ORIGINAL ARTICLE

Pleuropulmonary Features in Connective Tissue Diseases

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Abstract

Background: ***Pleuropulmonary involvement could be noticed in almost all connective tissue diseases (CTDs), often next to articulo-skeletal manifestations. Therefore, early detection of respiratory affection is pivotal for the prognosis, since such involvement may boost morbidity and mortality.***

Aim of the work: ***To recognize the frequency and outcome of pleuropulmonary features in CTD patients, alongside investigating their correlations with the duration of the disease.***

Patients and methods: ***This cross-sectional study was conducted on forty patients with respiratory symptoms. They were all known as definitive CTD cases, and scheduled for follow-up at the rheumatology outpatient clinic in Al-Hussein University Hospital.***

Results: ***Pulmonary hypertension (PHTN) and interstitial lung disease (ILD) were the most frequent styles of pleuropulmonary involvement in CTD (45% and 35%, respectively). Pleural effusion showed a statistically significant good clinical outcome. Whereas, all patterns of parenchymal involvement (except lung abscess and rheumatoid nodule), pyopneumothorax and PHTN were associated with statistically significant unfavourable clinical outcome. ILD, lung cancer and PHTN displayed a statistically significant positive correlation with CTD duration. However, pleural effusion showed a statistically significant negative correlation with the same term.***

Conclusion: ***A wide variety of pleuropulmonary features in CTD patients occurs in the form of parenchymal affection and PHTN. Risk factors for poor clinical outcome in the context of CTD include ILD, pneumonia, lung cancer, diffuse alveolar hemorrhage (DAH), pyopneumothorax and PHTN. Longer CTD duration is positively correlated with ILD, lung cancer and PHTN.***

Keywords: Pleuropulmonary; Connective tissue disease

1. Introduction

CTDs represent an assorted collection of autoimmune disorders that can impact numerous body systems. They can harm various organs, including the lungs, with a possibility of rising irreversible organ damage in severe situations.[1]

Pleuropulmonary manifestations in CTD may be asymptomatic or symptomatic, with varied degrees of severity. Symptoms usually include cough, dyspnea and pleuretic chest pain. Other presentations such as fever, loss of weight and hemoptysis are less common to occur.[2]

Pleuropulmonary involvement in patients with CTD may not only be due to the disease itself, but may be a sequel of immunosuppressive drugs as well, either through favoring infection by pathological bacteria or opportunistic organisms, or by provoking drug-induced ILD.[3]

Thus, the target of this work was to recognize the frequency and outcome of pleuropulmonary features in CTD patients, together with investigating their correlations with the duration of the disease.

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2. Patients and methods

This cross-sectional study was conducted during the period between January 2024 and January 2025. Forty patients with respiratory symptoms were included. either referred to the chest outpatient clinic or presented to the emergency department (Al-Hussein University Hospital). They were all known as definitive CTD cases, and scheduled for follow-up at the rheumatology outpatient clinic in Al-Hussein University Hospital.

Inclusion criteria

Adult patients previously diagnosed to have definitive CTDs (according to the classification criteria for each disease), [4, 5, 6, 7] and presented with respiratory symptoms.

Exclusion criteria

Patients were initially excluded if they were: aged <18 years, not complaining from respiratory symptoms, having picture of undifferentiated CTD, known to have chronic chest illness which is not possible to be related to CTD, giving history of prolonged or extra-ordinary exposure to dust, fumes, toxins or any occupational/environmental circumstances which may precipitate lung disease, diagnosed with systemic or extra-pulmonary disease capable of causing pulmonary manifestations or imaging shadows.

Data collection and methodology

All patients were subjected to detailed medical history taking, thorough general and local examinations (two discrete local examinations were performed for each patient; the first was done by the rheumatology physician to evaluate for CTD activity and modify treatment if required, whereas the second was done by the chest physician in order to assess the patient's complaint). Routine laboratory investigations, including CBC, ESR, RBS, renal function test, hepatic profile and serum electrolytes, were performed. Serological tests were requested whenever needed to assess disease activity. Further evaluation was applied via oxygen saturation estimation by pulse oximeter, high-resolution CT on chest, pulmonary function test using the apparatus Blue Cherry Version 1.2.2.4 (Geratherm Respiratory GmbH, Bad Kissingen, Germany) and trans-thoracic echocardiography to determine estimated systolic pulmonary artery pressure (esPAP), relying on recent studies which considered esPAP values of ≥35mmHg at rest an indicator of pulmonary hypertension.[8] Computed tomography pulmonary angiography (CTPA) was only requested in patients with suspected pulmonary thromboembolism, with normal renal function tests.

Follow-up and re-evaluation

Re-evaluation of admitted patients was performed at the end of the hospital stay. Moreover, all patients were followed up after one month from the date of presentation, and the patients' outcome was classified as follows: (a) completely improved; improvement of chest complaint, accepted level of oxygenation and totally resolved pulmonary clinical findings, (b) partially improved; improvement of symptoms and signs, but not to the limit of total resolution on the clinical level and (c) died.

Ethical consideration

The study protocol was initially approved by the Ethical Committee of Al-Azhar University. A detailed written informed consent form was obtained from each participant about the study's purpose and procedures. Data was gathered anonymously to guarantee patients' privacy, with a perfect commitment to the Declaration of Helsinki.

Statistical analysis

Data analysis was performed using the software program Statistical Package for the Social Sciences (SPSS) version 28 (IBM Corp., Armonk, NY, US). Categorical variables were described using their absolute frequencies and percentages. They were mostly compared using the chi-square test, but sometimes Fisher's exact test was used when appropriate. The Shapiro-Wilk test was used to evaluate whether the data set is normally distributed or not. Quantitative variables were described by their means and standard deviations. Measuring the linear correlation between two variables was accomplished with the aid of the Pearson correlation coefficient (r). P-value <0.05 was considered significant, while p-value ≤0.001 was considered highly significant.

3. Results

The mean age of studied patients was 46.08±10.29 years, among whom 82.5% were females. Smokers represented only 20%. Among the study population, 40% had rheumatoid arthritis (RA), 35% were diagnosed as systemic lupus erythematosus (SLE), 17.5% fulfilled the criteria of systemic sclerosis (SSc) and 7.5% were classified as mixed connective tissue disease (MCTD). Moreover, 25% of the studied patients were in active CTD state. The mean duration passed since the diagnosis of CTD was 7.3±5.34 years. Hypertension and diabetes mellitus were the most prevalent comorbidities among the studied patients (37.5% and 22.5%, respectively). Furthermore, Fatigue and dyspnea were the most common presenting symptoms (87.5% and 75%, respectively). (Table 1)

Table 1. Socio-demographic data and baseline characteristics in studied patients.

Variables	Studied patients N= 40	
Age (years)		
Mean±SD	46.08±10.29	
Sex	N	%
Male	7	17.5

Female	33	82.5
Smoking	8	20.0
Type of CTD		
RA	16	40
SLE	14	35
SSc	7	17.5
MCTD	3	7.5
Activity of CTD	10	25
Duration passed since the diagnosis of CTD (years)		
Mean±SD	7.3±5.34	
Comorbidities	N	%
HTN	15	37.5
DM	9	22.5
IHD	6	15
CKD	4	10
CLD	1	2.5
Presenting symptoms		
Fatigue	35	87.5
Dyspnea	30	75.0
Cough	24	60.0
Fever	12	30.0
Chest pain	8	20.0
Hemoptysis	8	20.0
Loss of weight	4	10.0

CTD; connective tissue disease, RA: rheumatoid arthritis, SLE, systemic lupus erythematosus, SSc; systemic sclerosis, MCTD: mixed connective tissue disease, HTN: hypertension, DM: diabetes mellitus, IHD: ischemic heart disease, CKD: chronic kidney disease, CLD: chronic liver disease, SD: standard deviation.

As illustrated in (Table 2), parenchymal disease was the most common pattern of pleuropulmonary involvement (62.5%), mainly existed as ILD (35%) and pneumonia (22.5%). Pulmonary vascular disease was manifested in 45% of patients, all of them showed variable degrees

of PHTN. Airway disease and pleural affection were detected among minority of cases (27.5% and 17.5%, respectively).

Table 2. Distribution of pleuropulmonary involvement in studied patients.

Pleuropulmonary involvement	Studied patients N= 40	
	N	%
Pleural disease	7	17.5
Pleuritis	1	2.5
Pleural effusion	5	12.5
Pyopneumothorax	1	2.5
Parenchymal disease	25	62.5
ILD	14	35.0
Pneumonia	9	22.5
Lung abscess	2	5.0
Rheumatoid nodule	1	2.5
DAH	1	2.5
Lung cancer	1	2.5
Pulmonary vascular disease	18	45.0
PHTN	18	45.0
Pulmonary embolism	2	5.0
Airway disease	11	27.5
Bronchiectasis	7	17.5
Bronchiolitis	2	5.0
Bronchitis	2	5.0

ILD: interstitial lung disease, DAH: diffuse alveolar hemorrhage, PHTN: pulmonary hypertension.

Pleural effusion showed a statistically significant good clinical outcome (p-value = 0.04), while pyopneumothorax exhibited a highly statistically significant poor clinical outcome (p-value ≤0.001). All patterns of parenchymal involvement were associated with statistically significant unfavorable clinical outcome, except lung abscess and rheumatoid nodule. As well, PHTN was significantly linked to mortality and disability (p-value ≤0.001). (Table 3)

Table 3. Comparison of features of pleuropulmonary involvement according to clinical outcome.

Pleuropulmonary involvement	Survived		Died	p-value
	Completely improved N= 19	Partially improved N= 18	N= 3	
Pleural disease				
Pleuritis	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.5
Pleural effusion	5 (26.3%)	0 (0.0%)	0 (0.0%)	0.04*
Pyopneumothorax	0 (0.0%)	0 (0.0%)	1 (33.33%)	≤0.001**
Parenchymal disease				
ILD	0 (0.0%)	12 (66.67%)	2 (66.67%)	≤0.001**
Pneumonia	6 (31.6%)	1 (5.6%)	2 (66.67%)	0.02*
Lung abscess	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.3
Rheumatoid nodule	1 (5.3%)	0 (0.0%)	0 (0.0%)	0.5
DAH	0 (0.0%)	0 (0.0%)	1 (33.33%)	≤0.001**
Lung cancer	0 (0.0%)	0 (0.0%)	1 (33.33%)	≤0.001**
Pulmonary vascular disease				
PHTN	3 (15.8%)	13 (72.2%)	2 (66.67%)	≤0.001**
Pulmonary embolism	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.3
Airway disease				
Bronchiectasis	5 (26.3%)	2 (11.1%)	0 (0.0%)	0.3
Bronchiolitis	0 (0.0%)	2 (11.1%)	0 (0.0%)	0.2
Bronchitis	2 (10.5%)	0 (0.0%)	0 (0.0%)	0.3

ILD: interstitial lung disease, DAH: diffuse alveolar hemorrhage, PHTN: pulmonary hypertension, *: statistically significant, **: statistically highly significant.

As enlightened in (Table 4), pleural effusion showed a statistically significant negative correlation with the duration passed since the diagnosis of CTD (r = –0.328, p-value = 0.039). Among types of parenchymal involvement, ILD demonstrated a statistically significant positive correlation (r = 0.345, p-value = 0.029), while lung cancer displayed a highly statistically significant strong positive correlation (r = 0.596, p-value ≤0.001) with CTD duration. Additionally, PHTN exhibited a statistically significant positive correlation with the same term (r = 0.324, p-value = 0.044).

Table 4. Correlations between features of pleuropulmonary involvement and the duration passed since the diagnosis of CTD.

Pleuropulmonary involvement	Duration passed since the diagnosis of CTD	
	r	p-value
Pleural disease		
Pleuritis	-0.163	0.315
Pleural effusion	-0.328	0.039*
Pyopneumothorax	-0.072	0.658
Parenchymal disease		
ILD	0.345	0.029*
Pneumonia	-0.027	0.869
Lung abscess	-0.082	0.617
Rheumatoid nodule	0.080	0.625
DAH	0.019	0.908
Lung cancer	0.596	<0.001**
Pulmonary vascular disease		
PHTN	0.324	0.044*
Pulmonary embolism	0.201	0.213
Airway disease		
Bronchiectasis	0.067	0.681
Bronchiolitis	0.158	0.331
Bronchitis	-0.125	0.442

CTD: connective tissue disease, r: Pearson correlation coefficient, ILD: interstitial lung disease, DAH: diffuse alveolar hemorrhage, PHTN: pulmonary hypertension, *: statistically significant, **: statistically highly significant.

4. Discussion

Respiratory involvement is certainly a serious feature of autoimmune diseases. It usually necessitates multidisciplinary integrated medical care, together with cautious and long-term monitoring, particularly as the immunological disorder progresses.[9]

Regarding socio-demographic data, the current study showed that the mean age of studied patients was 46.08±10.29 years, with a feminine predominance (82.5%). Smokers represented only 20% of the study population.

In agreement with the current study, Aboud et al.[10] revealed that the majority (89%) of patients with CTD were females, with an average age of 33 years. So, Alwan et al.[11] demonstrated that 78% of patients with CTD were females, with a mean age of 41.8±6.5 years and 22% of smokers among participants. The previous findings enlighten that CTD is fundamentally a disease of young to middle-aged females.

The distribution of CTD diagnoses among the participants was as follows: 40% had RA, 35% were diagnosed as SLE, 17.5% fulfilled the criteria of SSc, and 7.5% were classified as MCTD. Moreover, 25% of the studied patients were in an active CTD state. The mean duration passed since the diagnosis of CTD was 7.3±5.34 years.

Parallel to the current study, Mohamed and co-workers[1] documented the same order of CTD types allocation, with RA in the front (42%), then SLE (38%), SSc (12%), MCTD (4%), antiphospholipid syndrome (2%) and overlap CTD (2%). As well, Doualla-Bija et al.[12] reported that the most common CTD types were RA (53.7%), SLE (29.6%), SSc (12.9%) and lastly MCTD (3.8%).

On the flip side, Aboud et al.[10] stated that SSc (44.6%) and RA (33.8%) were the most commonly diagnosed CTDs. Also, Alwan et al.[11] displayed that SLE is the leading CTD, encountered in 43% of total cases, followed by RA (23%).

In the present study, Hypertension and DM were the most prevalent comorbidities among studied patients, accounting for 37.5% and 22.5%, respectively. Those results concur with Nuchin and his colleagues[13], who revealed that the most common comorbid conditions among CTD patients were hypertension (42%) and diabetes (26%). Likewise, Mohamed et al.[1] explored the same dominant comorbidities, but with lower prevalence (28% for hypertension and 16% for diabetes). However, Khanna et al.[14] specified anemia as the most common comorbidity in CTD patients (58%), followed by hypertension (42%).

Fatigue and dyspnea were the most common symptoms presented by the patients studied (87.5% and 75%, respectively). Cough and fever were frequent but less prevalent (60% and 30%, respectively). Coinciding with our conclusions, Stević et al.[15] designated fatigue as the leading symptom (75.8%) among their 84 patients with CTD hospitalized due to pleuropulmonary causes. Dyspnea and cough followed (63.8% for each), then fever and chest pain (41.4% and 39.6%, respectively). Alongside, an analogous study illustrated that dyspnea was the most common presenting symptom among CTD patients with pleuropulmonary involvement, existing among 70% of them, followed by cough (24%).[1] Besides, in the study conducted by Nuchin et al.[13], all patients (100%) presented with dyspnea, while more than half of them (56%) suffered from cough.

The distribution of pleuropulmonary involvement among the studied CTD patients revealed a diverse range of respiratory conditions, reflecting the complexity of CTDs. Pleural involvement was detected among 17.5% of the study population; 2.5% had pleuritis, 12.5% presented with pleural effusion and 2.5% suffered from pyopneumothorax. Parenchymal involvement was explored in 62.5% of participants; 35% had ILD, 22.5% developed pneumonia, 5% manifested by lung abscess, 2.5% exhibited rheumatoid nodule, 2.5% showed lung cancer and 2.5% experienced DAH. Taking into account pulmonary vascular involvement, which existed among 45% of patients, 45% had PHTN, and 5% presented with PE. Airway involvement was revealed among 27.5% of included patients; 17.5% had bronchiectasis, 5%

showed bronchiolitis, and 5% manifested bronchitis.

Integrating with the current study, Mohamed et al.[1] demonstrated that parenchymal involvement was the most common affection, detected among 86% of included patients, with ILD as the most common (36% of patients). Pulmonary vascular involvement was second, found in 62% of cases (52% among whom had PHTN).

When comparing categories of pleuropulmonary involvement according to clinical outcome, pleural effusion showed a statistically significant good clinical outcome (p-value = 0.04), while pyopneumothorax exhibited a highly statistically significant poor clinical outcome (p-value ≤0.001). All types of parenchymal involvement were associated with statistically higher unfavorable clinical outcomes, except lung abscess and rheumatoid nodule. Within CTD-related pulmonary vascular affection, PHTN was significantly linked to mortality and disability (p-value ≤0.001). On the other side, none of the features of airway involvement revealed a significant connection to clinical outcome.

Standing in the exact column, Mohamed and his colleagues1 recorded that mortality rate was higher among parenchymal involvement group including ILD. Total improvement was more within the pleural involvement group, while partial improvement and stationary course were more common in the airway affection group. Moreover, CTD-ILD was the main cause of requiring domiciliary oxygen at hospital discharge.

In the present work, there was a significant negative correlation between pleural effusion and the time passed since the diagnosis of CTD (r = 0.328-, p-value = 0.039), denoting that pleural effusion is less common as the disease progresses. A significant positive correlation was found between the duration of CTD and the development of ILD (r = 0.345, p-value = 0.029) and lung cancer (r 0.596, p-value ≤0.001), displaying that these conditions become more likely as the disease persists. In contrast, conditions like pleuritis, pyopneumothorax, pneumonia, lung abscess, rheumatoid nodule and DAH showed no significant associations with the illness duration. PHTN was the pulmonary vascular inclusion that evinced a significant positive correlation with disease duration (r = 0.324, p-value = 0.044), proving an increasing risk over time. Lastly, none of the airway implications exposed a significant correlation with the duration of CTD.

Previous findings are boosted by Joy et al.[16], who showed that the risk factors for ILD in patients with CTD included longer disease duration. Similarly, a Saudi study reported a significant association between pleuropulmonary involvement, as a whole, and longer disease duration in patients with RA.[17]

Adversely, Aboud et al.[10] mentioned that shorter CTD duration independently contributed to greater lung involvement (p-value= 0.004). Furthermore, Domouky and El-Beheidy[18] reported no significant association between ILD involvement and CTD duration.

The current study was limited by its small sample size, being a mono-centric research, the lack of exemplifying all subtypes of CTD, the restriction on CTD patients with respiratory presentation only, relaying on trans-thoracic echocardiography as a tool of assessing pulmonary hypertension instead of the gold standard right heart catheterization and ultimately, the relatively short follow-up period.

4. Conclusion

A wide variety of pleuropulmonary features in CTD patients occurs in the form of parenchymal affection and PHTN. Risk factors for poor clinical outcome in the context of CTD include ILD, pneumonia, lung cancer, DAH, pyopneumothorax and PHTN. Longer CTD duration is positively correlated with the development of ILD, lung cancer and PHTN. Conversely, a negative correlation is found between disease duration and the occurrence of pleural effusion.

Disclosure

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There are no conflicts of interest.

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