis/HIV coinfection, as well as for those undergoing tuberculosis retreatment. In addition, according to national statistics, the mean annual percentage change in cure rates for those categories showed a consistent downward trend. These results point to a worrisome pattern that calls into question the efficacy of the current tuberculosis treatment programs in the country.

The study has some potential flaws, because it relies too heavily on administrative data, which may not be entirely accurate or complete. To ensure the validity of the findings, the study could have profited from adding other data sources or validation techniques. In addition, individual-level characteristics that may affect the effectiveness of tuberculosis treatment may not be fully taken into account by an ecological time-series design. In order to gain a deeper understanding of the factors influencing the observed trends in cure indicators, future studies could incorporate more thorough analyses at the individual level.

Further investigation into the effects that socioeconomic variables, health care service accessibility, and the caliber of tuberculosis treatment programs have on cure rates in Brazil could be an avenue for future research. The efficacy of the efforts to control tuberculosis in the country could be increased by identifying the obstacles to effective treatment and devising solutions to overcome them. Research endeavors could also concentrate on assessing the execution of particular measures or regulations aimed at improving tuberculosis treatment results, such as closely monitored therapy and patient assistance initiatives. Future studies may be able to fill these gaps and help create more focused and efficient methods of controlling tuberculosis in Brazil.

AUTHOR CONTRIBUTIONS

HD and VW both contributed to the conception of the article. HD analyzed the data and wrote the article. VW supervised the drafting of the article. Both authors approved the final version to be published.

CONFLICTS OF INTEREST

None declared

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Authors' reply

Gabriel Pavinati[1], Lucas Vinícius de Lima[1], Pedro Henrique Paiva Bernardo[1], Jhenicy Rubira Dias[2], Bárbara Reis-Santos[3], Gabriela Tavares Magnabosco[1]

We appreciate the attention our recently published article in the *Jornal Brasileiro de Pneumologia*[1] has received. Our goal in addressing the concerning trend toward a decease in tuberculosis cure indicators in Brazil was to stimulate debate on this subject. However, appropriate conceptual definitions are crucial to ensure that the debate is appropriate. Albeit a suitable design to respond to the objective of the study, an ecological approach has some limitations. It is crucial to avoid the fallacy of attributing collective inferences to the individual level, and it was beyond the scope of the study to infer effectiveness or efficacy of tuberculosis control programs. We hope our study stimulates further detailed research and discussions.

We concur that the body of knowledge on the subject is still evolving. We recognize that our findings present a valuable opportunity to guide new, original, and unprecedented research. This approach can be pursued from various angles, such as using an ecological design that incorporates contextual and programmatic variables to evaluate their influence on the primary outcome and employing individual data sources (e.g., cohort and case-control studies) to develop a framework underpinning all tuberculosis control actions in the country. Continued research from diverse perspectives is essential for a comprehensive understanding of tuberculosis.

Concerns surrounding the utilization of administrative data in our research, particularly those relating to underreporting and filling errors within the information system, were acknowledged as factors that could influence the interpretation of the results[1]. However, this information system has been extensively studied, and the consistency of its attributes has been confirmed in previous studies[2]. Consequently, we are confident that this did not affect the results presented, which are also supported by operational publications[3]. Addressing data accuracy and reliability is vital for robust conclusions in tuberculosis research and policy development.

Discussions like these underscore the importance of addressing the complex problem of tuberculosis in depth and diligently. We believe that suggestions to explore other data sources and consider individual and contextual factors—as we partially did by segmenting by occurrence location and specific groups (e.g., people with pulmonary tuberculosis, people living with HIV, and people in retreatment)—are pertinent. They can unveil unexplored knowledge and contribute to eliminating the epidemic in our country. Ongoing dialogue and research are crucial for effective tuberculosis control strategies and achieving public health goals in Brazil.

Finally, it is worth reiterating that our findings indicated a concerning trend in the Brazilian context[1,3]: a decline in tuberculosis cure indicators. Therefore, we hope our article will continue to spark debate on the topic and serve as a launching pad for more detailed studies and the development of more assertive and robust policies. By acknowledging the existing reality, we can point out paths, trajectories, and trends. We should also consider the efforts of the Brazilian National Tuberculosis Program to implement policies and actions that bring us closer to the desired goal of eliminating tuberculosis as a public health problem—a commitment shared by all.

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Correspondence about the article: Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021

Marcelo Fouad Rabahi[1], Amanda da Rocha Oliveira Cardoso[2], José Eduardo Delfini Cançado[3]

We received with great interest the article published in the *Jornal Brasileiro de Pneumologia*, authored by Pinheiro et al.[1] and titled "Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021". Their article contains important data on mortality and hospitalizations associated with asthma in Brazil between 2008 and 2021 in the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System). The data were extracted from the Information Technology Department of the SUS (DATASUS) in 2022. The authors concluded that the number of deaths and hospitalizations for asthma decreased over the course of the period studied.

Our group analyzed asthma mortality data (ICD-10 codes J45 and J46) in Brazil from the National *Sistema de Informação sobre Mortalidade* (SIM, Mortality Database),[2] and observed that the number of asthma-related deaths is 3 to 6 times higher than that obtained by the DATASUS.[3] Pinheiro et al.[1] found that there were more than 8,000 asthma-related deaths in the 2008-2021 period. In the same period, according to SIM data, there were 34,163 deaths attributed to asthma: 2,696 in 2008 and 2,802 in 2022. Therefore, in 2022, there were an alarming seven asthma-related deaths per day in Brazil,[3] which is in contrast with the one death per day reported by Pinheiro et al.[1]

Given this context, it is important to emphasize that the mortality data generated by DATASUS come from the outcome "in-hospital death" from the "paid during the period" authorized hospital admissions (AHAs). This information reflects asthma-related deaths occurring only during hospitalization for the disease. On the other hand, the SIM provides information derived from death certificates and thus reports deaths occurring in the public and private health care systems, as well as those occurring outside the hospital setting. Consequently, if the AHA had been generated for a condition other than asthma, an in-hospital death attributed to asthma on the death certificate would not have been counted as an asthma-related death by the DATASUS, which constitutes an additional factor that differentiates DATASUS data from SIM data.

We stress that asthma-related mortality in Brazil has increased over the last 10 years, and that the mortality rate cited by Pinheiro et al.[1] reflects data from hospitalizations only within the SUS. We also emphasize that 19% and 67% of the asthma-related deaths in Brazil occurred in adults (≥ 40 and < 60 years of age) and the elderly (≥ 60 years of age), respectively. In conclusion, despite the availability of free asthma medication throughout the country, asthma mortality has been increasing, especially among adults and the elderly. Therefore, it is essential to improve access to the diagnosis and treatment of this disease, which is the second most prevalent respiratory disease in Brazil.

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◄ Voltar ao sumário
ISSN 1806-3756

Authors' reply

David Halen Araújo Pinheiro[1], João Victor Hermógenes de Souza[1], Alberto Fernando Oliveira Justo[2], Regina Maria Carvalho-Pinto[3], Fabiano Francisco de Lima[1], Celso R F Carvalho[1]

We received with great interest the correspondence JBPNEU-2024-0196, containing the comments from Rabahi et al. about our study entitled "Asthma in the Brazilian Unified Health Care System: an epidemiological analysis from 2008 to 2021."[1] They suggested that our results demonstrating a reduction in in-hospital asthma-related mortality run contrary to their results showing an increase in such mortality in the last ten years.[2] We consider that the results of the two studies are not contradictory but rather complementary and can further understanding of what has happened to individuals with asthma during the last decade.

It is widely known that asthma medication is freely available via the Brazilian *Sistema Único de Saúde* (SUS, Unified Health Care System), improving asthma treatment. In our opinion, the apparent difference between the results of the two studies is a consequence of inadequate treatment despite the available medication. When patients receive proper treatment for exacerbations during hospitalization (for instance), the number of deaths can be reduced.

We also emphasize that the two studies differed in terms of the databases consulted, which could explain the distinct results and misinterpretations. We used data from the Information Technology Department of the SUS (DATASUS), which includes only individuals treated via the public health care system, as was well stated by Rabahi et al. in their correspondence ("this information reflects asthma-related deaths occurring only during hospitalization for the disease" which was stated in our article). In contrast, Rabahi et al. used data from the Brazilian National Mortality Database, which includes individuals treated via the public and private health care systems. In addition, the increase in the number of asthma-related deaths observed by Rabahi et al.[2] represented a "special increase among adults in the last three years (2020 to 2022)"; that is, during the COVID-19 pandemic. This period presented a marked increase in the number of deaths caused by respiratory symptoms in adults and the elderly, which may have resulted in the cause of death being misrepresented. Furthermore, our data show a linear decline in the number of hospitalizations and deaths in the previous ten years, which continued during the COVID-19 pandemic. Moreover, the Brazilian Thoracic Society website recently published data referring to asthma in Brazil (also collected from DATASUS), indicating that in 2022 there were 83,155 hospitalizations for asthma and 524 deaths from the disease, stating that the "expansion of care and access to medications . . . led to a significant drop in hospitalizations for asthma", corroborating our results.[3] Finally, our study shows other relevant and associated findings, including hospitalization rates and costs in the various regions of Brazil.

In conclusion, we agree that not all patients with asthma receive proper medical treatment in Brazil, despite the availability of free asthma medication treatment throughout the country, and that we still have a lot of work to do. We are also anxious to carefully analyze the results presented by Rabahi et al.,[2] which will undoubtedly add important information on asthma-related deaths in Brazil. It will be important to understand whether the increase in the number of deaths was due to asthma itself or was a consequence of the pandemic.

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EDITAL DE SELEÇÃO

Brasília, 25 de junho de 2024

No período entre 01 de julho e 15 de setembro de 2024 estarão abertas as inscrições para candidatos ao cargo de Vice-Editor do Jornal Brasileiro de Pneumologia, com atuação no biênio 2025-2026. O Vice-Editor eleito assumirá a posição de Editor-Chefe em 2027, permanecendo na função por quatro anos (2027-2030) e, no biênio seguinte (2031-2032), assume novamente a função de Vice-Editor para auxiliar o novo Editor-Chefe.

Os interessados ao posto deverão ter experiência prévia como editor de periódicos de circulação internacional e enviar à administração da SBPT, em Brasília, suas propostas de gestão e Curriculum Vitae na plataforma Lattes.

As propostas dos candidatos deverão abranger os campos administrativo, científico e orçamentário, e deverão ser apresentadas em relação ao período de dois anos como Vice-Editor e aos quatro anos previstos para o futuro mandato como Editor-Chefe.

Os candidatos deverão conhecer as normas relativas à seleção do Vice-Editor e o funcionamento do Jornal Brasileiro de Pneumologia, descritas em seu regulamento, que pode ser obtido por meio de contato com a secretaria do JBP em Brasília.

Dra. Margareth Maria Pretti Dalcolmo
Presidente da SBPT

Dra. Marcia Margaret Menezes Pizzichini
Editora-Chefe do Jornal Brasileiro de Pneumologia

◄ Voltar ao sumário

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

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

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

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

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

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

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

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

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

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

Chegou: EGURINEL® (pirfenidona)

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

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

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