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ORIGINAL ARTICLE

Relative incidence of interstitial lung diseases in Brazil

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Study carried out in the Universidade Federal de São Paulo and at the Clínica de Pneumologia CACP, both located in São Paulo (SP) Brasil; in the Universidade Federal de Minas Gerais and at the Hospital Julia Kubistchek, both located in Belo Horizonte (MG) Brasil; in the Universidade Federal de Goiás, located in Goiânia (GO) Brasil, and at the Hospital São Rafael, located in Salvador (BA) Brasil.

ABSTRACT

Objective: To assess the relative frequency of incident cases of interstitial lung diseases (ILDs) in Brazil. **Methods:** This was a retrospective survey of new cases of ILD in six referral centers between January of 2013 and January of 2020. The diagnosis of ILD followed the criteria suggested by international bodies or was made through multidisciplinary discussion (MDD). The condition was characterized as unclassifiable ILD when there was no specific final diagnosis following MDD or when there was disagreement between clinical, radiological, or histological data. **Results:** The sample comprised 1,406 patients (mean age = 61 ± 14 years), and 764 (54%) were female. Of the 747 cases exposed to hypersensitivity pneumonitis (HP)-related antigens, 327 (44%) had a final diagnosis of HP. A family history of ILD was reported in 8% of cases. HRCT findings were indicative of fibrosis in 74% of cases, including honeycombing, in 21%. Relevant autoantibodies were detected in 33% of cases. Transbronchial biopsy was performed in 23% of patients, and surgical lung biopsy, in 17%. The final diagnoses were: connective tissue disease-associated ILD (in 27%), HP (in 23%), idiopathic pulmonary fibrosis (in 14%), unclassifiable ILD (in 10%), and sarcoidosis (in 6%). Diagnoses varied significantly among centers ($\chi^2 = 312.4$; $p < 0.001$). **Conclusions:** Our findings show that connective tissue disease-associated ILD is the most common ILD in Brazil, followed by HP. These results highlight the need for close collaboration between pulmonologists and rheumatologists, the importance of detailed questioning of patients in regard with potential exposure to antigens, and the need for public health campaigns to stress the importance of avoiding such exposure.

Keywords: Lung diseases, interstitial/epidemiology; Alveolitis, extrinsic allergic/epidemiology; Connective tissue diseases/epidemiology, Sarcoidosis/epidemiology; Idiopathic pulmonary fibrosis/epidemiology

INTRODUCTION

Interstitial lung diseases (ILDs) are a heterogeneous group of conditions that diffusely involve the lungs. Studies from several countries have shown that the frequency of the different types of ILDs varies widely.[1-13] In Brazil, hypersensitivity pneumonitis (HP) is a common ILD.[14]

A better understanding of the epidemiology of ILDs would enable the identification of possible risk factors and targets related to prevention and intervention. Additionally, it can help the health system make decisions about resource allocation that are of particular importance given the limited treatment options and the emergence of therapies that are often expensive.[15]

The accurate diagnosis of ILDs remains a challenge. The diagnostic criteria for the different diseases that comprise ILDs are amended and updated periodically, which makes epidemiological studies more difficult.[16,17] Two approaches are available in clinical practice for diagnosing ILDs: either a diagnosis based on strict clinical criteria, causing it not to be classified as specific ILDs in many cases; or a diagnosis based on clinical judgment, which results in fewer unclassifiable diseases. In many cases, there is a need for a multidisciplinary discussion (MDD) involving clinical, radiological, and pathological data.[18]

The present study evaluated the relative frequency of ILDs in Brazil using registries of incident cases in a multicenter setting and compared the findings with those observed in other countries.

METHODS

Study patients

This was a retrospective study involving six referral centers for ILD in Brazil (the Federal University of São Paulo and CACP Pulmonology Clinic, both located in the city of São Paulo; the Federal University of Minas Gerais and the Julia Kubistchek Hospital, both located in the city of Belo Horizonte; the Federal University of Goiás, located in the city of Goiânia; and the São Rafael Hospital, located in the city of Salvador). The study was approved by the

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Research Ethics Committee of the Federal University of São Paulo, the institution leading the research (Protocol no. 5.316.467), and by the committees of each center. The incident cases were consecutively identified between January 1, 2013, and January 31, 2020, from the medical records of patients diagnosed with ILD using a standardized evaluation sheet (see supplementary material; Chart S1).

Inclusion criteria

All participating centers had to be able to undertake a formal MDD with a pulmonologist experienced in ILDs, a thoracic radiologist, and a pulmonary pathologist, as well as to be able to perform ancillary procedures, including surgical lung biopsy (SLB) if necessary. There is no registration of referral centers for ILDs in the Brazilian Thoracic Society. We pooled a number of centers years ago, with the common goal of developing research studies. These groups standardized evaluation (Charts S1 and S2) and participated in periodic meetings with MDDs. In the present study, interstitial pneumonia with autoimmune features (IPAF) was included in the group of connective tissue diseases (CTDs).[19]

The central committee and the local centers reassessed undefined cases or cases with more than one possible diagnosis in an MDD. Several factors were considered in the initial diagnosis: the presence (or not) of CTD or relevant autoantibodies, systemic findings indicative of specific diseases, and biopsy reports from any site. Antinuclear antibodies (ANA), rheumatoid factor, anti-Ro, anti-LA, and anti-Jo1 were the most commonly measured antibodies. A positive family history was characterized by at least two cases of ILD among first-degree relatives, including the index case.[20] Because gastroesophageal reflux disease (GERD) is a common condition associated with various ILDs, an ILD was ascribed to GERD only when pH monitoring was abnormal in patients with bronchiolocentric fibrosis on SLB or HRCT in the absence of environmental exposure to organic antigens or CTD.

The distribution and predominance of tomographic findings and patterns were registered, as were age, gender, and environmental exposure history. Fibrosis identified by HRCT was characterized by reticular abnormalities with traction bronchiectasis or bronchiolectasis, with or without honeycombing. Drug-induced lung disease was characterized by the use of drugs potentially causing damage to the lungs preceding ILD, a compatible biopsy, or improvement after discontinuation of the suspected drugs.

CTDs were characterized in accordance with recent criteria.[21] Criteria suggested by the joint statement of the American Thoracic Society (ATS), the European Respiratory Society (ERS), and the World Association of Sarcoidosis and other Granulomatous Disorders statement were applied for the diagnosis of sarcoidosis.[22]

The diagnosis of fibrotic HP were based on criteria suggested by the designated CHEST Guideline.[23] Antigen eviction, followed by a noticeable improvement in ILD, was considered a criterion for supporting the diagnosis of HP.[24] HP with no antigen exposure was only considered if SLB or a transbronchial lung biopsy displayed typical findings on analysis. The diagnoses of IPF were those suggested by a 2018 official clinical practice guideline.[17] In cases with honeycombing or reticulation on HRCT and exposure to a known antigen, patients ≥ 60 years of age and those < 60 years of age, respectively, were considered to have IPF and fibrotic HP, but other findings were also considered, such as a mosaic pattern on HRCT, elevated lymphocytes in BALF, and biopsy results. In the absence of such findings, a diagnosis of unclassifiable ILD was made.

The clinical diagnosis of unclassifiable ILD was characterized by insufficient data for a specific final diagnosis after detailed MDD, loss of follow-up, contraindications or patient refusal to SLB, or disagreement between clinical, radiological, and histological data.

Exclusion criteria

Patients with ILDs secondary to neoplastic diseases, infections, or heart disease were excluded from the study, as were cases with no HRCT results available during evaluation from the time of diagnosis (± 6 months), cases with inadequate HRCT image quality, and in those cases with no clinical or functional data for review or no MDD.

Statistical analysis

A proportion formula was used to calculate the sample size.[24] Assuming that 20% of the subjects in the population have the factor of interest, the study would require a sample size of 246 participants for estimating the expected proportion with 5% absolute precision and 95% confidence.[25]

Categorical variables were expressed as absolute and relative frequencies with 95% confidence intervals. The chi-square test was used in order to compare the frequency of categorical variables among groups.

RESULTS

The most common final diagnoses (> 1%) are shown in Figure 1. The most common diagnosis was CTD-associated ILD (CTD-ILD; 26.8%; 95% CI: 24.5-29.2), followed by HP (23.2%; 95% CI: 21.0-26.6), IPF (14.1%; 95% CI: 12.0-16.0), unclassifiable ILD (10.2%; 95% CI: 9.0-12.0); and sarcoidosis (6.3%; 95% CI: 5.1-8.0). The most common CTD-ILD was systemic sclerosis (31.2%), followed by rheumatoid arthritis (17.6%), IPAF (14.7%), Sjögren's syndrome (10.9%), autoimmune myositis (9.9%), and others (15.7%). The characteristics of the main ILD groups are described in the supplementary material (Table S1), as are the distribution according to the center of origin (Table S2) and according to the main ILD (Table S3).

The general characteristics of the 1,406 patients who comprised the sample are described in Table 1. There was a slight predominance of the female gender

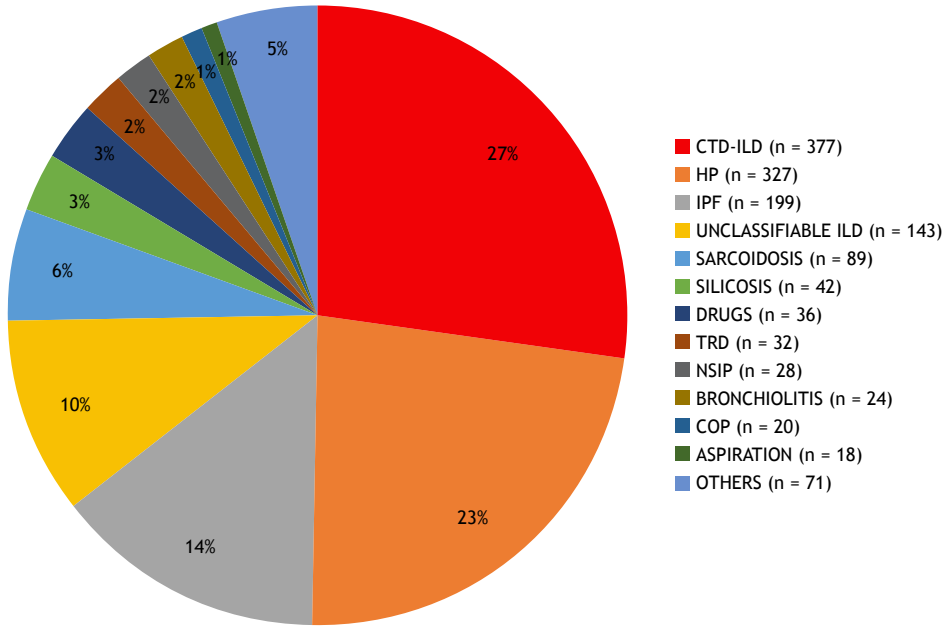

Figure 1. Distribution of the most commonly diagnosed interstitial lung diseases (ILDs) in a cohort of 1,406 cases in six centers in Brazil, 2013-2019. CTD-ILD: connective tissue disease-associated ILD; HP: hypersensitivity pneumonitis; IPF: idiopathic pulmonary fibrosis, TRD: tobacco-related disease; NSIP: nonspecific interstitial pneumonia; and COP: cryptogenic organizing pneumonia.

(54%). The presence of exposure to organic antigens were common; 747 cases had potential exposure to HP-related antigens, but only 327 (44%) of these had a final diagnosis of HP. The major types of organic antigen exposure were to avian antigens and molds (Figure 2). Five patients who reported no exposure to known antigens were diagnosed with HP based on typical HRCT findings and bronchiolocentric fibrosis identified by SLB, and so were another 5 by SLB findings only. The major inorganic antigen were to silica, in 58 (4.6%); metals, in 13 (1.0%); and asbestos, in 10 (0.8%). Of those exposed to silica, 53% had a final diagnosis of silicosis. Of 1,293 patients questioned about GERD symptoms, 49% reported the presence of at least one. The final diagnosis of fibrosis due to microaspiration was made in 15 cases, 10 of which had bronchiolocentric fibrosis identified by SLB.

The use of drugs or radiation was noted in 253 cases, but a final diagnosis of drug-induced lung disease was made in only 36 (14.2%) of these cases—in 7 of 51 patients treated with amiodarone (13.7%), in 2 of 52 (3.8%) of those treated with methotrexate, and in 2 of 77 (2.5%) of those treated with statins. Radiation was the cause in 5 cases, and nitrofurantoin, in 3. Other causes were present in 17 cases.

Positive autoantibodies were seen in 398 of the 1,219 cases tested for autoantibodies (32.6%)—in isolation, in 23.2%, and in combination, in 9.6% (Table S4). ANA at a titer of 1:≥ 320 were observed in 31.4%, 8.7%, and 4.4% of patients with CTD, HP, and IPF, respectively. Anti-Ro antibodies, antisynthetase antibodies (including Jo-1), and anti-Scl 70 antibodies were present in 66 (5.4%), in 27 (2.1%), and in 42 (3.4%) of cases, respectively.

A family history of ILD was evaluated in 1,112 patients and was present in 8% of cases. Other relatives with ILD were present in 41 of the 160 cases of IPF (26.6%), in 42 of the 308 cases of HP (13.6%), in 13 of the 85 cases of unclassifiable ILD (15.3%), and in 10 of 306 (3.3%) of the cases of CTD ($\chi^2 = 87.1$; $p < 0.001$).

Previous or current smoking was reported by 66.5% of patients with IPF, by 54.5% of those with unclassifiable ILD, and by 44.1%, 36.8%, and 32.9% of those with HP, CTD-ILD, and sarcoidosis, respectively ($\chi^2 = 126.3$; $p < 0.001$).

HRCT findings indicative of fibrosis were found in 1,036 patients (73.7%), as were consolidation or ground glass pattern without fibrosis in 212 (20.3%), honeycombing in 301 (21.4%), and mosaic pattern in 209 (14.9%).

Transbronchial biopsy was performed in 323 patients (22.9%), and final or compatible diagnoses were achieved in 106 of these cases: sarcoidosis, in 23; HP, in 33; CTD-ILD, in 13; silicosis, in 11, and other diagnoses, in 26. SLB was performed in 241 (17.1%) of the patients, and results were inconclusive in 10 (4.1%), including 1 with findings of terminal lung only. Of the 231 remaining cases submitted to SLB, 58 (25.1%) had bronchiolocentric fibrosis, 52 (22.5%) had usual interstitial pneumonia, 41 (17.8%) had classic HP, 18 (7.8%) had diffuse alveolar damage, and 10 (4.3%) had bronchiolitis. Of the 52 biopsies from other sites, 36 were compatible with sarcoidosis, as were 11, 2, and 3 compatible with CTD-ILD, vasculitis, and other

Table 1. General characteristics of a cohort of patients with incident interstitial lung diseases at six centers in Brazil between 2013 and 2019 (N = 1,406).[a]

Variable	Result
Age, years	61.1 ± 13.9
Sex, female	764 (54.3)
Smoker or former smoker (n = 1,395)	657 (47.1)
Family history of ILD (n = 1,112)	112 (8.0)
Exposure to organic agents (n = 1,336)	747 (55.9)
Exposure to inorganic agents (n = 1,266)	164 (12.9)
Gastroesophageal reflux (n = 1,293)	634 (49.0)
Drugs (n = 1,321)	253 (19.1)
"Velcro" crackles (n = 1,367)	726 (53.1)
FVC, % predicted (n = 1,208)	68.0 ± 19.2

ILD: interstitial lung disease. [a]Values expressed as n (%) or mean ± SD.

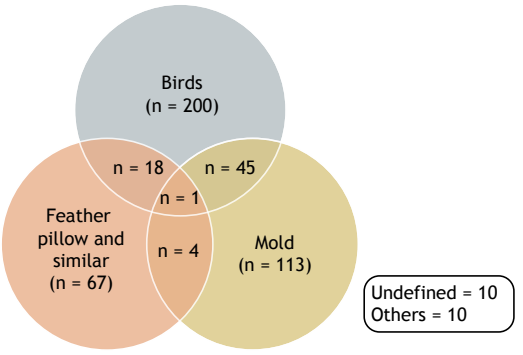

Figure 2. Distribution of the main types of exposure in the 327 cases of hypersensitivity pneumonitis.

diseases, respectively. Distribution of lung biopsy types by center is described in Table S5, as are the diagnostic yield of transbronchial biopsy in Table S6 and final diagnoses by SLB in Table S7.

Unclassifiable ILD was the final diagnosis in 10.2% of all cases. The mean age was 67.8 years; 67.4% were smokers or former smokers; and environmental exposure causing HP was present in 68.4% of cases, as were relevant autoantibodies in 13.8% and a familial history of ILD in 15.3%. With regard to HRCT findings, fibrotic disease was present in 90.9%, as was honeycombing in 20.3% of these. The main reasons for a diagnosis of unclassifiable ILD were incomplete data (in 55 cases), loss to follow-up (in 37 cases), and contraindications to SLB (in 35 cases). In 2 cases, SLB was inconclusive in 1 and unclassifiable in 1.

There was a statistically significant difference in final diagnoses among centers ($\chi^2 = 312.37$; $p < 0.001$), the proportion of CTD-ILD cases ranging from 15.0% to 38.2%; that of HP ranging from 13.2 to 36.5%; that of IPF ranging from 6.4% to 22.3%; that of unclassifiable ILD ranging from 3.1% to 18.9%, and that of sarcoidosis ranging from 0.0% to 9.4%.

The distribution of ILDs according to studies from several countries and to present study is shown in Figure 3. In New Mexico and in the Australasian registry,[6,12] IPF was the most common type of ILD, with 31.2% and 34% of cases, respectively. In Flanders and in most studies,[4,5,7,8,10,11,13] IPF (range, 18.2-38.6%) and sarcoidosis (range, 14.9-38.3%) were the most common ILDs. In studies carried out in China[3,9] and Saudi Arabia,[2] FPI and CTD-ILD were the most common ILDs. Only the Indian registry[1] showed that HP was the major ILD (47.3%), followed by CTD-ILD (13.9%).

DISCUSSION

In the present survey of 1,406 cases in six referral centers in Brazil, the most commonly diagnosed ILDs, in descending order, CTD-ILD, HP, IPF, unclassifiable ILD, and sarcoidosis.

IPF and sarcoidosis are the most common ILDs, but the frequency of the diagnoses of the various ILDs varies widely.[1-13] Several factors may explain these differences. One of these factors is the diagnostic criteria used for IPF, as these have changed in recent years.[16,17] The presence of autoimmune findings associated with the presence of ILD without definitive diagnostic criteria for a CTD was designated IPAF in 2015.[19] Today, it is recognized that there are several conditions within this group, including antisynthetase antibody syndrome, scleroderma sine scleroderma, and others. In the present study, IPAF was included in the classic CTD group.

In a single-center study conducted in Saudi Arabia, the most common ILDs were CTD-ILD (34.8%), followed by IPF (23.3%), sarcoidosis (20%), and HP (6.3%).[2] IPAF cases were included in the CTD group. Two studies conducted in China found that IPF was the most common diagnosis, followed closely by CTD-ILD.[3,9]

In the literature, the frequency of HP ranges from 1.5% to 47.3%, but in 9 of 13 studies,[1-13] this proportion was below 10%. An impressive proportion of 47.3% was observed in a prospective registry study undertaken in India, which included more than 1,000 patients.[1] Exposure to mold from the use of dirty air coolers or air conditioners or mold present at home, in addition to exposure to birds, were the most common types of exposure.[1]

A seminal study from Spain showed, in a case-cohort study, that in a sample of 46 patients with IPF, diagnosed according to the 2011 ATS/ERS/Japanese Respiratory Society (JRS)/*Asociación Latinoamericana de Tórax* (ALAT) guidelines, 20 (43%; 95% CI: 29-58%) had a subsequent diagnosis of chronic HP.[26] In a multicenter study, the diagnostic agreement among MDD teams in the diagnosis of IPF was good, but it was poor in that of HP.[27] This was attributed, at least in part, to the lack of guidelines for the diagnosis of HP. In 2020 and 2021, the ATS/JRS/ALAT and the *Chest* journal published guidelines for diagnosing HP, with some differences in the diagnostic criteria.[23,28]

In our study, antigens from molds, birds, and feather pillows were the most common causes for HP. Brazil is a country of continental dimensions with particular issues. Climatic conditions vary widely, and regions with high air humidity (forest and coastal regions and cities with frequent rain) increase mold exposure.[29]

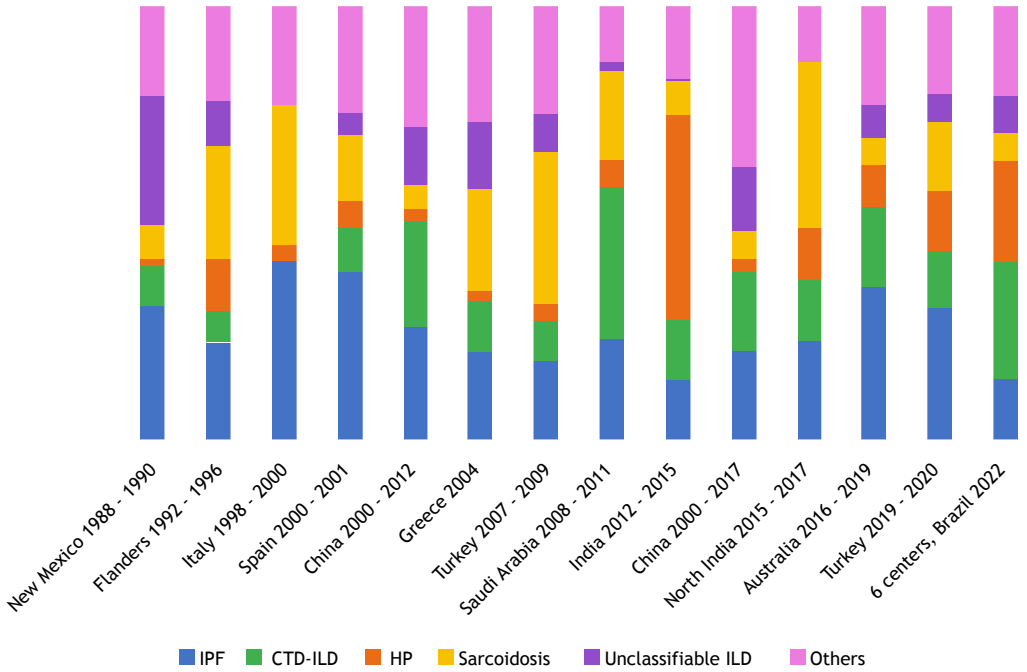

Figure 3. Distribution of interstitial lung diseases (ILDs) in different international prospective registry studies in comparison with the current study. IPF: idiopathic pulmonary fibrosis; CTD-ILD: connective tissue disease-associated ILD; and HP: hypersensitivity pneumonitis.

Socioeconomic conditions vary widely too. Many people live in poor housing with damp indoor spaces. In Brazil, there are about 41.3 million captive birds.[30]

In the literature, several studies show a large proportion of cases diagnosed as HP with no apparent exposure to antigens.[31] In contrast, in our study, 53% of the total number of patients with ILDs displayed potential exposures to HP-related antigens. However, the number of patients with a final diagnosis of HP in this group was only 44%. In our survey, only 10 (3%) of HP cases were diagnosed with no apparent antigen exposure.

Unclassifiable ILD comprises a heterogeneous group of diseases.[32] In the present study, the incidence of unclassifiable ILD was 10.2%. A meta-analysis of 22 studies reported that the prevalence of unclassifiable ILD was 11.9% (95% CI: 8.5-15.6), with a lower prevalence in centers that reported the use of a formal MDD (9.5% vs. 14.5%).[32] In our study, 15.3% of cases of unclassifiable ILD were cases of familial ILD. In many cases of familial ILD, atypical findings on HRCT and in pathology specimens can be identified, making the diagnosis more difficult.[33,34] The incidence of sarcoidosis was 6.3% in the present study. In comparison with prevalence studies, a lower proportion is expected due to a better prognosis of sarcoidosis.[35] Moreover, the incidence and prevalence of sarcoidosis vary across regions and even within countries.[35] In Brazil, the epidemiology of sarcoidosis is largely unknown.

In this study, ILD was attributed to drugs or radiation in 2.6% of cases. Although statins and methotrexate were used by many patients, less than 5% of the cases of ILD were considered to be caused by these drugs. The relationship between methotrexate and the lung seems to be twofold. Methotrexate can induce unpredictable subacute granulomatous pneumonitis, but it seems not to be associated with an increased risk of chronic fibrotic ILD in rheumatoid arthritis, and perhaps it even reduces that risk.[36] Symptoms of GERD were very common in ILD patients, but in only 15 cases was GERD the final diagnosis ascribed to microaspiration. In 10 cases, bronchiolocentric fibrosis was characterized by SLB.

Given the fact that ILD may complicate the course of any CTD, and that ILD can precede signs of CTD, and these signs can be subtle, an underlying CTD should be ruled out in every ILD, even if clinical suspicion is low or absent. Autoantibody screening should be performed in patients with ILD with an unclear diagnosis after careful clinical evaluation. Although autoantibodies can be found in conditions other than CTD, ANA and rheumatoid factor in significant levels can be seen in HP, and ANA can also be seen in patients with IPF.[37,38] Recently, greater importance has been given to the panel of autoantibodies related to autoimmune myositis that are frequently associated with ILD. However, at the time of data collection, this panel was scarcely available.[39]

Registry studies have strengths and limitations. The main advantage is that data from a large number of cases are available, making it possible to estimate the incidence of diseases within a narrow margin of error, especially when well-defined criteria are applied to

the diagnosis and reviewed by a central committee, as was the case in the current study; however, some limitations should be noted. First, data were collected in a "real-life" scenario, and such data were missing in several patients. Second, the patients were treated at referral centers for ILDs, which may have resulted in selection bias. The variation across centers in the proportions for individual entities deserves future studies.

In conclusion, in this sample of patients in Brazil, the most common types of ILD were, in decreasing order, CTD-ILD, HP, IPF, and sarcoidosis. In 10% of cases, the disease was unclassifiable. These results highlight the need for close collaboration between pulmonologists and rheumatologists, the need for detailed questioning of patients regarding potential exposures that may result in HP, the importance of public health campaigns to make people aware of the dangers of such exposures, and the need for more stringent workplace regulations to protect employees from environmental exposures. Understanding the epidemiology of ILDs in Brazil allows the health care system to make informed decisions about mastering allocation of resources to meet local needs, which are of particular importance in the era of emerging ILD therapies, which often have high costs.[40]

AUTHOR CONTRIBUTIONS

SLKM and CACP: conceptualization, data curation, formal analysis, investigation, project administration, and drafting, reviewing, and editing of the manuscript. MRS and EVM: formal analysis (support), and reviewing and editing of the manuscript. FCVF, MACM, FMAB, TAP, and GCJ: data collection. All of the authors read and approved the final version of the manuscript.

CONFLICTS OF INTEREST

None declared.

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