Zagazig University Medical Journal
www.zumj.journals.ekb.eg
https://dx.doi.org/10.21608/zumj.2021.44366.1955 Volume 28, Issue 6, November 2022(1356-1367)
**Manuscript ID** ZUMJ-2009-1955 (R3)
**DOI** **10.21608/zumj.2021.44366.1955**

**ORIGINAL ARTICLE**

# Diagnosis of Interstitial Lung Disease in Connective Tissue Disease Children: Retrospective Radiological Study

***Ayat M. Domouky*[1*], *Rabab M. El-Beheidy*[2]**
[1] *Human Anatomy & Embryology Department, Faculty of Medicine, Zagazig University, Egypt.*
[2] *Pulmonology, Immunology and Allergy Unit, Pediatrics Department, Faculty of Medicine, Zagazig University, Egypt.*

***Corresponding author:**
**Ayat Mahmoud Domouky**
Human Anatomy & Embryology Department
Faculty of Medicine, Zagazig University, Egypt
Email:
drayat_pedia@outlook.com,
AMSalim@medicine.zu.edu.eg

| | |
|---|---|
| **Submit Date** | 2020-10-02 |
| **Revise Date** | 2022-06-08 |
| **Accept Date** | 2021-01-11 |

## ABSTRACT

**Background:** Interstitial lung disease (ILD) is a crucial issue which impact the prognosis of connective tissue diseased patients and can cause uncontrolled systemic disease activity. So, this work aimed to describe lung functions, radiological abnormalities, and the lung biopsy findings in a group of childhood interstitial lung disease (chILD) caused by underlying connective tissue disease.

**Methods:** Retrospective analysis, diagnostic modalities of chILD in 40 CTD children (JSLE, JIA, JDM, JSS, JMCTD) were evaluated; clinical manifestation, chest imaging (x-ray, HRCT) and lung biopsy in selected cases. Moreover, Spirometer Pulmonary function testing (PFT), 6-minute walk test (6MWT), and transthoracic echocardiography were also evaluated to assess severity and follow up. Histopathological analysis for H&E sections were applied.

**Results:** For ILD associated with juvenile CTD, HRCT was the gold standard for diagnosis and diminish need for lung biopsy with common finding was widespread irregular interlobular septal thickening, ground-glass attenuation, ILD severity showed statistically significant with pulmonary function test and 6-minute walk test parameter.

**Conclusions:** For early prediction and follow up of development of ILD in CTD children, it is recommended to do routine checks of PFT even in the lack of respiratory warning sign, while HRCT is the gold standard to confirm and specify diagnosis.

**Keywords:** childhood interstitial lung disease; connective tissue disease; pulmonary function test.

## INTRODUCTION

Connective tissue diseases (CTD) may involve any organ or system beside have a large variety of disease characteristics and severity [1]. Affected children may only demonstrate with rash or arthritis, but others may possibly demonstrate with renal or respiratory failure. The diagnosis of CTD is often postponed and identifying the specific type of CTD can be difficult [1]. Juvenile (Systemic Lupus Erythematosus (SLE), Dermatomyositis (DM), rheumatoid arthritis (RA), Systemic Scleroderma (SSc), and Mixed Connective Tissue Disease (MCTD)) can present with pulmonary manifestations. In SLE, about half of patients have any shape of respiratory immersion throughout the progression of the illness [2-5].

Interstitial lung disease (ILD) is the typical presentation of respiratory system involvement in autoimmune connective tissue disease, it's not limited to the interstitial tissue but also alveoli, pleura, lymphatics, vascular, and airways of all lengths may all be included. ILD when present, is frequently accompanying by significant morbidity and mortality [3]. Similarly, [5,6]. mentioned that Interstitial lung disease (ILD) is one of the crucial issues that impact the prognosis of connective tissue disease patients and be able to trigger wild

systemic disease exacerbation in CTD patients. CTD complicated with ILD can be lethal, and rapidly discovering of the disease is, consequently, essential [7,8].

The pathogenesis of ILD in rheumatic diseases is complex, multifactorial, and incompletely understood [9-11]. The clinical manifestation and progression of ILD involves both inflammatory/immune and fibrotic/tissue components, which often represent a progressive uncontrolled tissue repair reaction in response to injury, finally leading to irreversible remodelling of the lung and diminished lung function [12]. So, our aim to describe lung functions, radiological abnormalities, and histopathological findings in the lung biopsy related to group of childhood interstitial lung disease (chILD) caused by underlying connective tissue disease.

## METHODS

**Study population:** CTD children were gathered from the medical record database between October 2019 and April 2020 from Rheumatology and Rehabilitation Department, and Pediatric department; Pulmonology, Immunology and Allergy Unit, faculty of medicine, Zagazig University. Written informed consent was obtained from all participants. The study was done according to The Code of Ethics of the World Medical Association for studies involving humans, and approved accordance with the guidelines of Institutional Review Board (IRB) of Faculty of Medicine, Zagazig University, Egypt (Approval No.: ZU-IRB #544459/14-7-2019). Out of 40 CTD children, 16 were already diagnosed with interstitial lung disease, and 4 patients were newly diagnosed between October 2019 and April 2020.

Totally, the study include the connective tissue diseased children aged 5-15 years at primary diagnosis, according to the following classification criteria: the 2010 European League Against Rheumatism (EULAR) criteria for rheumatoid arthritis (RA) [13], the 2019 European League against Rheumatism (EULAR) criteria for systemic lupus erythematosus (SLE) [14], the 2017 European League against Rheumatism (EULAR) criteria for dermatomyositis (DM) [15]**,** The 2007 Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis (SSc) [16]**,** and The 2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases [17]. While we exclude patients less than 5 years or more than 15 together with patients with Active malignancy, and active acute or chronic infections.

The sample size was calculated using open Epi according to the following Kl-6 in patient group was 33.75+46 and in control group 3.9+7 [3], so the power of study 80% and C.I 95% the sample was calculated to be 40. The participants were distributed into two groups, Group 1 (CTD only group): included (20) connective tissue diseased children without interstitial lung disease; Group 2 (CTD+ILD group): which consisted of (20) connective tissue diseased children with interstitial lung disease.

**Diagnostic approach to chILD:** The diagnostic approach depends on "respiratory symptoms (cough, rapid and or difficult breathing, or exercise intolerance), respiratory signs (resting tachypnea, adventitious sounds, retractions, digital clubbing, failure to thrive, or respiratory failure)" [20], chest x-ray, HRCT, and surgical lung biopsy/ histopathological examination. Diagnostic approach was revised in all patients already diagnosed as ILD and carried on all patients have any of CTD to prove or exclude presence of ILD, according to [18-20].

**Lung HRCT:** Patients were evaluated by lung HRCT. All patients were scanned from the apex to the basis of the lung by routine end-inspiratory spiral CT, slice thickness 5.0 mm. High-resolution re-establishment was used to re-establish the image, and a slice thickness of 0.6 mm, lung X-ray, HRCT were interpreted by both radiologist and pediatric pulmonologist.

**Anthropometric dimensions:** Haller index and was defined as the ratio of the anteroposterior distance between the anterior thoracic wall and the spine to the widest transverse diameter of the chest according to Ewert et al. (2017) [21], cardiothoracic index was defined as the ratio of widest transverse heart diameter to the widest transverse chest diameter.

**Surgical Lung biopsy:** SLB for only four patients who have nonspecific HRCT in spite of clearly clinical manifestation and restrictive pulmonary function. In the four cases, lung biopsy was completed by mini-thoracotomy. Two large lung samples were brought from two separate portions, with one chest tube introduced prior to stitching the chest.

Histopathological evaluation to lung biopsy were carried blindly by two pathologists, sections were coded enabling blind examination & evaluation: Interstitial thickening, inflammatory cell infiltration, congestion, and edema were all classified as 0 (absent), 1 (weak), 2 (moderate), 3 (strong), or 4 (severe) for grading of lung injury. The total lung injury score was calculated by adding up the individual scores of each category.

**Detection, Severity, and follow up of chILD:**

**Pulmonary function test (PFT):** underwent the PFT using Jeager Vyntus spirometry. The following parameters were recorded: forced expiratory volume in 1 s (FEV1), forced vital capacity (FVC), FEV1/FVC ratio. These parameters were all conveyed as a percentage of measured value/predicted value. Interpretation of PFTs was done according to Jiang et al [42]: pulmonary function value FVC, FEV1>80% of predicted values was considered as normal. Patients were considered as having mild ILD if they had (60%<FVC, FEV1<80% of predicted values) in PFT. Patients were considered as having severe ILD if they had (FVC, FEV1<60% of predicted values) in PFT.

**6-minute walk test:** 6MWT was performed in all participants, matching with the ATS statement. In Brief, participants were examined in the consistent situation. participants held pulse oximeters, heart rate and oxygen saturation (SpO2) were recorded. Then, participants were ordered to walk for 6min, recording SpO2 and heart rates on the pulse oximeter directly after the test. To assess dyspnea grade, participants were requested to rate their dyspnea applying the modified Borg scale, by choosing a number from 0 to 10, with 0 being no significant dyspnea and 10 being highest grade of dyspnea.

**Transthoracic echocardiography:** Additional, examination for pulmonary hypertension by echocardiography may impact the diagnosis, alter treatment, and influence prognosis, as pulmonary hypertension accompanying with ILD expects higher death rate.

**Statistical analyses:**

Quantitative data were given as mean ± standard deviation (SD). The results from the spirometry were expressed as a percentage of predictive values. Paired sample T test was used to calculate difference between two quantitative variables in the same group. One-way ANOVA were used to contrast the mean of more than two groups when data were normally distributed. Multiple comparisons were estimated by the least significant difference (LSD) test when data were normally distributed. Chi-square test used to assess qualitative data.

All statistical analyses were applied using SPSS for Windows 15 statistical software. A value of $p<0.05$ was accepted as statistically significant. A value of $p<0.001$ was accepted as highly statistically significant. A value of $p>0.05$ was accepted as non-statistically significant.

## RESULTS

**Demographic and clinical characteristics of patient (table 1):**

Study groups contained 40 patients with CTD (20 of them had ILD: (12 mild, 8 severe)); The mean age of CTD only group was 13 ± 2.2 years, versus 11.2 ± 2.2 and 13.6 ± 1.2 years in mild ILD group and severe ILD group, respectively.

In CTD only group 60% (n = 12) of the patients were female and 40% (n = 8) were male, in mild ILD_group 67% (n = 8) were female and 33% (n = 4) were male, in severe ILD group

75% (n = 6) were female and 25% (n = 2) were male, with no significant differences.

The CTD duration was 3.2 ± 2.5, 1.2 ± 0.7 and 3.6 ± 1.2 years in CTD only group, mild ILD group and severe ILD group, respectively. Analysis of ILD patients indicated that 12 in the ILD had mild ILD, while 8 patients had severe form of ILD, the ILD duration was 0.2 ± 0.1 and 1.2 ± 0.7 years in mild ILD group and severe ILD group, respectively.

**Results of diagnostic approach of ILD**:

**Symptoms/signs in CTD+ILD group:** The presenting clinical manifestations was often subtle and nonspecific. The onset of symptoms was gradual in most cases (80%). However, most of patients (75%) has symptoms for less than one year at time of examination. 2 of mild ILD children were asymptomatic diagnosed by HRCT. The common symptoms/signs at presentation were dyspnea (80%), cough (60%, dry not interrupt sleep), exercise limitation (60%), frequent respiratory infections (50%), wheezing (33.3%), tachypnea and chest wall retraction (10%), clubbing (10%) and asymptomatic (10%). The symptoms/signs severity correlate positively with severity of the disease dyspnea as assessed by clinical examination (table 4 for comparison and significant).

**Chest x-ray finding in CTD+ILD group (figure 1):** chest x-ray was done to all CTD patients showed any pulmonary Symptoms/signs and was revised in already diagnosed ILD patients, the common findings on chest x-ray were basal infiltration in one or both side in 70% of patients, increase bronchovascular marking (60%), prehilar consolidation (50%), involvement of the supporting tissue of the lung parenchyma resulting in reticular opacities (40%), mild to moderate Pleural effusion (30%), and accentuated pulmonary notch at left side (10%).

**High-resolution computerized tomography (HRCT) finding in CTD+ILD group (figure 2):** same as x-ray, HRCT was done to all CTD patients showed any pulmonary Symptoms/signs (out of 24 CTD patients 4 patients were diagnosed as ILD) and was revised in already diagnosed ILD patients: The HRCT findings of ILD were irregular interlobular septal thickening (80%), ground-glass apperance (40%), and thickened intralobular lines (40%), cystic change (40%) and patchy consolidation (40%).

**Surgical lung biopsy (SLB) finding in CTD+ILD group (figure 3):** Surgical lung biopsy was already done for 4 patients who had nonspecific HRCT. The lung histological patterns which observed were NSIP (Non-specific interstitial pneumonia, 3 patients), and DIP (Desquamative interstitial pneumonia, patients). NSIP showed mild to moderate interstitial chronic inflammation and Alveolar (type 2) epithelial cells hyperplasia. DIP showed alveoli packed with macrophages, thickened alveolar septa, dispersed varied inflammatory cells and slight fibrosis. Lung injury scored was ranged from (14 to 11 out of 16).

**Comparison of PFT, 6MWT among different groups (table 2,3):**

Pulmonary function test reflected a restrictive lung problem with decreased lung compliance and lung volumes. CTD only group showed a forced expiratory volume in 1 s (FEV1) (% predicted) 101 ± 7, forced vital capacity (FVC) (% predicted) 95 ± 7, the mild ILD group showed a FEV1% 77 ± 10, FVC% 72 ± 7, and the severe ILD group showed a FEV1% 55 ± 5, FVC% 49 ± 8, with significance different between groups.

Subgroup analysis indicated that in CTD only group 8 patients had JSLE, 5 had JRA, 1 had JDM, 2 had JSSc, and 4 had JMCTD, whereas in mild ILD group 7 patients had JSLE, 3 had JRA, and 2 had JMCTD, while in severe ILD group 3 patients had JSLE, 2 had JRA, 1 had JSSc, and 2 had JMCTD.

In 6MWT, the mean end-test SpO2 was 96% ± 3 of CTD only group Vs 92% ± 2, 67% ± 5 in mild ILD and severe ILD groups respectively. The mean end-test dyspnea level graded with the modified Borg scale was 2± 1 of CTD only group Vs 3 ± 2, 4 ± 3 in mild ILD and severe ILD groups respectively.

**Comparing mild ILD and severe ILD subgroups (table 4):**

16.7% of mild patients were asymptomatic discovered only with PFT screening, in contrast, severe ILD patients had more prevalence of exercise limitation, tachypnea and clubbing regarding to symptoms and signs, and had more prevalence of cystic change and patchy consolidations regarding to HRCT findings. Moreover, Severe ILD patients had more prevalence of pulmonary hypertension. Both the Haller and cardiothoracic indexes assessment in mild ILD and severe ILD cases showed no statistically significant.

**Table 1:** Demographic and clinical characteristics of study groups

| | *CTD groups* | | | *P value* |
|---|---|---|---|---|
| | *CTD only group (20 n.)* | *CTD+ILD group (20 n.)* | | |
| | | *mildILD* | *severeILD* | |
| *Age (years)* | *13±2.2* | *11.2±2.2* | *13.6±1.2* | *0.3847* |
| *n. of Female* | *12 (60%)* | *8 (67%)* | *6 (75%)* | *0.09072* |
| *Duration of CTD (years)* | *3.2±2.5* | *1.2±0.7* | *3.6±1.2* | *0.3394* |
| *Duration of ILD (years)* | ---------- | *0.2±0.1* | *1.2±0.7* | *0.0001* |
| *CTD subgroup* | | | | |
| *JSLE* | *8 (40%)* | *7 (58.3%)* | *3 (37.5%)* | *0.97036* |
| *JRA* | *5 (25%)* | *3 (25%)* | *2 (25%)* | *0.97036* |
| *JDM* | *1 (5%)* | *0 (0%)* | *0 (0%)* | *0.97036* |
| *JSSc* | *2 (10%)* | *0 (5%)* | *1 (12.5%)* | *0.97036* |
| *JMCTD* | *4 (20%)* | *2 (16.7%)* | *2 (25%)* | *0.97036* |

JRA: juvenile rheumatoid arthritis, JSLE: juvenile systemic lupus erythematosus, JSSc: juvenile systemic sclerosis, JDM: juvenile dermatomyositis, JMCTD: juvenile mixed connective tissue disease.
One-way ANOVA, Chi-Square, and Paired sample T tests, P > 0.05: no significant differences, P < 0.05: significant differences, P < 0.001: highly significant differences

**Table 2:** Pulmonary function test outcomes.

| **Variable** | **CTD only group (20 n.)** | **CTD+ILD group** | | **P value** |
|---|---|---|---|---|
| | | mildILD (12 n.) | severeILD (8 n.) | |
| FVC, % predicted | 95±7 | 72±7* | 49±8*,** | 0.0000 |
| FEV1, % predicted | 101±7 | 77±10* | 55±5*,** | 0.0000 |

One-way ANOVA, least significant difference (LSD):
P > 0.05: no significant differences, P < 0.05: significant differences, P < 0.001: highly significant differences, (* Vs CTD only group, ** Vs mildILD group).

**Table 3:** 6 minute walk test outcomes.

| Variable | CTD only group (20 n.) | CTD+ILD group | | P value |
|---|---|---|---|---|
| | | mildILD (12 n.) | severeILD (8 n.) | |
| [1]SpO2 at start of the test, % | 98±2 | 95±3 | 88±4*,** | 0.0000 |
| [2]SpO2 at end of the test, % | 97±3 | 92±2* | 67±5*,** | 0.0000 |
| P value (1 vs 2) | 0.2225 | 0.0086 | 0.0001 | |
| [3]Dyspnea at start of the test | 0 | 1±0.5* | 3±1*,** | 0.0000 |
| [4]Dyspnea at end of the test | 2±1 | 3±2 | 4±3* | 0.0101 |
| P value (3 vs 4) | 0.0001 | 0.0028 | 0.3862 | |

One-way ANOVA, least significant difference (LSD), Paired sample T tests:
P > 0.05: no significant differences, P < 0.05: significant differences, P < 0.001: highly significant differences, (* Vs CTD only group, ** Vs mildILD group).

**Table 4:** Comparison between mildILD and severeILD subgroups

| | mildILD subgroup (12 n.) | | severeILD subgroup (8 n.) | | P value |
|---|---|---|---|---|---|
| ILD duration | 3 month ±3 | | 2 year ±1 | | <0.001* |
| Symptoms/ signs | Dyspnea | 10 (83.3%) | Dyspnea | 6 (75%) | 0.648 |
| | Cough | 6 (50%) | Cough | 6 (75%) | 0.263 |
| | Exercise limitation | 5 (41.7%) | Exercise limitation | 7(87.5%) | 0.040* |
| | Wheeze | 2 (16.7%) | Wheeze | 2 (25%) | 0.263 |
| | Frequent resp. infection | 4 (33.3%) | Frequent resp. infection | 2 (25%) | 0.690 |
| | Asymptomatic | 2 (16.7%) | Asymptomatic | 0 | 0.0000* |
| | Tachypnea | 0 | Tachypnea | 2 (25%) | 0.0000* |
| | Clubbing | 0 | Clubbing | 2 (25%) | 0.0000* |
| Chest x-ray | Basal infiltration | 10(83.3%) | Basal infiltration | 4 (50%) | 0.111 |
| | Prehilar consolidation | 6 (50%) | Prehilar consolidation | 4 (50%) | 1.0 |
| | Increase bronchovascular marking | 8 (66.7%) | Increase bronchovascular marking | 4 (50%) | 0.456 |
| | Reticular obacities | 3 (25%) | Reticular obacities | 1(12.5%) | 0.493 |
| | Accentuated pulmonary notch | 2 (16.7%) | Accentuated pulmonary notch | 2 (25%) | 0.263 |
| | Pleural effusion | 2 (16.7%) | Pleural effusion | 4 (50%) | 0.111 |
| Cardiothoracic index | | 0.48±0.09 | | 0.56±0.11 | 0.0913 |
| HRCT | Intralobular septal thickening | 10 (83.3%) | Intralobular septal thickening | 6 (75%) | 0.648 |
| | Ground glass appearance | 3 (25%) | Ground glass appearance | 5(62.5%) | 0.093 |
| | Thickened intralobar lines | 4 (33.3%) | Thickened intralobar lines | 4 (50%) | 0.263 |
| | cystic change | 2 (16.7%) | cystic change | 6 (75%) | 0.009* |
| | Patchy consolidations | 2 (16.7%) | Patchy consolidations | 6 (75%) | 0.009* |
| Haller index | | 0.52±0.12 | | 0.63±0.17 | 0.1059 |
| Transthoracic echocardiography | pulmonary hypertension | 2 (16.7%) | pulmonary hypertension | 6 (75%) | 0.009* |

Chi-Square, and Paired Sample T tests, P > 0.05: no significant differences, P < 0.05: significant differences, P < 0.001: highly significant differences. * Significant difference.

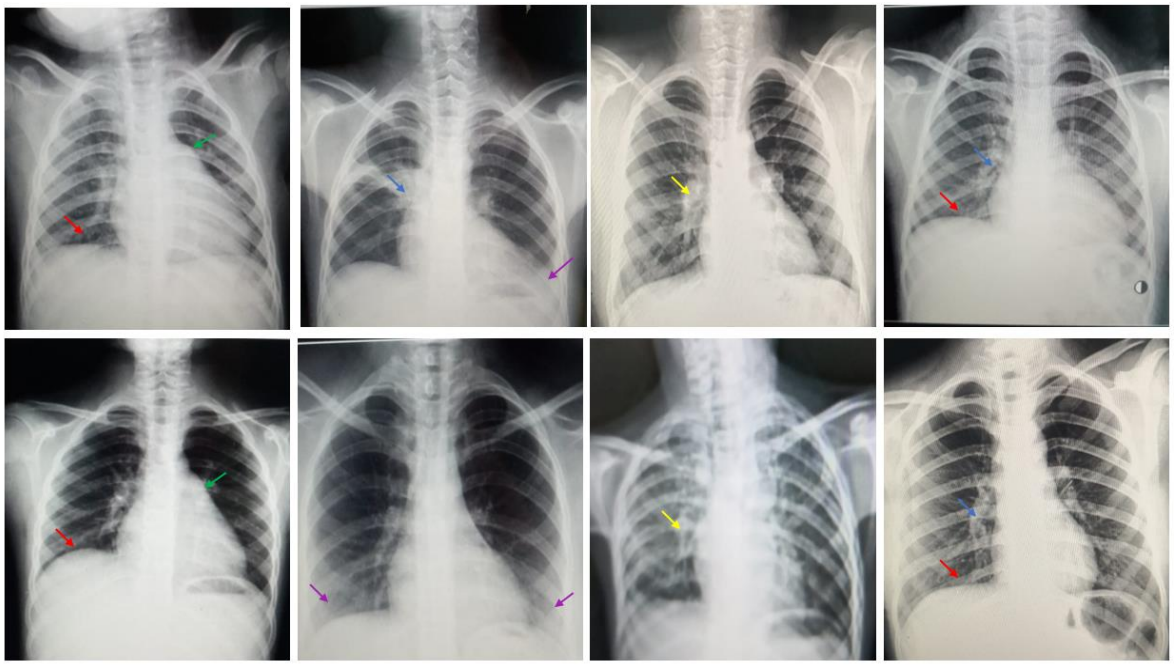

**Figure 1:** Chest X-ray of CTD+ILD group shows basal infiltration (red arrows), prehilar consolidation (yellow arrows), increase bronchovascular marking (blue arrows), accentuated pulmonary notch at left side (green arrows), and pleural effusion (purple arrows), (Dr. Rabab Elbehedy, Dr. Mohamod Zaiton).

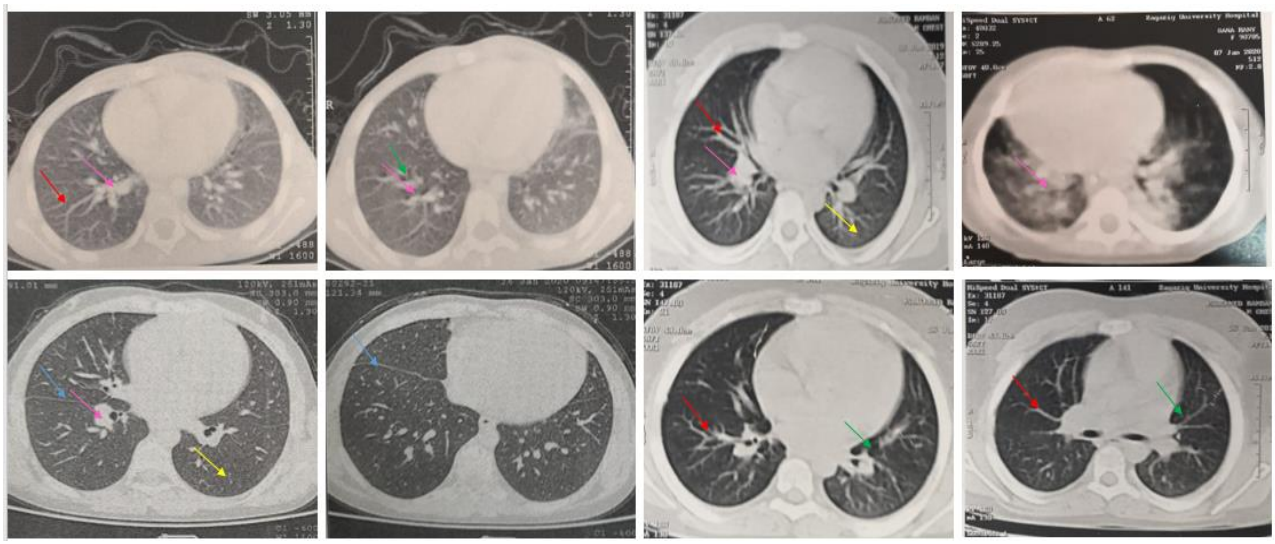

**Figure 2-7:** HRCT of CTD+ILD group shows irregular interlobular septal thickening (red arrows), ground-glass attenuation (yellow arrows), thickened intralobar lines (blue arrows), cystic change (green arrows), and pathcy consolidations (purple arrows) (Dr. Rabab Elbehedy, Dr. Mohamod Zaiton).

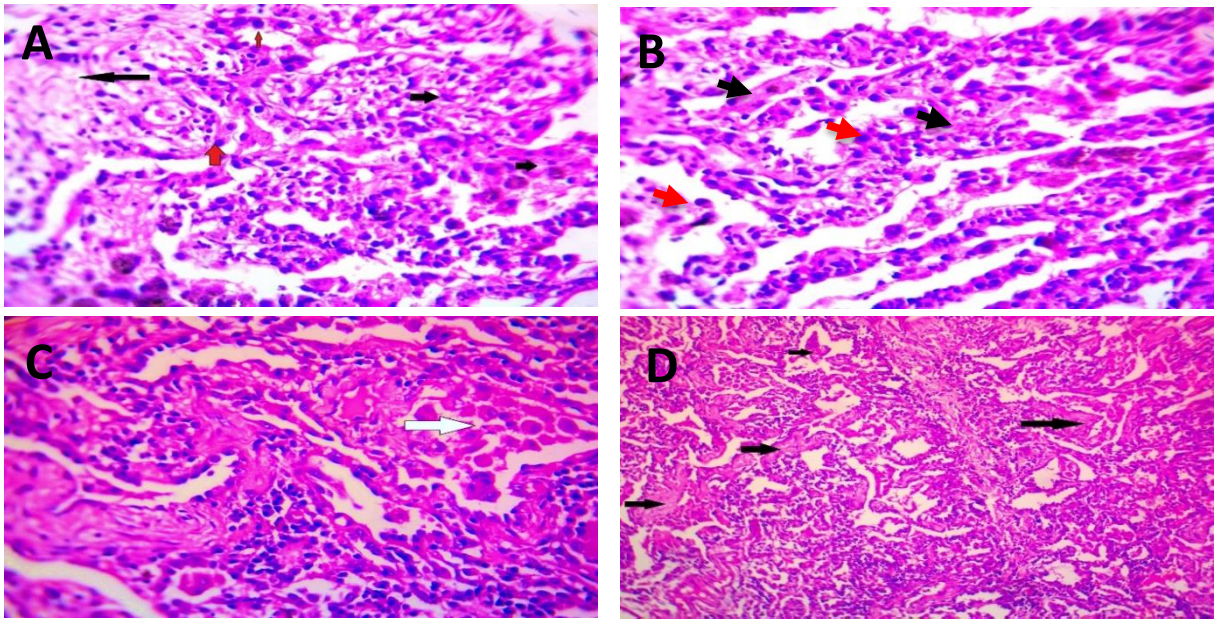


**Figure 3:** Characteristic lung biopsy of ILD patients, A,B: section of lung showed interstitial fibrosis and hyalinosis black arrow with reactive type II pneumocytes red arrow C,D: section of lung showed desquamated cells (white arrow), interstitial fibrosis (black arrows), (HE x400) (Dr. Hayam Rashed).

## DISCUSSION

Juvenile CTD has a high morbidity and mortality that may alter any organs. Yet, ILD is a rare but it is one of the most serious complications of CTD [3,22]. Interstitial lung disease (ILD) refers to a varied group of conditions with abnormal gas exchange due to distorted structure of the interstitial of the lung [20]. As a result of this solid review, our study aims to describe lung functions, radiological abnormalities, and the lung biopsy findings in a group of childhood interstitial lung disease (chILD) accompanied by underlying connective tissue disease. Because of the rarity of ILD, our study design was retrospective, all CTD children between October 2019 and March 2020 were examined for presence of ILD, all diagnostic modalities were revised.

Our study concluded that, there is no significance difference in the mean age of the study groups, with female predominance in all groups. While, our study showed more prevalence of SLE (18 cases) in study groups followed by JRA (10 cases), in contrast to Lee et al., and Barut et al. who said that "JIA is the most common CTD of childhood" [23,24].

Regarding to symptoms/signs in ILD groups, the clinical manifestations was frequently slight and vague as reported by Fan et al., [25]. The onset of symptoms was insidious in most cases (80%). However, most of patients (75%) has symptoms for less than one year at time of examination. The clinical manifestations diverged from only radiological finding without symptoms suggestive ILD to more specific clinical presentations. The common symptoms at presentation were dyspnea (80%), cough (60%, dry and not interrupt sleep), exercise limitation (60%), frequent respiratory infections (50%), wheezing (33.3%), tachypnea and chest wall retraction (10%), clubbing (10%) and asymptomatic (10%). The symptoms and signs severity correlate positively with severity of the disease dyspnea as assessed by clinical examination.

Those results were not totally agreement with Tang et al. who said that "the most common symptoms and signs in children with ILD were cough (71%), tachypnea (66%) and exercise intolerance (52%), dyspnea (22%) followed with hypoxia, failure to thrive, clubbing" [26].

Moreover, Quadrelli et al. mentioned that "interstitial lung disease (ILD) is rare in

pediatric patients with JSLE, but it may follow as a complication of acute lupus pneumonitis" [27]. Richardson et al. (28) reported that JSLE may had more perniciously with a chronic dry cough, dyspnoea on exertion and pleuritic chest pain, while ILD with JDM had rising cough and dyspnoea, even if asymptomatic [28].

Furthermore, our study showed that transthoracic echocardiography (TTE) examination revealed mild to moderate pulmonary hypertension in 40% of ILD patients. As well as Tang et al. mentioned that "echocardiography was performed in 98.3% of the patients and pulmonary arterial hypertension (PH) was found in 12%" [26].

Spirometry and chest x-ray should be performed on all children with SLE at diagnosis and at any point during their follow-up if they became symptomatic, and HRCT was done in those with abnormal findings [29]. In our study chest x-ray's common findings in ILD were basal infiltration in one or both side in 70% of patients, increase bronchovascular marking (60%), prehilar consolidation (50%), involvement of the supporting tissue of the lung parenchyma resulting in reticular opacities (40%), mild to moderate Pleural effusion (30%), and accentuated pulmonary notch at left side (10%). Nevertheless, Copley and Bush mentioned that HRCT define the degree of ILD, detect disease involvement and are more sensitive than X-rays in spotting structural alterations related to chILD [30].

Regarding to finding of HRCT in ILD groups, the most common findings were irregular interlobular septal thickening (80%), widespread ground-glass attenuation (40%), and thickened intralobular lines (40%), cystic change (40%) and patchy consolidation (40%). HRCT was useful for ILD diagnosis, monitor disease activity and severity, follow up, and choice site of lung biopsy.

Those results were nearly agreement with Tang et al. who said that the findings of HRCT were ground glass opacities (85%), reticular patches (44%), nodules, cysts, consolidation, pleural thicken and effusion (16%), and pneumothorax (3%) [26].

Moreover, Dong et al. reported that "different findings of abnormalities and distribution in HRCT from 206 patients with CTD-ILD were reticular pattern (92.7%), ground-glass attenuation (87.4%), and vascular bundle thickening (82%), followed by pleural effusion (62.1%), airspace consolidation (34.5%), nodules (31.6%), fibrotic streak (31.1%), cystic changes (25.2%), honeycombing (20.4%), subpleural curvilinear shadow (18%), lung bullae (4.9%), and mosaic perfusion (4.4%). Also, bilateral infiltrates (99%), with abnormalities predominantly in the lower lobes (89.3%) and subpleural areas (81.1%). Moreover, a few lesions were hilum distributed (8.7%)" [31].

Also, Hetlevik et al. mentioned that HRCT findings in JMCTD patients were reticular thickening and ground-glass opacitied, interlobular septal thickening, alveoli amalgamations, and/or traction bronchiectasis, the most common deformity was a reticular thickening (25%) [32].

HRCT is the gold standard to assess for signs of early ILD in adults. But, due to the disease infrequency in juvenile age, a lung biopsy may be needed to verify the diagnosis [33]. lung biopsy is the cornerstone to assess lung disease in JIA preceding to starting therapy [34].

Regarding to Surgical lung biopsy (SLB), the lung histological patterns which observed were NSIP (Non-specific interstitial pneumonia, 3 patients), and DIP (Desquamative interstitial pneumonia, 1patients). These results coped with Chung et al., who reported that in patients with CTD, NSIP is the most common type of lung disease [35]. And, with [36,37].

Because of, respiratory assessing by PFTs is used to monitor for early signs of respiratory deterioration [28], our study concluded that Spirometry is a useful investigation for assess the severity and to follow up of ILD. Normally, in ILD, pulmonary function malfunctions reflected a restrictive lung problem with decreased lung compliance and lung volumes. CTD group showed a forced expiratory volume in 1 s (FEV1) (% predicted) 101 ± 7, forced vital capacity (FVC) (% predicted) 95 ± 7, the

mild ILD group showed a FEV1% 77 ± 10, FVC% 72 ± 7, and the severe ILD group showed a FEV1% 55 ± 5, FVC% 49 ± 8.

PFTs usually evaluated include FVC, FEV1 and FEV1/FVC ratio. A restrictive type in JSLE is the most seen defect [38], and also Hetlevik et al. mentioned that "in a cohort of 52 patients with JMCTD, patients with JMCTD had lower forced vital capacity (FVC), mostly as mild disease, and did not progress" [32]. PFTs in diagnosis and monitoring of JIA is vital. PFT deviations take place in many of children with JIA, with more frequent restrictive lung functions [39].

The 6MWT is a useful investigation for functional condition of patients, and an indicator of morbidity and mortality. The mean end-test SpO2 was 96% ± 3 of CTD group Vs 92% ± 2, 67% ± 5 in mild ILD and severe ILD groups respectively. The mean end-test dyspnea grade evaluated with the modified Borg scale was 2 ± 1, 3 ± 2, 4 ± 3 in CTD, mild ILD and severe ILD groups respectively.

As mentioned by Hetlevik et al. JMCTD Patients walked a mean 65 m less on the 6MWT than controls [32]. 6MWT remained significantly lower in patients than in their matched controls. As mentioned by Chetta et al., the 6MWT was clearly reduced compared with that of controls, but within the expected normal range [40].

While comparing mild ILD and severe ILD subgroups, 16.7% of mild patients were asymptomatic discovered only with PFT screening, in contrast, severe ILD patients had more prevalence of exercise limitation, tachypnea and clubbing regarding to symptoms and signs, and had more prevalence of cystic change and patchy consolidations regarding to HRCT findings. Moreover, Severe ILD patients had more prevalence of pulmonary hypertension. This result synchronised with Chung et al., in study carried on 136 adults with autoimmune interstitial pneumonia, mentioned that CT findings that were linked with bad prognosis were the percentage of reticulation, the honeycombing appearance, emphysema, and pulmonary artery widening [35]. As well as Condliffe et al. mentioned that pulmonary hypertension is a known manifestation of CTD and has bad predictive consequences [41].

## CONCLUSIONS

For early prediction and follow up of development of ILD in CTD children, it is recommended to do routine checks of PFT even in the lack of respiratory warning sign, while HRCT is the gold standard to confirm and specify diagnosis.

**Conflict of Interest:** None.

**Financial disclosure:** None.

## REFERENCES

1. Solomon JJ, Fischer A. Connective Tissue Disease-Associated Interstitial Lung Disease: A Focused Review. Journal of intensive care medicine. 2015;30(7):392-400.
2. Malattia C, Martini A. Paediatric-onset systemic lupus erythematosus. Best practice & research Clinical rheumatology. 2013;27(3):351-62.
3. Oguz EO, Kucuksahin O, Turgay M, Ates A, Kinikli G, Duzgun N, et al. Association of serum KL-6 levels with interstitial lung disease in patients with connective tissue disease: a cross-sectional study. Clin Rheumatol Clinical Rheumatology. 2016;35(3):663-6.
4. Navallas M, Inarejos Clemente EJ, Iglesias E, Rebollo-Polo M, Antón J, Navarro OM. Connective Tissue Disorders in Childhood: Are They All the Same? Radiographics : a review publication of the Radiological Society of North America, Inc. 2019;39(1).
5. Saper VE, Chen G, Deutsch GH, Guillerman RP, Birgmeier J, Jagadeesh K, et al. Emergent high fatality lung disease in systemic juvenile arthritis. Annals of the rheumatic diseases. 2019;78(12):1722-32.
6. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. JOIM Journal of Internal Medicine. 2006;260(5):429-34.
7. Olson AL, Brown KK, Fischer A. Connective tissue disease-associated lung disease. Immunology and allergy clinics of North America. 2012;32(4):513-36.
8. Fischer A, Chartrand S. Assessment and management of connective tissue disease-associated interstitial lung disease. Sarcoidosis Vasc Diffuse Lung Dis. 2015; 22(32):2–21.
9. Atzeni F, Boiardi L, Sallì S, Benucci M, Sarzi-Puttini P. Lung involvement and drug-induced lung disease in patients with rheumatoid arthritis. Expert review of clinical immunology. 2013;9(7):649-57.
10. Assayag D, Lee J, King T. Rheumatoid arthritis associated interstitial lung disease: a review. Medicina (B Aires). 2014;74:158–165.

11. Shaw M, Collins BF, Ho LA, Raghu G. Rheumatoid arthritis-associated lung disease. Eur Respir Rev European respiratory review : an official journal of the European Respiratory Society. 2015;24(135):1-16.
12. Wynn T. Integrating mechanisms of pulmonary fibrosis. J Exp Med. 2011;208:1339–1350.
13. Aletaha D, Neogi T, Silman AJ, Funovits J, Felson DT, Bingham CO, et al. 2010 Rheumatoid Arthritis Classification Criteria An American College of Rheumatology/European League Against Rheumatism Collaborative Initiative. Arthritis and rheumatism. 2010;62(9):2569-81.
14. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Annals of the rheumatic diseases. 2019;78(9):1151-9.
15. Lundberg IE, Tjärnlund A, Bottai M, Werth VP, Pilkington C, Visser M, et al. 2017 European League Against Rheumatism/American College of Rheumatology classification criteria for adult and juvenile idiopathic inflammatory myopathies and their major subgroups. Annals of the rheumatic diseases. 2017;76(12):1955-64.
16. Zulian F, Woo P, Athreya BH, Laxer RM, Medsger TA, Lehman TJA, et al. The Pediatric Rheumatology European Society/American College of Rheumatology/European League against Rheumatism provisional classification criteria for juvenile systemic sclerosis. ART Arthritis Care & Research. 2007;57(2):203-12.
17. Tanaka Y, Kuwana M, Fujii T, Kameda H, Muro Y, Fujio K, et al. 2019 Diagnostic criteria for mixed connective tissue disease (MCTD): From the Japan research committee of the ministry of health, labor, and welfare for systemic autoimmune diseases. Modern Rheumatology. 2020:1-5.
18. Popler J, Lesnick B, Dishop MK, Deterding RR. New Coding in the International Classification of Diseases, Ninth Revision, for Children's Interstitial Lung Disease. CHEST Chest. 2012;142(3):774-80.
19. Kurland G, Deterding RR, Hagood JS, Young LR, Brody AS, Castile RG, et al. An official American Thoracic Society clinical practice guideline: classification, evaluation, and management of childhood interstitial lung disease in infancy. American journal of respiratory and critical care medicine. 2013;188(3):376-94.
20. Bush A, Cunningham S, de Blic J, Barbato A, Clement A, Epaud R, et al. European protocols for the diagnosis and initial treatment of interstitial lung disease in children. Thorax. 2015;70(11):1078-84.
21. Ewert F, Syed J, Wagner S, Besendoerfer M, Carbon RT, Schulz-Drost S. Does an external chest wall measurement correlate with a CT-based measurement in patients with chest wall deformities? J Pediatr Surg. 2017 Oct;52(10):1583-1590. doi: 10.1016/j.jpedsurg.2017.04.011. Epub 2017 Apr 27. PMID: 28499711.
22. Satoh H, Kurishima K, Ishikawa H, Ohtsuka M. Increased levels of KL-6 and subsequent mortality in patients with interstitial lung diseases. J Intern Med Journal of Internal Medicine. 2006;260(5):429-34.
23. Lee J, Lee Y, Ha Y, Kang E, Lee Y, Song Y. Serum KL-6 levels reflect the severity of interstitial lung disease associated with connective tissue disease. Arthritis Research & Therapy. 2019;21(1):1-8.
24. Barut K, Adrovic A, Şahin S, Kasapcopur O. Juvenile Idiopathic Arthritis. Balkan Medical Journal. 2017;34(2):90–101.
25. Fan LL, Kozinetz CA, Deterding RR, Brugman SM. Evaluation of a diagnostic approach to pediatric interstitial lung disease. Pediatrics. 1998;101(1 Pt 1):82-5.
26. Tang X, Li H, Liu H, Xu H, Yang H, Liu J, et al. Etiologic spectrum of interstitial lung diseases in Chinese children older than 2 years of age. Orphanet J Rare Dis. 2020;15(1):25-.
27. Quadrelli SA, Alvarez C, Arce SC, Paz L, Sarano J, Sobrino EM, et al. Pulmonary involvement of systemic lupus erythematosus: analysis of 90 necropsies. Lupus. 2009;18(12):1053-60.
28. Richardson AE, Warrier K, Vyas H. Respiratory complications of the rheumatological diseases in childhood. Arch Dis Child. 2016;101(8):752-8.
29. Beresford MW, Cleary AG, Sills JA, Couriel J, Davidson JE. Cardio-pulmonary involvement in juvenile systemic lupus erythematosus. Lupus. 2005;14(2):152-8.
30. Copley SJ, Bush A. HRCT of paediatric lung disease. Paediatr Respir Rev. 2000;1(2):141-7.
31. Dong X, Zhou J, Guo X, Li Y, Xu Y, Fu Q, et al. A retrospective analysis of distinguishing features of chest HRCT and clinical manifestation in primary Sjögren's syndrome-related interstitial lung disease in a Chinese population. Clin Rheumatol. 2018;37(11):2981-8.
32. Hetlevik SO, Flatø B, Aaløkken TM, Lund MB, Reiseter S, Mynarek GK, et al. Pulmonary Manifestations and Progression of Lung Disease in Juvenile-onset Mixed Connective Tissue Disease. J Rheumatol. 2019;46(1):93-100.
33. Dell BSD, Schneider R. 57 - Pulmonary Involvement in the Systemic Inflammatory Diseases of Childhood. In: In: Wilmott RW KE, Boat TF, et al. eds., editor. Kendig and Chernick's disorders of the respiratory tract in children USA: Saunders: Elsevier; 2012. p. 822–47.
34. Rabinovich C, Fels E, Shanahan J, Majure J, Thomas M. Chapter 10—pulmonary manifestations of rheumatoid diseases. In: Turcios NL FR, editor. Pulmonary manifestations of pediatric diseases. USA: Saunders: Elsevier; 2009. p. 201–82.

35. Chung JH, Montner SM, Adegunsoye A, Lee C, Oldham JM, Husain AN, et al. CT Findings, Radiologic-Pathologic Correlation, and Imaging Predictors of Survival for Patients With Interstitial Pneumonia With Autoimmune Features. AJR Am J Roentgenol. 2017;208(6):1229-36.
36. Kim HC, Ji W, Kim MY, Colby TV, Jang SJ, Lee CK, et al. Interstitial pneumonia related to undifferentiated connective tissue disease: pathologic pattern and prognosis. Chest. 2015;147(1):165-72.
37. Omote N, Taniguchi H, Kondoh Y, Watanabe N, Sakamoto K, Kimura T, et al. Lung-Dominant Connective Tissue Disease: Clinical, Radiologic, and Histologic Features. Chest. 2015;148(6):1438-46.
38. Kakati S, Doley B, Pal S, Deka UJ. Pulmonary manifestations in systemic lupus erythematosus (SLE) with special reference to HR CT. J Assoc Physicians India. 2007;55:839-41.
39. Alkady EAM, Helmy HAR, Mohamed-Hussein AAR. Assessment of cardiac and pulmonary function in children with juvenile idiopathic arthritis. Rheumatol Int. 2012;32(1):39-46.
40. Chetta A, Zanini A, Pisi G, Aiello M, Tzani P, Neri M, et al. Reference values for the 6-min walk test in healthy subjects 20-50 years old. Respir Med. 2006;100(9):1573-8.
41. Condliffe R, Kiely DG, Peacock AJ, Corris PA, Gibbs JS, Vrapi F, et al. Connective tissue disease-associated pulmonary arterial hypertension in the modern treatment era. Am J Respir Crit Care Med. 2009;179(2):151-7.

To Cite:
Domouky, A., El-Beheidy, R. Diagnosis of Interstitial Lung Disease in Connective Tissue Disease Children: Retrospective Study. *Zagazig University Medical Journal*, 2022; (1356-1367): -. doi: 10.21608/zumj.2021.44366.1955