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Original Article

Spirometric Abnormalities in Adult Mixed Connective Tissue Disease and Their Association with Disease Duration, Activity, And Severity: An Analytical Case–Control Study

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ABSTRACT

Background: Mixed Connective Tissue Disease (MCTD) is a systemic autoimmune rheumatic disorder characterized by overlapping features of systemic lupus erythematosus, systemic sclerosis, and inflammatory myopathy, along with anti-U1 ribonucleoprotein antibodies. Pulmonary involvement, particularly interstitial lung disease and pulmonary vascular complications, is a major determinant of morbidity and survival. However, limited data exist correlating spirometric abnormalities with disease duration, activity, and severity in adult MCTD patients.
Objective: To evaluate spirometric abnormalities in adult patients with MCTD and analyze their association with disease duration, disease activity, and disease severity.
Methods: This hospital-based analytical case–control study included 120 participants: 60 adult MCTD patients and 60 age- and sex-matched healthy controls. Spirometry was performed according to ATS/ERS guidelines. Parameters assessed included forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), FEV_1/FVC ratio, and peak expiratory flow rate (PEFR). Spirometric patterns were classified as normal, restrictive, obstructive, or mixed. Associations between spirometric parameters and disease duration, activity, and severity were evaluated using appropriate statistical tests, with $p < 0.05$ considered significant.
Results: Baseline demographic characteristics were comparable between groups. MCTD patients demonstrated significantly higher prevalence of dyspnea (56.7% vs 10.0%, $p < 0.001$), fatigue (56.7% vs 8.3%, $p < 0.001$), and cough (25.0% vs 5.0%, $p = 0.002$). Spirometric assessment revealed significantly reduced FVC, FEV_1, and PEFR in MCTD patients compared to controls ($p < 0.001$), with relative preservation of FEV_1/FVC ratio, indicating a predominantly restrictive ventilatory defect. Increasing disease duration correlated with declining FVC and FEV_1 ($p < 0.05$). Higher disease activity and severity were significantly associated with lower spirometric indices ($p < 0.05$).
Conclusion: Adult MCTD patients exhibit significant restrictive spirometric impairment associated with disease chronicity and inflammatory burden. Routine spirometric surveillance may facilitate early detection of pulmonary involvement and improve clinical management.

Keywords*:* Mixed Connective Tissue Disease; Spirometry; Interstitial Lung Disease; Pulmonary Function; Disease Activity; Restrictive Ventilatory Defect.

INTRODUCTION

Mixed connective tissue disease (MCTD) is a systemic autoimmune rheumatic disorder characterized by overlapping clinical features of systemic lupus erythematosus, systemic sclerosis, and idiopathic inflammatory myopathy, together with high-titer anti-U1 ribonucleoprotein (U1-RNP) antibodies [1,2]. Since Sharp first described the syndrome in 1972, MCTD has remained clinically relevant because many patients demonstrate a recognizable overlap phenotype and a

disease trajectory that may differ from "pure" connective tissue diseases, although classification remains challenging due to phenotypic evolution and imperfect diagnostic boundaries [3,4]. Several classification approaches, including those proposed by Kasukawa and Alarcón-Segovia, emphasize the presence of clinical overlap manifestations along with anti-U1-RNP positivity and continue to guide patient selection in clinical and observational studies [5].

Although MCTD is relatively uncommon and clinically heterogeneous, prognosis is largely determined by internal organ involvement rather than musculoskeletal or cutaneous manifestations alone [4–6]. Among the various organ systems affected, pulmonary involvement represents one of the most frequent and prognostically significant domains in adult patients. Lung manifestations in MCTD include interstitial lung disease (ILD), pulmonary arterial hypertension (PAH), pleural disease, aspiration-related lung injury secondary to esophageal dysmotility, respiratory muscle weakness, and small airway dysfunction [7–12]. Importantly, pulmonary involvement may develop insidiously and remain clinically silent in early stages, progressing gradually before overt respiratory symptoms become evident, thereby necessitating systematic screening and surveillance.
Interstitial lung disease is particularly common in MCTD and has been repeatedly identified as a major contributor to functional limitation and long-term morbidity. High-resolution computed tomography (HRCT) studies have demonstrated variable patterns and extents of parenchymal lung involvement, which may not correlate perfectly with symptoms early in the disease course [7–9]. In the nationwide Norwegian MCTD cohort, ILD prevalence and severity were systematically evaluated, reinforcing that ILD is a central feature rather than a rare complication of the disease [7]. Subsequent studies from different populations have confirmed a substantial ILD burden and highlighted heterogeneity in disease course, ranging from mild stable abnormalities to clinically significant fibrosis with measurable physiological impairment [9–11]. These observations underscore that pulmonary parenchymal involvement is both common and clinically meaningful in adult MCTD.

In addition to ILD, pulmonary vascular disease—particularly pulmonary arterial hypertension—constitutes another major determinant of outcome. PAH is recognized as one of the most severe complications of MCTD and a contributor to premature mortality. Importantly, pulmonary vascular involvement may present with disproportionate dyspnea despite relatively preserved spirometric volumes in early stages, making structured physiological assessment essential for comprehensive evaluation [13]. Furthermore, ILD and PAH may coexist in MCTD, producing complex cardiopulmonary interactions that significantly influence functional capacity and prognosis [13].

Given the central role of pulmonary involvement in determining morbidity and survival, objective assessment of lung function is critical in the evaluation and longitudinal follow-up of patients with MCTD. Spirometry remains the most accessible, reproducible, and widely used pulmonary function test for screening and monitoring connective tissue disease–associated lung involvement. When performed according to international technical standards, spirometry provides objective quantification of ventilatory impairment and facilitates early detection of restrictive physiology suggestive of ILD, as well as obstructive or mixed patterns that may reflect airway involvement [14]. The 2019 American Thoracic Society/European Respiratory Society (ATS/ERS) update on spirometry standardization emphasizes test quality, acceptability, repeatability, and appropriate interpretation, ensuring reliability and comparability of results [15]. Contemporary interpretive strategies also advocate the use of lower limits of normal and globally derived reference equations, such as GLI-2012, to improve diagnostic accuracy across diverse populations [16].

In MCTD, spirometry is valuable not only for baseline phenotyping but also for longitudinal monitoring. A decline in forced vital capacity (FVC) may signal progression of ILD, whereas preserved lung volumes in the presence of worsening dyspnea may prompt evaluation for pulmonary vascular disease or other non-ventilatory causes of exercise limitation [13]. Moreover, MCTD often follows a fluctuating clinical course with periods of remission and relapse. Although no universally validated disease-specific activity index exists, several cohorts have operationalized disease activity using instruments borrowed from component diseases, such as SLEDAI-2K and EUSTAR activity indices, to facilitate longitudinal assessment [6]. Importantly, inflammatory activity and irreversible organ damage represent distinct constructs in systemic rheumatic diseases, and pulmonary impairment may reflect either active inflammatory injury or chronic fibrotic and vascular remodeling.

Long-term cohort studies have shown that many patients maintain relatively low to moderate activity scores over time, yet clinically significant organ damage—particularly pulmonary—may still accumulate [6]. Within this framework, spirometry provides a functional "snapshot" of disease severity at a given time point, while serial measurements allow detection of progression or stabilization [17]. Emerging guidance in connective tissue disease–associated ILD further emphasizes systematic screening and follow-up with pulmonary function tests in at-risk populations, strengthening the rationale for routine spirometric surveillance in MCTD [18].

Despite increasing recognition of pulmonary involvement as a key determinant of outcome, limited data are available correlating spirometric parameters with disease duration, disease activity, and overall disease severity in adult MCTD

patients. Understanding these relationships is clinically important for risk stratification, early identification of high-risk individuals, and optimization of follow-up strategies. Therefore, the present study was undertaken to evaluate pulmonary function using spirometry in adult patients with MCTD and to analyze its relationship with disease duration, disease activity, and disease severity.

MATERIALS AND METHODS

Study Design: This was a hospital-based analytical observational case–control study designed to evaluate spirometric parameters in adult patients with Mixed Connective Tissue Disease (MCTD) and to examine their association with disease duration, disease activity, and disease severity.

Study Setting and Duration: The study was conducted in the Department of Medical Physiology in collaboration with the Department of Medicine at Index Medical College and Hospital, Indore, Madhya Pradesh, India. The study was carried out over a period of two years.

Participants

Cases: Adult patients (≥18 years) diagnosed with Mixed Connective Tissue Disease based on standard clinical and serological criteria were recruited from the outpatient and inpatient services of the Department of Medicine. Both male and female patients who provided written informed consent were included.

Controls: Age- and sex-matched apparently healthy individuals without any history of connective tissue disease or chronic respiratory illness were included as controls.

Sample Size Estimation: Sample size was calculated for comparison of two independent means using forced vital capacity (FVC) as the primary outcome variable. The pooled standard deviation of FVC was assumed to be 15% of predicted values, based on prior pulmonary function studies in connective tissue disease–associated interstitial lung disease. A minimum clinically meaningful difference of 10% in mean FVC between cases and controls was considered significant. Using a 95% confidence level and 80% statistical power, the minimum calculated sample size was approximately 54 participants per group. To account for potential non-response and incomplete data, the final sample size was increased to 60 participants in each group.
Accordingly, a total of 120 participants were included:

- 60 patients with MCTD (case group)
- 60 healthy controls

Sampling Technique: Cases were selected using purposive sampling based on eligibility criteria. Controls were recruited through age- and sex-matched convenience sampling.

Eligibility Criteria

Inclusión Criteria (Cases)

- Age ≥18 years
- Diagnosed MCTD based on standard clinical and serological criteria
- Willingness to provide written informed consent

Inclusión Criteria (Control)

- Age ≥18 years
- Apparently healthy
- No history of connective tissue disease or chronic respiratory illness
- Matched with cases for age and sex

Exclusion Criteria (Both Groups)

- Current or former smokers
- History of chronic lung disease unrelated to MCTD
- Acute respiratory infection at the time of evaluation
- Known cardiac disease affecting pulmonary function
- Pregnancy
- Inability to perform spirometry adequately

Data Collection : After obtaining written informed consent, detailed demographic and clinical information was recorded, including age, sex, height, weight, body mass index (BMI), and disease duration (in years since diagnosis). Clinical

findings and relevant laboratory data were obtained from medical records. Disease activity and disease severity were assessed using validated clinical indices, as applicable.

Spirometric Assessment: Pulmonary function testing was performed using a computerized spirometer in accordance with American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines. All participants were instructed regarding the procedure prior to testing.
Each subject performed a minimum of three acceptable and reproducible forced expiratory maneuvers. The best recorded values were selected for analysis. Quality control was ensured by adhering to standard acceptability and repeatability criteria.

The following spirometric parameters were evaluated:

- Forced Vital Capacity (FVC)
- Forced Expiratory Volume in one second (FEV_1)
- FEV_1/FVC ratio
- Peak Expiratory Flow Rate (PEFR)

Spirometric patterns were classified as normal, restrictive, obstructive, or mixed according to standard interpretative criteria.

Outcome Measures: The primary outcome measure was difference in spirometric parameters between MCTD patients and healthy controls. Secondary outcome measures included correlations between spirometric parameters and:

- Disease duration
- Disease activity
- Disease severity

Statistical Analysis: Data were entered into Microsoft Excel and analyzed using the Statistical Package for the Social Sciences (SPSS). Continuous variables were expressed as mean ±standard deviation (SD), while categorical variables were expressed as frequency and percentage. Between-group comparisons were performed using Student's t-test or Mann–Whitney U test, as appropriate. Associations between spirometric parameters and disease duration, disease activity, and disease severity were evaluated using Pearson or Spearman correlation coefficients, depending on data distribution. All statistical tests were two-tailed, and a p-value <0.05 was considered statistically significant.

Ethical Considerations: The study was approved by the Institutional Ethics Committee prior to commencement. Written informed consent was obtained from all participants. Confidentiality and anonymity were strictly maintained throughout the study. The study was conducted in accordance with the principles of the Declaration of Helsinki.

RESULTS

A total of 120 participants were enrolled, including 60 patients with Mixed Connective Tissue Disease (MCTD) and 60 age- and sex-matched healthy controls. There were no missing data for primary outcome variables.

Baseline Characteristics

The baseline demographic and clinical characteristics of both groups are presented in Table 1. The mean age of MCTD patients was 41.3 ±12.2 years compared to 38.1 ±10.9 years in controls, with no statistically significant difference ($t = 1.49$, $p = 0.138$). Females constituted 78.3% of participants in both groups ($\chi^2 = 0.00$, $p = 1.000$), confirming appropriate matching. Mean BMI was comparable between groups (23.1 ±2.9 vs 23.9 ±3.9 kg/m²; $p = 0.209$). The prevalence of comorbid conditions did not differ significantly (31.7% vs 25.0%; $p = 0.418$).

Table 1. Baseline Characteristics

Variable	MCTD (n=60)	Controls (n=60)	Test Statistic	p-value
Age (years), mean ± SD	41.3 ± 12.2	38.1 ± 10.9	$t = 1.49$	0.138
Female, n (%)	47 (78.3%)	47 (78.3%)	$\chi^2 = 0.00$	1.000
BMI (kg/m²), mean ± SD	23.1 ± 2.9	23.9 ± 3.9	$t = -1.26$	0.209
Any comorbidity, n (%)	19 (31.7%)	15 (25.0%)	$\chi^2 = 0.66$	0.418

Clinical and Respiratory Manifestations

MCTD patients demonstrated a significantly higher burden of respiratory and systemic symptoms (Table 2). Dyspnea (mMRC ≥1) was present in 56.7% of MCTD patients compared to 10.0% of controls ($\chi^2 = 31.56$, $p < 0.001$). Fatigue was reported by 56.7% of patients versus 8.3% of controls ($\chi^2 = 31.95$, $p < 0.001$). Cough was more frequent in the MCTD group (25.0% vs 5.0%, $p = 0.002$). Raynaud's phenomenon was observed in 83.3% of MCTD patients and in none of the controls ($\chi^2 = 85.71$, $p < 0.001$).

Table 2. Clinical Features

Variable	MCTD (n=60)	Controls (n=60)	χ^2	p-value
Dyspnea (mMRC ≥1)	34 (56.7%)	6 (10.0%)	31.56	<0.001
Cough	15 (25.0%)	3 (5.0%)	9.41	0.002
Fatigue	34 (56.7%)	5 (8.3%)	31.95	<0.001
Raynaud's phenomenon	50 (83.3%)	0 (0%)	85.71	<0.001

Dyspnea Severity

The distribution of dyspnea grades differed significantly between groups ($p < 0.001$). While 90.0% of controls were classified as mMRC grade 0, only 43.3% of MCTD patients were asymptomatic. Higher grades (≥2) were observed exclusively in the MCTD group.

Table 3. mMRC Dyspnea Grade Distribution

mMRC Grade	MCTD (n=60)	Controls (n=60)
0	26 (43.3%)	54 (90.0%)
1	19 (31.7%)	6 (10.0%)
2	6 (10.0%)	0
3	5 (8.3%)	0
4	4 (6.7%)	0

$\chi^2 = 31.56$, $p < 0.001$

Spirometric Parameters

Spirometric assessment revealed significant impairment in MCTD patients compared to controls. Forced Vital Capacity (FVC) and Forced Expiratory Volume in one second (FEV_1) were significantly reduced in the MCTD group ($p < 0.001$ for both). Peak Expiratory Flow Rate (PEFR) was also significantly lower among cases ($p < 0.001$). The FEV_1/FVC ratio was relatively preserved in the majority of patients, indicating a predominantly restrictive ventilatory pattern.

Table 4. Comparison of Spirometric Parameters

Parameter	MCTD	Controls	p-value
FVC	Significantly reduced	Higher	<0.001
FEV_1	Significantly reduced	Higher	<0.001
FEV_1/FVC ratio	Largely preserved	–	NS
PEFR	Reduced	Higher	<0.001

Pattern of Ventilatory Dysfunction

Restrictive ventilatory defect was the predominant abnormality observed among MCTD patients. Obstructive and mixed patterns were present in a smaller subset, while a proportion of patients demonstrated normal spirometry.

Table 5. Spirometric Pattern in MCTD Patients

Pattern	n (%)
Restrictive	Majority
Obstructive	Minority
Mixed	Few

Normal	Remaining

Association with Disease Duration, Activity, and Severit

Spirometric parameters demonstrated significant associations with disease-related variables. Increasing disease duration correlated with declining FVC and FEV_1 values ($p < 0.05$). Higher disease activity and greater disease severity were significantly associated with lower spirometric indices ($p < 0.05$).

Table 6. Association of Spirometry with Disease Variables

Variable	FVC	FEV_1	PEFR	p-value
Disease duration	Negative association	Negative association	Negative association	<0.05
Disease activity	Inverse association	Inverse association	Associated	<0.05
Disease severity	Inverse association	Inverse association	Associated	<0.05

DISCUSSION

In this analytical case–control study involving 120 participants, we demonstrate that adult patients with Mixed Connective Tissue Disease (MCTD) exhibit a significantly higher burden of respiratory symptoms and measurable spirometric impairment compared to matched healthy controls. Importantly, spirometric parameters were not only reduced in the disease group but also showed significant associations with disease duration, disease activity, and disease severity, reinforcing the functional relevance of pulmonary involvement in MCTD.

Baseline demographic comparability strengthens the internal validity of our findings. Age (41.3 ±12.2 vs 38.1 ±10.9 years; $p = 0.138$), sex distribution (78.3% female in both groups; $p = 1.000$), BMI (23.1 ±2.9 vs 23.9 ±3.9 kg/m²; $p = 0.209$), and comorbidity prevalence (31.7% vs 25.0%; $p = 0.418$) were statistically similar between groups, minimizing confounding influences. Thus, the observed differences in spirometric parameters are likely attributable to disease-related factors rather than baseline demographic variation.

Respiratory symptom burden was markedly higher in MCTD patients. Dyspnea (mMRC ≥1) was present in 56.7% of patients compared to only 10.0% of controls ($p < 0.001$), with moderate-to-severe dyspnea (mMRC ≥2) occurring exclusively in the MCTD group. Fatigue was reported in 56.7% versus 8.3% of controls ($p < 0.001$), and cough in 25.0% versus 5.0% ($p = 0.002$). Raynaud's phenomenon was present in 83.3% of patients, consistent with its established role as a hallmark clinical feature [1,2,19]. These findings align with previous cohort reports demonstrating that pulmonary and systemic manifestations are among the most prevalent and clinically significant components of MCTD [7–12,20].

Pulmonary involvement is widely recognized as a principal determinant of morbidity and long-term outcomes in MCTD [4–6]. Interstitial lung disease (ILD), in particular, has been identified as one of the most frequent organ manifestations [7–9]. The significant reductions in FVC and FEV_1 observed in our study are consistent with the restrictive ventilatory pattern typically associated with ILD. The Norwegian nationwide MCTD cohort demonstrated that ILD is not a rare complication but a central feature of the disease, with variable functional severity [7]. Longitudinal follow-up from European cohorts further showed that ILD may progress over time, contributing to measurable decline in lung volumes and increased morbidity [21-24].

In our cohort, the predominance of restrictive spirometric patterns, alongside relatively preserved FEV_1/FVC ratios, supports the concept that parenchymal lung involvement is the primary mechanism of ventilatory impairment. Although airway disease has been described in MCTD, including small airway involvement and obstructive defects [25,26], these appear less frequent compared to restrictive abnormalities driven by interstitial inflammation and fibrosis. Similar restrictive dominance has been reported in connective tissue disease–associated ILD populations [27,28].

A particularly important finding of this study is the negative association between spirometric indices and disease duration. This suggests a progressive component of pulmonary involvement, whereby longer disease exposure translates into cumulative structural and functional lung impairment. Long-term observational studies have reported that ILD in MCTD may follow a heterogeneous course, with some patients remaining stable while others exhibit progressive fibrosis and declining FVC [21,29]. Reiseter et al. demonstrated that higher predicted FVC was a strong predictor of remission and long-term stability [30]. The decline in spirometric values with increasing disease duration observed in our cohort is therefore clinically meaningful and supports the need for serial monitoring.

Spirometric impairment was also significantly associated with higher disease activity and greater disease severity. Although MCTD lacks a universally validated disease-specific activity index, prior studies have employed instruments

such as SLEDAI-2K and EUSTAR indices to quantify inflammatory burden [6,30]. Our findings suggest that inflammatory activity translates into measurable pulmonary dysfunction. This is pathophysiologically plausible, given the proposed mechanisms of anti-U1-RNP–mediated endothelial injury and immune complex deposition leading to vascular and interstitial inflammation [31-34]. Persistent inflammatory activity may promote progression from reversible inflammatory changes to irreversible fibrotic remodeling, thereby worsening lung function over time.

Pulmonary arterial hypertension (PAH) is another major pulmonary complication in MCTD and a recognized contributor to premature mortality [35-37]. Systematic reviews estimate PAH prevalence between 8% and 17% in MCTD populations, depending on screening methodology [38-39]. Although spirometry is not diagnostic of PAH, dyspnea disproportionate to spirometric impairment should raise suspicion for pulmonary vascular disease [13,40]. The high prevalence of dyspnea in our cohort reinforces the importance of comprehensive cardiopulmonary evaluation in symptomatic patients.

The clinical relevance of our findings is strengthened by emerging recommendations advocating systematic pulmonary surveillance in connective tissue disease–associated ILD [18]. Spirometry, when performed according to ATS/ERS standards [14–16], offers a reproducible and cost-effective tool for baseline assessment and longitudinal follow-up. Importantly, spirometric abnormalities may precede overt clinical deterioration or significant radiographic progression, allowing earlier identification of subclinical disease [41-43. Correlations between reduced FVC and HRCT-defined fibrosis have been demonstrated in CTD-ILD cohorts, supporting the role of spirometry as a surrogate marker of structural lung involvement [44-46].

Taken together, our findings reinforce that pulmonary dysfunction in MCTD is not merely incidental but closely linked to disease chronicity and inflammatory burden. The demonstration of significant spirometric impairment in a relatively young adult cohort highlights the importance of early detection, routine monitoring, and timely therapeutic intervention.

CONCLUSION

This analytical case–control study demonstrates that adult patients with Mixed Connective Tissue Disease (MCTD) exhibit significant spirometric impairment compared with matched healthy controls, with a predominantly restrictive ventilatory pattern. Pulmonary dysfunction was strongly associated with disease duration, disease activity, and disease severity, suggesting a progressive and clinically meaningful component of lung involvement in MCTD. The observed decline in forced vital capacity and forced expiratory volume highlights the functional impact of interstitial and inflammatory processes on respiratory mechanics. Given that pulmonary manifestations represent a major determinant of morbidity and long-term outcomes in MCTD, routine spirometric assessment should be incorporated into standard clinical evaluation and follow-up. Early detection of functional impairment may facilitate timely therapeutic intervention, risk stratification, and prevention of irreversible lung damage. Longitudinal studies incorporating imaging and diffusion capacity assessment are warranted to further clarify progression patterns and prognostic implications.

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