RESEARCH ARTICLE

Received: 06 AUG 2025 | Accepted: 11 SET 2025 | **DOI:** https://doi.org/10.57849/ulisboa.fm.jscml.0000037.2026

JORNAL DA SOCIEDADE DAS CIÊNCIAS MÉDICAS DE LISBOA

Interstitial Lung Disease in Mixed Connective Tissue Disease: A Single-Center Cohort Study

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ABSTRACT: **Background**: Mixed connective tissue disease is a rare systemic autoimmune condition characterized by overlapping features of different connective tissue diseases and the presence of anti-U1-ribonucleoprotein antibodies. Its association with interstitial lung disease represents one of the main causes of morbidity and mortality in affected patients. **Objective:** To characterize the clinical, immunological, and radiological phenotype of patients with mixed connective tissue disease-associated interstitial lung disease, and to evaluate the evolution of pulmonary function over time. **Methods:** All patients had at least one high-resolution computed tomography scan and two pulmonary function tests available during the 48 ± 12 months follow-up period. The extent of lung involvement was assessed using semi-quantitative visual evaluation of high-resolution computed tomography scans. Severe progression was defined as an annual ≥10% absolute decline in forced vital capacity or a ≥15% absolute decline in diffusion capacity of the lungs for carbon monoxide. **Results:** Thirteen patients were included. Raynaud's phenomenon, puffy fingers, and arthritis were the most common manifestations. Anti-SSA/Ro antibodies were detected in 4 patients. Dyspnea was reported in 7 patients. The predominant radiological pattern was nonspecific interstitial pneumonia, present in 9 patients. Three patients exhibited interstitial lung disease involvement >20%. At baseline, mean predicted FVC and DLCO values were significantly reduced (72.7% ± 17.3% and 58.0% ± 11.9%, respectively). Throughout follow-up, there was a mean increase of 2.5% ± 8.3% in forced vital capacity and a mean decrease of 2.2% ± 11.0% in total lung capacity; diffusion capacity of the lungs for carbon monoxide remained unchanged, with a mean variation of -0.5% ± 10.6%. A total of two patients experienced major interstitial lung disease progression during the follow-up period. **Conclusions:** In this cohort, pulmonary function remained relatively stable over time, with few cases of severe pulmonary function decline, suggesting a slow progression of interstitial lung disease in mixed connective tissue disease.

KEYWORDS: Mixed Connective Tissue Disease; Interstitial Lung Disease; Progression; Prognosis

INTRODUCTION

Mixed connective tissue disease (MCTD) is a rare systemic autoimmune disease characterized by overlapping features of systemic lupus erythematosus, dermatomyositis, systemic sclerosis, and rheumatoid arthritis. MCTD is associated with the presence of specific autoantibodies, namely anti-U1-ribonucleoprotein (anti-U1-RNP) antibodies, which serve as key immunological markers for diagnosis[1]. Raynaud's phenomenon (RP) is among the most prevalent clinical manifestations, alongside puffy fingers[2].

No diagnostic criteria have been universally established for MCTD; however, four classification criteria are commonly used: those proposed by Sharp, Kasukawa, Alarcón-Segovia, and Khan[3,4].

Interstitial lung disease (ILD) represents a severe complication of connective tissue diseases and significantly impacts morbidity and mortality[5]. In MCTD, pulmonary involvement affects up to 78% of patients, with dyspnea being the most frequently reported symptom[6]. Other respiratory symptoms may include dry cough, pleuritic chest pain, hemoptysis, and wheezing.

Nonspecific interstitial pneumonia (NSIP) is the most common radiological pattern, observed in up to 90% of patients. Usual interstitial pneumonia and organizing pneumonia patterns are observed less frequently[3,7]. Pulmonary function tests (PFTs) may reveal a reduced diffusing capacity for carbon monoxide (DLCO), forced vital capacity (FVC), and forced expiratory volume in one second (FEV1), consistent with a restrictive ventilatory pattern[8].

ILD and pulmonary hypertension (PH) are the two leading causes of mortality in patients with MCTD, with longer disease duration correlating with worse outcomes[3]. Several factors have been identified as associated with the presence of ILD in patients with MCTD, including older age, skin thickening, upper gastrointestinal symptoms, FVC <80%, DLCO <80%, anti-topoisomerase (Scl-70) autoantibodies, anti-SSA/Ro antibodies, cryoglobulinemia, and elevated C-reactive protein. Digital ulcers (DU) were identified as a risk factor for FVC decline >10% and mortality was higher in patients with MCTD-associated ILD (MCTD-ILD)[9].

MCTD remains a rare and understudied condition in the literature. Its association with ILD is even less common, and consequently, few studies have evaluated the clinical progression and long-term prognosis of affected patients.

This study aims to characterize the phenotype of MCTD-ILD at the time of diagnosis and to evaluate its evolution over time in a cohort of patients followed at our tertiary center.

METHODS

This was a retrospective, single-center cohort study conducted in the Rheumatology Department of ULS Santa Maria, Centro Académico de Lisboa, Portugal.

Inclusion criteria were as follows:[1] age ≥18 years at diagnosis;[2] a diagnosis of MCTD fulfilling one of the four accepted classification criteria (Sharp, Kasukawa, Alarcón-Segovia, or Kahn) and positive anti-U1-RNP antibodies;[3] diagnosis of ILD by high-resolution computed tomography (HRCT) at baseline;[4] availability of at least two PFTs, one at diagnosis and one during follow-up.

ILD was diagnosed based on the presence of typical HRCT features, including ground-glass opacities, consolidations, reticular pattern, interlobular septal thickening, traction bronchiectasis, or honeycombing. Imaging findings were not standardized and were reported according to our local radiology team[10,11].

Clinical data were extracted in a standardized manner from medical records, including sex, smoking status (current, passive, or never smoker), age at MCTD diagnosis, age at ILD diagnosis, interval between MCTD and ILD diagnoses, clinical manifestations, PFTs, immunological profile, and treatment. Baseline was defined as the time of ILD diagnosis ± 12 months.

Clinical features assessed included RP, DU, puffy fingers, limited or diffuse cutaneous thickening, arthritis, myositis, upper and/or lower gastrointestinal involvement, and PH.

Lung involvement was evaluated by the presence of dyspnea and through HRCT (to assess ILD pattern and extent) and PFTs, including FVC, total lung capacity (TLC) and DLCO, all expressed as a percentage of the predicted value. These parameters were assessed at ILD diagnosis and annually thereafter (± 6 months), when available.

The immunologic profile comprised the analysis of antinuclear antibodies (ANA), anti-double-stranded DNA (dsDNA), anti-SSA/Ro, anticentromere, anti-Scl-70, anti-cyclic citrullinated peptide (CCP), and anti-polymyositis/scleroderma (Pm/Scl) autoantibodies.

Recorded immunosuppressive therapies included glucocorticoids, hydroxychloroquine (HCQ), methotrexate (MTX), mycophenolate mofetil (MMF), azathioprine (AZA), rituximab (RTX), cyclosporine, le-

flunomide, tacrolimus, tumor necrosis factor inhibitors (TNF inhibitors), belimumab, cyclophosphamide, and intravenous immunoglobulin (IVIG).

ILD severity – ILD extent was assessed using semi-quantitative visual evaluation of HRCT scans, with lung involvement categorized as mild (<10%), moderate (10-20%), or severe (>20%), based on the extent of the lesions. The >20% threshold was selected as it represents the most commonly used cutoff in the literature[12].

ILD progression during Follow-up – Annual assessment periods were analyzed to classify ILD functional progression throughout the follow-up period. Patients were stratified into three subgroups according to annual changes in predicted FVC and DLCO, assessed over a follow-up of 48 ± 12 months. Severe ILD progression was defined as an annual ≥10% absolute decline in FVC or ≥15% absolute decline in DLCO. Moderate ILD progression was defined as an annual 5-10% decline in FVC or a 10-15% decline in DLCO. Pulmonary function was considered stable or improved when the annual variation in FVC and DLCO was less than 5% and 10%, respectively, regardless of whether this represented a decrease or an increase from the previous assessment.

Ethical considerations – This study was approved by the Ethics Committee of Centro Académico de Medicina de Lisboa (CAML) (reference number 319/25), in accordance with the principles of the Declaration of Helsinki.

Statistical Analysis – Data normality was assessed using the Shapiro-Wilk test. Continuous variables were reported as mean ± standard deviation (SD) for normally distributed data or median [interquartile range, IQR] for non-normally distributed data.

RESULTS

BASELINE ANALYSIS

Study Population And Patient Characteristics – The study population consisted of 13 patients with MCTD-ILD. Of these, 12 were female (92.3%), and 1 patient (7.7%) reported either active or passive tobacco exposure. At the time of MCTD diagnosis, the median age was 35.0 [16.5] years, while the median age at MCTD-ILD diagnosis was 37.0 [14.0] years. The median time from MCTD to MCTD-ILD diagnosis was 14.0 [21.0] months (see Table 1).

TABLE 1. Patient characteristics

	MCTD-ILD (n=13)
Demographics	
Female, n (%)	12 (92.3)
Smoking, n (%)	1 (7.7)
Clinical features	
Age at diagnosis of MCTD, years, median [IQR]	35.0 [16.5]
Age at diagnosis of ILD, years, median [IQR]	37.0 [14.0]
Time from MCTD to MCTD-ILD diagnosis, months, median [IQR]	14.0 [21.0]
Raynaud's phenomenon, n (%)	12 (92.3)
Digital ulcers, n (%)	5 (38.5)
Puffy hands/fingers, n (%)	9 (69.2)
Limited skin thickening, n (%)	1 (7.7)
Diffuse skin thickening, n (%)	0 (0.0)
Arthritis, n (%)	9 (69.2)
Myositis, n (%)	4 (30.8)
Upper and lower gastrointestinal tract involvement, n (%)	1 (7.7)
Pulmonary hypertension, n (%)	1 (7.7)
Pulmonary features	
NSIP, n (%)	9 (69.2)
Dyspnea, n (%)	7 (53.8)
Extent of CT findings	
<10%, n (%)	3 (23.1)
10-20%, n (%)	7 (53.8)
>20%, n (%)	3 (23.1)
FVC (%), mean ± SD	72.7 ± 17.3
TLC (%), mean ± SD	78.4 ± 14.7
DLCO (%), mean ± SD	58.0 ± 11.9
Biological features	
ANA, n (%)	13 (100.0)
Anti-dsDNA, n (%)	2 (15.4)
Anti-SSA/Ro, n (%)	4 (30.8)
Anticentromere, n (%)	0 (0.0)
Anti-Scl-70, n (%)	0 (0.0)
Anti-CCP, n (%)	2 (15.4)
Anti-Pm/Scl, n (%)	0 (0.0)
Treatment	
Prednisolone, n (%)	12 (92.3)
Hydroxychloroquine, n (%)	9 (69.2)
Methotrexate, n (%)	8 (61.5)
Mycophenolate mofetil, n (%)	5 (38.5)
Azathioprine, n (%)	3 (23.1)
Rituximab, n (%)	2 (15.4)
Cyclophosphamide, n (%)	0 (0.0)
Others, n (%)	3 (23.1)

Legend: IQR = interquartile range; **SD** = standard deviation; **ANA** = antinuclear antibody; **Anti-CCP** = anti-cyclic citrullinated peptide antibody; Anti-dsDNA = anti-double-stranded DNA antibody; Anti-Pm/Scl = anti-polymyositis/scleroderma antibody; Anti-SSA/Ro = anti-Sjögren's syndrome-related antigen A/Ro antibody; CT = computed tomography; DLCO = diffusing capacity of the lungs for carbon monoxide; FVC = forced vital capacity; ILD = interstitial lung disease; MCTD = mixed connective tissue disease; NSIP = nonspecific interstitial pneumonia; TLC = total lung capacity.

Regarding clinical features, RP was the most frequent manifestation, observed in 12 patients (92.3%), followed by puffy fingers and arthritis in 9 patients (69.2%). DU were documented in 5 patients (38.5%) and myositis in 4 patients (30.8%). Limited cutaneous thickening was present in 1 patient (7.7%), whereas diffuse cutaneous thickening was not observed in any patient. Upper and lower gastrointestinal tract involvement, as well as PH, were each reported in one patient (7.7%).

Baseline Pulmonary Involvement – Regarding clinical manifestations, dyspnea was reported by 7 patients (53.8%). On HRCT, the most frequently identified lung pattern was NSIP, observed in 9 patients (69.2%).

Regarding the extent of radiological abnormalities on HRCT, 3 patients (23.1%) had less than 10% involvement, 7 patients (53.8%) had 10–20% pulmonary involvement and 3 patients (23.1%) had more than 20% involvement.

PFTs showed a mean FVC of 72.7% ± 17.3%, mean TLC of 78.4% ± 14.7%, and mean DLCO of 58.0% ± 11.9%.

Immunologic Profile – All 13 patients (100%) tested positive for ANA. Anti-SSA/Ro antibodies were positive in 4 patients (30.8%). Anti-CCP antibodies were positive in 2 patients (15.4%), as were anti-dsDNA antibodies (15.4%). All patients tested negative for anticentromere, anti-Scl-70, and anti-Pm/Scl antibodies.

Treatment – Prednisolone was the most frequently used immunosuppressant, prescribed to 12 patients (92.3%), followed by HCQ, prescribed to 9 patients (69.2%). MTX was prescribed to 8 patients (61.5%) and MMF to 5 patients (38.5%). The least commonly used immunosuppressants were AZA, prescribed to 3 patients (23.1%), and RTX, prescribed to 2 patients (15.4%).

LONGITUDINAL PULMONARY FUNCTION ANALYSIS

Overall Cohort Analysis (Baseline To Last Visit) – The median follow-up period was 40.0 [30.0] months.

From baseline until the last available data time point, we observed an overall increase in mean FVC by 2.5% ± 8.3%, a decrease in TLC, of 2.2% ± 11.0%, and stability in DLCO, with a variation of -0.5% ± 10.6% (see Table 2).

TABLE 2. Changes in pulmonary function parameters in MCTD-ILD until the last visit.

Variables	Baseline	Last Visit	Variation
FVC (%), mean	72.7	75.2	+2.5 ± 8.3
TLC (%), mean	78.4	76.2	-2.2 ± 11.0
DLCO (%), mean	58.0	57.6	-0.5 ± 10.6

Time Point Specific Analysis – The longitudinal analysis considered five time points: at diagnosis, and at 12, 24, 36, and 48 months of follow-up. Data availability varied across time points (13 patients at baseline, 9 at 12 months, 5 at 48 months).

12-Month Early Follow-Up Analysis – At 12 months of follow-up, an improvement in pulmonary function was observed. Regarding general data available for this time point, mean FVC increased from 72.7% ± 17.3% to 78.6% ± 15,6% (corresponding to an absolute change of 5.9% ± 8.9%), as well as mean TLC, which rose from 78.4% ± 14.7% to 80.2% ± 14.7% (1.8% ± 5.0%). However, mean DLCO decreased from 58.0% ± 11.9% to 56.7% ± 9.2% (-1.3% ± 12.9%).

By this time point, 1 patient experienced severe ILD progression, with predicted DLCO decreasing from 88% to 54%, which corresponds to an absolute decrease of 34%; 2 patients experienced moderate ILD progression and 6 patients experienced stable or improved ILD disease.

48-Month Late Follow-Up Analysis – At 48 months of follow-up, FVC showed a mean value of 71.6% ± 11.8%, reflecting an absolute change of -1.1% ± 9.0% from baseline. TLC decreased to a mean value of 71.4% ± 9.7%, representing an absolute change of -7.0% ± 11.7%. DLCO reached 56.6% ± 7.4%, corresponding to a change of -1.4% ± 1.5%.

Longitudinal changes in lung function at different time points, including 24 and 36 months, are presented in Table 3 and Figure 1.

TABLE 3. Pulmonary function parameters evolution over time.

Parameter	Baseline n=13	12 Months n=9	24 Months n=7	36 Months n=4	48 Months n=5
FVC (%)	72.7 ± 17.3	78.6 ± 15.6	77.4 ± 14.1	*73.3 ± 10.2*	*71.6 ± 11.7*
TLC (%)	78.4 ± 14.7	80.2 ± 14.7	77.9 ± 18.1	*78.8 ± 13.5*	*71.4 ± 9.7*
DLCO *(%)*	*58.0 ± 11.9*	*56.7 ± 9.2*	*59.6 ± 12.7*	*64.7 ± 5.5*	*56.6 ± 7.4*

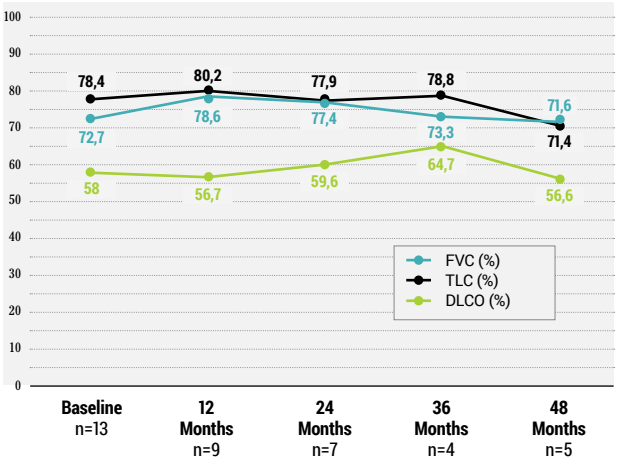

FIGURE 1. Evolution of FVC (%), TLC (%) and DLCO (%) over time

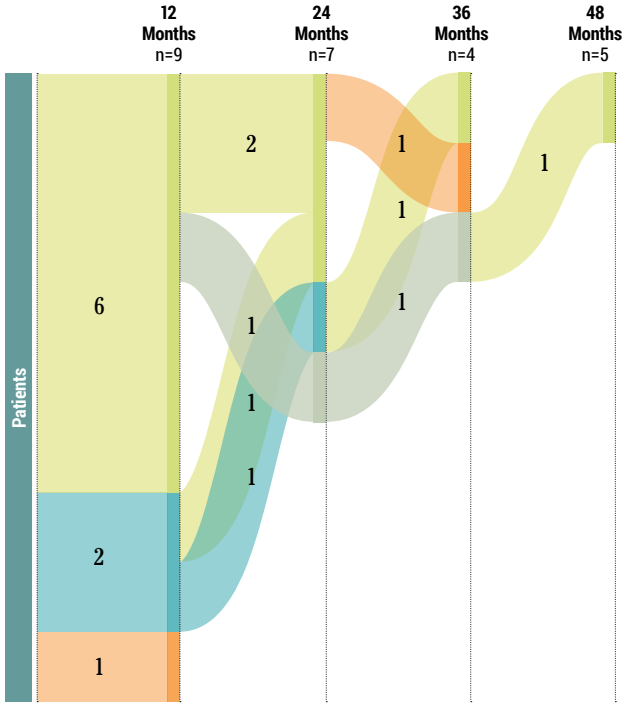

FIGURE 2. Sankey diagram showing annual transitions in ILD progression status over 48 ± 12 months of follow-up. Flow width represents the number of patients in each category. Categories include stable or improved disease (green), moderate progression (orange), severe progression (red), and missing data (gray).

Disease Progression Classification – Annual assessment periods were analyzed to classify ILD functional progression throughout the follow-up period and a total of 16 patient-assessment periods were analyzed.

As stated in the Methods section, disease progression was defined as follows:

- ***Severe:*** ≥10% decline in FVC or ≥15% decline in DLCO;
- ***Moderate:*** 5-10% decline in FVC or 10-15% decline in DLCO;
- ***Stable/Improved:*** <5% decline or any improvement in FVC or <10% decline or any improvement in DLCO.

Of the 16 analyzable annual periods, functional progression was classified as follows (see Figure 2):

- ***Severe progression:*** 2 periods (12.5%), occurring in 2 different patients at different time points;
- ***Moderate progression:*** 3 periods (18.8%);
- ***Stable/Improved:*** 11 periods (68.8%).

MORTALITY

No deaths were documented during the follow-up period.

DISCUSSION

ILD is a clinically significant manifestation of MCTD, standing as a major contributor to long-term morbidity and mortality[5]. In this single-center retrospective cohort study, we analyzed the clinical, radiological, and functional characteristics of 13 patients with MCTD-ILD over a median follow-up period of 40.0 [30.0] months, aiming to characterize the trajectories of pulmonary function in this population and identify potential patterns of disease progression. Given the rarity of MCTD and the even lower frequency of MCTD-ILD, our findings provide valuable insights to an underexplored area of the literature.

In this cohort of 13 patients, consistent with the known clinical spectrum of this disease, RP, puffy fingers, and arthritis were the most prevalent clinical features[2]. Myositis and DU were less frequently observed, and gastrointestinal involvement or PH were rare.

From a pulmonary standpoint, dyspnea was reported in 53.8% of patients, underscoring its relevance as a key clinical symptom of ILD. Regarding imaging findings, the NSIP pattern was the most common, identified in 69.2% of patients, aligning with current evi-

dence that this is the predominant radiologic pattern in MCTD-ILD[3]. As for PFTs, mean predicted FVC and DLCO values at diagnosis were already significantly reduced (72.7% ± 17.3% and 58.0% ± 11.9%, respectively), findings that reflect a restrictive ventilatory pattern, and suggest that ILD was functionally advanced at the time of diagnosis.

In the longitudinal analysis of pulmonary function, overall variations were minimal, with a general trend toward stability with minimal changes in FVC and DLCO. However, a more detailed evaluation of mean values at each time point revealed a biphasic trajectory. An initial phase of mild functional improvement was observed at 12 and 24 months, especially in FVC and TLC. This was followed by a subsequent gradual decline in all evaluated parameters, from 36 months onward, becoming more evident in the last year of follow-up. This pattern may reflect an initial positive therapeutic response to early diagnosis and prompt initiation of immunosuppressive treatment, followed by a stable course of ILD. The initial improvement may represent a "window of opportunity" during which MCTD-ILD is more responsive to immunomodulatory therapy. These variations should be interpreted with caution due to the small sample size and the already impaired pulmonary function at baseline.

Despite the overall trends observed in mean pulmonary function, individual trajectories varied considerably. While some patients experienced a decline in pulmonary function, others remained stable, and a few even improved. The overall prognosis in our cohort appeared favorable, with only a minority of patients exhibiting major functional decline and no deaths during follow-up. During follow-up, only two patients fulfilled the criteria for severe ILD progression. There were also three episodes of moderate progression, while the majority of assessments (eleven episodes) indicated stability or improvement in ILD progression.

This study emphasizes the heterogeneity of MCTD-ILD progression: while some patients stabilize or improve, others experience decline, underscoring the need for extended and regular monitoring beyond the first years, even in cases that initially appear stable. Early recognition of functional deterioration and timely therapeutic adjustment may have an important role in mitigating irreversible pulmonary damage.

More than one-third of patients had DU, which has been reported as a risk factor for ILD progression. In out cohort, most patients nonetheless had mild or stable disease. Similarly, while anti-SSA/Ro antibodies have been linked to severe ILD in MCTD, most patients in our cohort maintained mild or stable disease. Although baseline reduced FVC and DLCO are considered risk factors for ILD in MCTD, our cohort exhibited these values while maintaining a favorable pulmonary course. This apparently favorable pulmonary outcome may reflect the overall low prevalence of other high-risk features: cutaneous skin thickening was uncommon, advanced age was rare, only one patient had upper gastrointestinal involvement, and no patients had anti-Scl-70, an antibody associated with worse pulmonary outcomes[13]. In fact, among the two patients who experienced severe disease progression, neither had anti-SSA/Ro antibodies, and only one had a prior history of DU (data not shown).

When compared to the study from Kawano-Dourado et al.[14], which followed 39 patients with MCTD-ILD over 10 years, our findings regarding FVC are consistent with the ones shown in this study, supporting the overall stability of this parameter over time. The relative preservation of PFTs values in both cohorts aligns with existing literature describing MCTD-ILD progressing less aggressively than other ILD subtypes.

This study has several limitations. First, the small sample size, although expected due to the rarity of the disease. The second limitation relates to the study design, single-center and retrospective, which restricts the generalizability of findings. In addition, incomplete data, particularly at later time points, which may have introduced bias or underestimated the real rate of ILD progression. A final limitation is that the study did not explore the impact of specific or cumulative immunosuppressive regimens on pulmonary function trajectory.

In spite of these limitations, this study contributes to the scarce literature on MCTD-ILD, as well as reinforces existing data regarding its pulmonary course. The findings support the concept of heterogeneity of disease progression at the individual level and highlight the importance of personalized monitoring strategies. Lastly, future prospective multicentric studies are needed to validate these findings and to assess the impact of therapeutic interventions, including antifibrotic agents, in patients with progressive phenotypes of MCTD-ILD.

CONCLUSION

This study allowed for a detailed characterization of MCTD-ILD patients followed at our center, the Department of Rheumatology of ULS Santa Maria, and, more importantly, the evolution of their respiratory function over a mean follow-up period of 48 ± 12 months.

Baseline PFTs revealed a significant restrictive pattern. However, during follow-up, results showed that pulmonary function remained relatively stable. Individual analysis of patients demonstrated notable heterogeneity in disease progression, with the majority of cases showing stability or improvement, and only a few experiencing significant ILD progression.

These findings suggest that ILD progression in MCTD is generally slow in our cohort. The data obtained contribute to the understanding of this rare entity and reinforces the need for prospective multicentric studies to further explore the role of different therapeutic regimens.

Author Contributions: *Conceptualization, K.D.H, F.C., G.B. and J.E.F.; methodology, F.C., I.S. and G.B.; formal analysis, K.D.H., F.C., I.S. and G.B.; investigation, K.D.H, F.C., G.B., and N.K.; writing - original draft preparation, K.D.H.; writing - review and editing, G.B. and J.E.F.; visualization, F.C., I.S. and N.K..; supervision, G.B. and J.E.F. All authors have read and agreed to the published version of the manuscript.*

Funding: *The authors received no specific funding for this work.*
Ethical Compliance: *This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee, with reference number 319/25, of the Centro Académico de Medicina de Lisboa (CAML) signed off on 26 November 2025.*
Written informed consent was waived by the Ethics Committee considering the retrospective nature of this study and the appropriate measures that were taken to ensure compliance with the General Data Protection Regulation (GDPR) (EU).
Conflicts of Interest: *The authors declare no conflicts of interest.*
Data Availability Statement*: The data underlying this article will be shared on reasonable request to the corresponding author. The data are not publicly available due to data protection.*

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