Subclinical High Resolution Chest CT Scan Features In Psoriasis

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Abstract

Background: Although psoriasis is considered a systemic disease, no clear association has been established between psoriasis and lung diseases.

Methods: Adult psoriasis patients with no known active pulmonary disease or respiratory symptoms were screened for subclinical pulmonary manifestations and possible parenchymal changes using high-resolution computed tomography (HRCT) scan of the chest. Patients were classified according to the severity of skin manifestations. The clinical characteristics and radiographic findings of these patients were evaluated.

Results: A total of 59 patients with psoriasis were included, among which 47 (79.7%) had abnormal HRCT scan features. Micronodules were the most common detected lung lesions (66.1%), followed by interlobular septal thickening (23.7%), fibrosis (11.9%), and ground-glass opacity (6.8%). Other HRCT findings included emphysematous changes and calcified granulomas. Abnormal HRCT findings correlated with older age and duration of psoriasis but not with the severity of skin manifestations.

Conclusions: Micronodules and interlobular septal thickening were the most detected lung lesions in patients with psoriasis. These findings of the pilot study highlight the possible pulmonary involvement in patients with psoriasis. Larger multicenter studies are needed to further clarify these findings.

Introduction

Psoriasis is a chronic inflammatory and disabling disease (1, 2) that results from genetic, environmental, and immunologic factors (3, 4). It affects 2–3% of the population and is characterized by scaly and erythematous skin patches, papules, and plaques (5, 6). Psoriasis does not only affect the skin, but also known to have a systemic component as it was reported to affect various organs (7), leading to joint disorders (8), enthesitis (9, 10), cardiovascular events (11), arterial hypertension (12), diabetes (13), and non-alcoholic fatty liver (14). It remains controversial whether psoriasis can be considered as an independent risk factor for these diseases (15, 16). Patients with psoriasis are routinely screened for prevalent well-known comorbidities, including cardiovascular diseases and diabetes mellitus (7–14). However, lung involvement is not routinely investigated unless respiratory symptoms manifest. (17) Hence, asymptomatic, mild parenchymal involvement associated with psoriasis may have been underdiagnosed and when incidentally found, raises the question of association. (17) Respiratory comorbidities are poorly characterized in psoriasis with conflicting findings (18, 19). Several studies have illustrated a correlation between psoriasis and several types of respiratory comorbidities such as asthma (17, 18, 19), COPD (20–23) and ILD (24). Although there is increasing evidence of association between psoriasis and lung involvement, data regarding chest CT features in psoriasis remains scarce (24). Identifying various subclinical parenchymal lung manifestations in psoriasis is significant to better understanding of the disease spectrum in relation to various confounding factors that might affect the lung parenchyma of these patients who are susceptible to infections (17, 18, 25–27) and various

pulmonary side effects of different therapeutic agents used along the disease course which have been linked to ILD in psoriasis cases (28, 29).

This study aims to utilize high-resolution CT scan of the chest (HRCT) to detect and describe subclinical pulmonary involvement in patients with psoriasis and explore if such involvement correlates with the severity of psoriatic skin manifestations.

Materials And Methods

Participants, Study Design, Specimen, and Data Collection:

This single-center observational cross-sectional study was conducted at King Abdullah University Hospital (KAUH), Irbid, Jordan. All adult patients (≥ 18 years) with psoriasis who visited KAUH dermatology clinic between June 1, 2019, and March 20, 2020 were eligible for the study. The study included those diagnosed with various degrees of cutaneous psoriasis. We excluded pregnant female patients, patients who have concomitant connective tissue disease, active pulmonary symptoms, uncontrolled cardiac diseases or established pulmonary diseases such as interstitial lung disease (ILD), asthma or chronic obstructive lung disease (COPD). Patients with psoriasis who received methotrexate or biologic agents for more than two weeks or within 6 months prior to time of the HRCT were also excluded. The coexistence of connective tissue diseases that might cause ILD was excluded through clinical evaluation and laboratory tests including autoantibodies. Symptomatic asthma cases were screened out using internationally recognized life quality questionnaire (LQ), (Winder JA, 2000). Candidates with significant history of smoking were screened for undiagnosed clinical COPD using COPD Assessment Test (CAT), patients with CAT score of 10 or more were excluded from the study (Nisha Gupta, 2014). Only psoriasis cases with no active respiratory symptoms at the time of the study recruitment were included. Pregnancy was ruled out by submitting a serum beta human chorionic gonadotropin (β-HCG) pregnancy test prior to HRCT scan examination in all female candidates in their childbearing age.

Low dose radiation HRCT of the chest was the method applied to evaluate the involvement of pulmonary parenchyma. Images were reviewed by a board-certified pulmonologist and radiologist (S.S and K.Z.). Psoriasis area and severity index (PASI) was used to objectively assess the severity of psoriasis cutaneous involvement. Patients were divided according to PASI-scores into 3 groups, mild (less than 5), moderate (5–10) and severe (greater than 10). Electronic medical records of all patients were reviewed for demographic, clinical, radiological, and treatment details. Data not available in the medical records was obtained through direct communication with patients and their families. Written informed consent was obtained from all recruited patients prior to study commencement. This study was approved by the institutional review board (IRB) and the research and ethics committee at Jordan University of Science and Technology (#20190178).

Definitions

The following radiological definitions were used as a guide to characterize HRCT findings:

- **Nodule**: well marginated round opacity and no greater than 3 cm in maximum diameter.
- **Interstitial fibrosis**: describes an excess of fibrotic tissue in the lung; this includes honeycombing, traction bronchiectasis, lung architectural distortion, reticulation, and interlobular septal thickening.
- **Interlobular septal thickening (ILST)**: a computed tomography finding of increased width of the walls (septa) between the pulmonary lobules.
- **Reticulation/reticular changes**: innumerable interlacing line shadows that suggest a mesh.
- **Ground glass opacity (GGO)**: hazy increased opacity or attenuation of the lung parenchyma with preservation of the bronchial and vascular margins.
- **Mosaic changes**: a patchwork of different attenuation regions interpreted as secondary to regional differences in perfusion or air trapping.
- **Emphysema**: focal region or regions of low attenuation without visible walls.
- **Peripheral**: referring to pulmonary structures within 1–2 cm of any visceral pleura.

Statistical Analysis

Data was processed and analyzed using the IBM Statistical Package for Social Sciences Software (SPSS) for Windows, version 23.0. ANOVA test was used to analyze the significant relations between the continuous variables, whereas Chi-Square was used to analyze the suggested relations between the categorical variables. A 2-sided *p*-value of less than 0.05 was considered statistically significant.

Results

A total of 228 patients with psoriasis visited the dermatology clinic at KAUH during the study recruitment period from June 1, 2019, to March 20, 2020. After applying the study criteria, a total of 59 patients were included in the study, **(**Fig. 1**).** The mean age was 41.6 years and ranged from 18 to 71 years. More than half of the patients (66.1%) were males. Patients were divided according to the HRCT findings into 2 groups: One with normal HRCT features and the other with abnormal HRCT findings. Table 1 describes the demographic characteristics and PASI-scores of both groups at the time of the HRCT.

Table 1
patients demographics, Normal Vs abnormal CT findings

	Total **n = 59**	**Normal HRCT** **n = 12, (20.3%)**	**Abnormal HRCT** **n = 47, (79.8%)**	***p*-value**
Age, years (mean)	41.6	32.6	44	**0.02**
Male gender	39(66.1%)	8(66.7%)	31(66%)	1
Psoriasis duration, years (mean)	13.2	7.2	14.8	**0.044**
Smoking				0.692
Smoker	26(44.1%)	4(33.3%)	22(46.8%)	
Ex-smoker	9(15.3%)	2(16.7%)	7(14.9%)	
Non-smoker	24(40.7%)	6(50%)	18(38.3%)	
Comorbidities	26(44.1%)	4(33.3%)	22(46.8%)	0.521
Diabetes mellitus	11(18.6%)	1(8.3%)	10(21.3%)	0.431
Hypertension	11(18.6%)	2(16.7%)	9(19.1%)	1
Coronary artery disease	7(11.9%)	2(16.7%)	5(10.6%)	0.599
PASI Categories				
Mild	22(37.3%)	4(33.3%)	18(38.3%)	0.518
Moderate	17(30.9%)	3(25%)	14(29.8%)	
Severe	20(33.9%)	5(41.7%)	15(31.9%)	
* odd for smokers and ex-smokers / non- smokers				

A minority of patients had normal HRCT features (n = 12, 20.3%) while the majority (n = 47, 79.7%) had abnormal findings in their HRCT. The group of psoriasis cases with abnormal HRCT findings were older (44.0 vs 32.6 years, $p = 0.02$) and had psoriasis for a longer duration compared to the group with normal HRCT, (14.8 vs 7.2 years, $p = 0.044$). There was no difference in PASI-scores between the two groups.

Lung nodules were the most prominent parenchymal lung lesion detected by HRCT scan (39, 66.1%), followed by features of ILD (19, 32.2%) manifested as interlobular septal thickening (14, 23.7%), fibrosis (7, 11.9%) and ground glass opacity (4, 6.8%). A total of 6 patients had a combination of more than one ILD manifestation. Other HRCT findings included emphysematous changes (12, 20.3%), and calcified granuloma (10, 16.9%), (Table 2**).** Most lung nodules were less than 6 mm in diameter (87.2%). Only one patient had a nodule measuring more than 8 mm. Apart from this patient, all nodules detected in patients with mild cutaneous psoriasis were < 6 mm in diameter. None of the (6–8 mm) nodules were detected in the group with mild cutaneous psoriasis, compared to the severe group (3/4, 75%) and moderate group

(1/4, 25%). Similarly, all parenchymal changes detected in the study population were mild in nature. GGO, ILST and irregular reticular changes were peripheral and predominantly involved the lower lung lobes. Sample of HRCT scans are shown in Figs. 2 **(A-D)**. None of the abnormal HRCT findings correlated with the severity of cutaneous psoriasis manifestations/PASI-scores. Although not statistically significant, all GGO and most of fibrotic findings were seen in the group with moderate and severe skin manifestation, (4/4 (100%), and 6/7 (85%), respectively).

Table 2
Patient's demographics and CT scan findings in correlation to PASI scores

	Total (n = 59)	**Mild *(PASI < 5)* 22(37.3%)**	**Moderate *(PASI 5–10)* 17(28.8%)**	**Severe *(PASI > 10)* 20(33.9%)**	***p*-value**
Age, years (mean)	41.6	43	40	41.6	0.834
Male gender	39(66.1%)	14(63.6%)	13(76.5%)	12(60%)	0.547
Psoriasis duration	13.2	17.1	8.8	12.9	0.091
Smoking (n/%)					0.381
Smoker	26(44.1%)	8(36.4%)	9(53%)	9(45%)	
Ex-smoker	9(15.3%)	2(9.1%)	4(23.5%)	3(15%)	
Non-smoker	24(40.7%)	12(54.5%)	4(23.5%)	8(40%)	
Comorbidities	26(44.1%)	7(31.8%)	10(58.8%)	7(35%)	0.241
Diabetes mellitus	11(18.6%)	4(18.2%)	2(11.8%)	5(25%)	0.587
Hypertension	11(18.6%)	2(9.1%)	3(17.6%)	6(30%)	0.219
Coronary artery disease	7(11.9%)	3(13.6%)	2(11.8%)	2(10%)	0.936
CT findings					
Normal	12(20.3%)	4(18.2%)	3(17.6%)	5(25%)	0.816
Mosaic attenuation	4(6.8%)	2(9.1%)	1(5.9%)	1(5%)	0.857
Calcified granuloma	10(16.9%)	4(18.2%)	3(17.6%)	3(15%)	0.959
Emphysema	12(20.3%)	4(18.2%)	4(23.5%)	4(20%)	0.918
ILD	19(32.2%)	5(22.7%)	8(47.1%)	6(30%)	.263
ILST	14(23.7%)	4(18.2%)	6(35.3%)	4(20%)	0.410
GGO	4(6.8%)	0	2(11.8%)	2(10%)	0.273
fibrosis	7(11.9%)	1(4.5%)	3(17.6%)	3(15%)	0.395
Nodules	39(66.1%)	13(59.1%)	12(70.6%)	14(70%)	0.680

	Total (n = 59)	Mild *(PASI < 5)* 22(37.3%)	Moderate *(PASI 5–10)* 17(28.8%)	Severe *(PASI > 10)* 20(33.9%)	*p*-value
Nodule number	13(33.3%)	7(53.8%)	2(16.7%)	4(28.6%)	0.268
- 1	9(23%)	4(30.7%)	3(25%)	2(14.3%)	
- 2–3	17(43.5%)	2(15.4%)	7(58.3%)	8(57.1%)	
- > 3					
Nodule size					
- < 6 mm	34(87.2%)	12(92.3%)	11(91.7%)	11(78.6%)	
- 6–8 mm	4(10.3%)	0	1(8.3%)	3(21.4%)	0.261
- > 8mm	1(2.5%)	1(7.7%)	0	0	

When HRCT manifestations were distributed according to the smoking history (Table 3), patients with smoking history were found to be predominately male (34/35, 97.1%) and actively smoking patients were younger than patients who quit smoking or never smoked, ($p = 0.029$). Smoking did not correlate with the duration of psoriasis and none of the HRCT findings correlated with the smoking history. However, emphysematous changes were seen more in patients with smoking history (83.3%). When nodules were subdivided according to their size and numbers of nodules detected in each case, most of the larger-sized nodules (≥ 6 mm) were detected in patients with smoking history (4/5, 80%). Most of the cases with higher number of nodules (> 3) detected were among the smoker and ex-smoker groups, whereas more cases with (2–3) nodules were among the group that never smoked, ($p = 0.038$).

Table 3
HRCT scan findings in correlation to smoking history

	Smokers	**Ex-smokers**	**Non-smokers**	***p*-value**
	26(44.1%)	***9(15.3%)***	***24(40.7%)***	
Age, years (mean)	37.7	53.1	41.6	**0.029**
Psoriasis Duration, years	12.16	19.1	12.04	0.258
Male gender	25(96.2%)	9(100%)	5(20.8%)	**0.000**
PASI categories				0.381
Mild	8(30.8%)	2(22.2%)	12(50%)	
Moderate	9(34.6%)	4(44.4%)	4(16.7%)	
Severe	9(34.6%)	3(33.3%)	8(33.3%)	
CT findings				
Normal	4(15.4%)	2(22.2%)	6(25%)	0.692
Mosaic attenuation	1(3.8%)	0	3(12.5%)	0.324
Calcified granuloma	3(11.5%)	4(44.4%)	3(12.5%)	0.058
Emphysema	7(26.9%)	3(33.3%)	2(8.3%)	0.152
ILD	9(34.6%)	3(33.3%)	7(29.2%)	0.916
ILST	6(23.1%)	3(33.3%)	5(20.8%)	0.750
GGO	3(11.5%)	0	1(4.2%)	0.397
fibrosis	3(11.5%)	1(11.1%)	3(12.5%)	0.992
Nodules	16(61.5%)	8(88.9%)	15(62.5%)	0.291
Nodule number	5(31.3%)	1(12.5%)	7(46.7%)	**0.038**
- 1	1(6.3%)	2(25%)	6(40%)	
- 2–3	10(62.5%)	5(62.5%)	2(13.3%)	
- > 3				
Nodule size				
- < 6 mm	13(81.3%)	7(87.5%)	14(93.3%)	0.759
- 6–8 mm	2(12.5%)	1(12.5%)	1(6.7%)	
- > 8mm *	1(6.2%)	0	0	

The study included 19 patients that previously received methotrexate or biological therapy. Out of 18 patients that received methotrexate, 5 (27.8%) patients had normal HRCT scan, (Table 4**)**. No difference in HRCT lung lesions was detected between the group who had exposure to methotrexate and the group with no methotrexate exposure, but most of the GGO (3/4, 75%) was found in the methotrexate group. Out of the 2 patients that had biological therapy in our study sample, one received adalimumab without methotrexate and had a lung nodule detected in the HRCT scan, while the second patient received etanercept and had methotrexate exposure in the past and was found to have normal HRCT features.

Table 4
History of Methotrexate intake and HRCT findings

	Methotrexate **n = 18**	**No Methotrexate** **n = 41**	**P value**
Age, years (mean)	43.8	32	0.47
Psoriasis duration, years (mean)	16.6	12.6	0.119
CT findings			
Normal	5(27.8%)	7(17.1%)	0.483
Mosaic attenuation	1(5.6%)	3(7.3%)	1
Calcified granuloma	3(16.7%)	7(17.1%)	1
Emphysema	2(11.1%)	10(24.4%)	0.311
ILD	7(38.9%)	12(29.3%)	0.55
ILST	4(22.2%)	10(24.4%)	0.569
GGO	3(16.7%)	1(2.4%)	0.08
fibrosis	3(16.7%)	4(9.8%)	0.664
Nodules	12(66.7%)	27(65.9%)	1
Nodule number	5(41.7%)	8(29.6%)	0.875
- 1	2(16.7%)	7(25.9%)	
- 2–3	5(41.7%)	12(44.5%)	
- > 3			
Nodule size			
- < 6 mm	12(100%)	22(81.5%)	0.280
- 6–8 mm	0	4(14.8%)	
- > 8mm	0	1(3.7%)	

Discussion

Various manifestations of parenchymal lung involvement have been detected by HRCT in the majority of our psoriasis patients (30). Lung nodules were the most common lung lesion detected (66.1%), this incidence is markedly higher than the estimated annual incidence of lung nodules in all population in the United States in 2012 (6.6/1000 person) (30). Additionally, out of a total of 24 nonsmokers, (62.5%) were found to have a lung nodule, which is a much higher incidence than that reported by Winter et al (16.9%) among healthy non-smokers (31). Detecting lung nodules did not correlate with smoking history, severity of psoriatic dermatologic manifestations or duration of disease. Except for one case, all nodules detected in our patients were less than 8 mm in diameter. Almost all lung nodules detected in patients with mild psoriasis were smaller-sized (< 6 mm) nodules, whereas larger-sized nodules (≥ 6 mm) were detected in patients with severe than moderate cutaneous psoriasis. This might indicate that micronodules can be part of the disease's natural course that might progress to a certain degree along with the extent of psoriasis cutaneous involvement. Smoking might be a contributing factor. Larger and higher number of nodules were detected in the cases with smoking history compared to non-smokers.

High incidence of interstitial changes was detected in our psoriasis patients, (32.2%). HRCT ILD changes mainly manifested as ILST/reticular changes, fibrosis and GGO or a combination of those. ILST changes were scattered mild linear, and smooth (non-nodular), with no distinctive pattern. However, they tend to involve the periphery of the lower lobes and are not associated with lobular distortion or apparent surrounding parenchymal tissue or alveolar involvement. This is the first study to describe this ILD pattern in psoriasis patients. ILST is a HRCT scan finding that usually represents pathology in the periphery of the pulmonary lobules (interlobular septa). This area is comprised of the pulmonary veins, capillaries and their associated interstitium (32). A more extensive ILST pattern is most characteristic of interstitial pulmonary edema and lymphatic carcinomatosis. Less common causes include lymphoproliferative disease, pulmonary veno-occlusive disease, and, rarely seen in septal form of amyloidosis (32–35). It was also reported in a case with coal worker pneumoconiosis (36). Such a mild form of ILST pattern of ILD seen in our cases has not been reported in the literature and the significance of this finding is yet to be determined.

The prevalence of idiopathic pulmonary fibrosis, one of the most common ILD forms, was estimated to be less than 0.01% in the general population (17). There is an increasing number of case reports describing the simultaneous existence of psoriasis and ILD. A recent case series described 6 patients with psoriatic arthritis who also developed interstitial lung disease (28). ILD has not been previously recognized as a psoriasis comorbidity in epidemiologic studies searching for comorbidities in psoriasis, which suggests low or rare incidence of a clinically relevant ILD in patients with psoriasis. Therefore, chest CT would not be routinely performed as part of psoriasis evaluation. A relatively higher prevalence of ILD was also reported in two studies by Kawamato et al (8 out of 392, 2%) (17) and Ishikawa et al (37) (21 out of 447, 4.7%). Higher incidence in above mentioned studies and in our study might be contributed to the use of CT scan resulting in detecting more subclinical ILD. Additionally, our study is the first to describe HRCT features in patients with mild and moderate cutaneous psoriasis, mostly managed with

topical treatments, in contrast to the study by Kawamato et al, that only included patients with severe psoriasis who needed biologic agents (17). None of the above studies concluded a solid association between psoriasis and ILD and the existence of such an association remains yet to be determined.

Most associations between psoriasis and ILD were reported as drug induced pneumonitis secondary to concomitant use of immunosuppressants (29, 37). Nevertheless, a recent study indicated ILD cases in psoriasis with no previous or concomitant exposure to immunosuppressive therapy directed against psoriasis (28). There was no association found in our study between Methotrexate exposure and ILD.

A large population-based study from Denmark demonstrated a strong association between psoriasis and risk of sarcoidosis (38). Many cytokines such as IL-23/IL-17 axis were found to play a central role in the pathogenesis and development of psoriasis. IL-23/IL17 axis were also found to be elevated in other connective tissue diseases that involve the lungs, such as rheumatoid arthritis and inflammatory bowel disease, which might give an insight into their role in the development of lung diseases that are associated with autoimmune conditions (37, 38). Clinically available anti-IL17 and anti-IL 23 have been shown to be effective not only in treating the cutaneous manifestation of psoriasis, but they were also reported to be effective in reducing ILD severity in psoriatic patients. Kawamato et al (17) found that the inhibition of the IL-23/IL-17 axis ameliorated not only psoriasis skin lesions but also ILD changes. That observation was supported by serial chest CT scans and suggested a possible common mechanism between the development of psoriasis and ILD. A recent study by Miyachi et al (39) reported a case showing improvement in ILD during psoriasis by IL-23/IL-17 inhibition. Although these studies support that inhibition of this pathway with biologic agents may be effective for psoriasis-associated ILD, few other studies reported that biologic agents might potentially induce ILD (17) (38, 40–46). In our study, there was no ILD changes detected in the two patients who had biologic agents.

Emphysema and calcified granulomas were also common HRCT findings in our study group. Although our study included psoriasis cases with no respiratory symptoms or established diagnosis of COPD, emphysematous changes were a common HRCT manifestation in our study population, (20.3%), indicating a large proportion of undiagnosed COPD in psoriasis patients, predominantly in cases with smoking history. Almost all cases with smoking history were male (34/35, 97.1%). The emphysematous changes detected in the two non-smoker cases were very mild and involved the upper lobes. Both cases were females with cutaneous psoriasis who had no history of smoking or related exposure history, but they seem to have symptoms consistent with an underlying reactive airway disease. This common finding of subclinical CT-evidence emphysema is concordant with a meta-analysis that concluded that patients with psoriasis have a two-fold higher risk of developing COPD, particularly in patients with severe form of psoriasis (21). Taking into consideration the significantly higher prevalence of smoking among psoriasis patients (47), and that the severity of psoriasis was found be proportionate to a high number of cigarettes smoked per day (22, 23). Whether the correlation between smoking and COPD events is circumstantial or casual in psoriasis patients remains to be answered (23). The degree of emphysematous changes in our study did not correlate with disease duration or the severity of psoriasis skin manifestations/PASI-scores.

This study has several limitations. This study was cross-sectionally designed and performed in a single center using a single CT technique (HRCT) to evaluate the lung parenchyma. The sample size was small and excluded patients with active respiratory symptoms who would probably have substantial pulmonary involvement and CT manifestations. Laboratory data collection was deficient and did not include various inflammatory markers that could have been helpful in establishing a possible correlation with the parenchymal lung involvement. Future larger and prospective studies are therefore needed.

Conclusions

The study showed a high incidence of detected subclinical small lung nodules and interstitial lung disease in HRCT scans of patients with psoriasis. These findings correlated with older age and psoriasis duration but not with the severity of cutaneous manifestations or methotrexate exposure. A larger scale study with objective radiologic assessment using software analysis might be helpful to look for subtle early changes in the lung parenchyma to better clarify the underlying pathophysiology of parenchymal lung abnormalities in patients with psoriasis.

Declarations

Compliance with Ethical Standards:

All procedures performed in this study involving human participants were reviewed and ethically approved by the Institutional Review Board (IRB) and the research and ethics committee at Jordan University of Science and Technology. This study was conducted following the 1975 Helsinki declaration, as revised in 2008 and its later amendments or comparable ethical standards.

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Data Availability:

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Informed consent:

Written informed consent was obtained from all individual participants included in the study.

Consent to publication:

Not applicable

Declaration of interests:

The authors declare that they have no competing interests.

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Figures

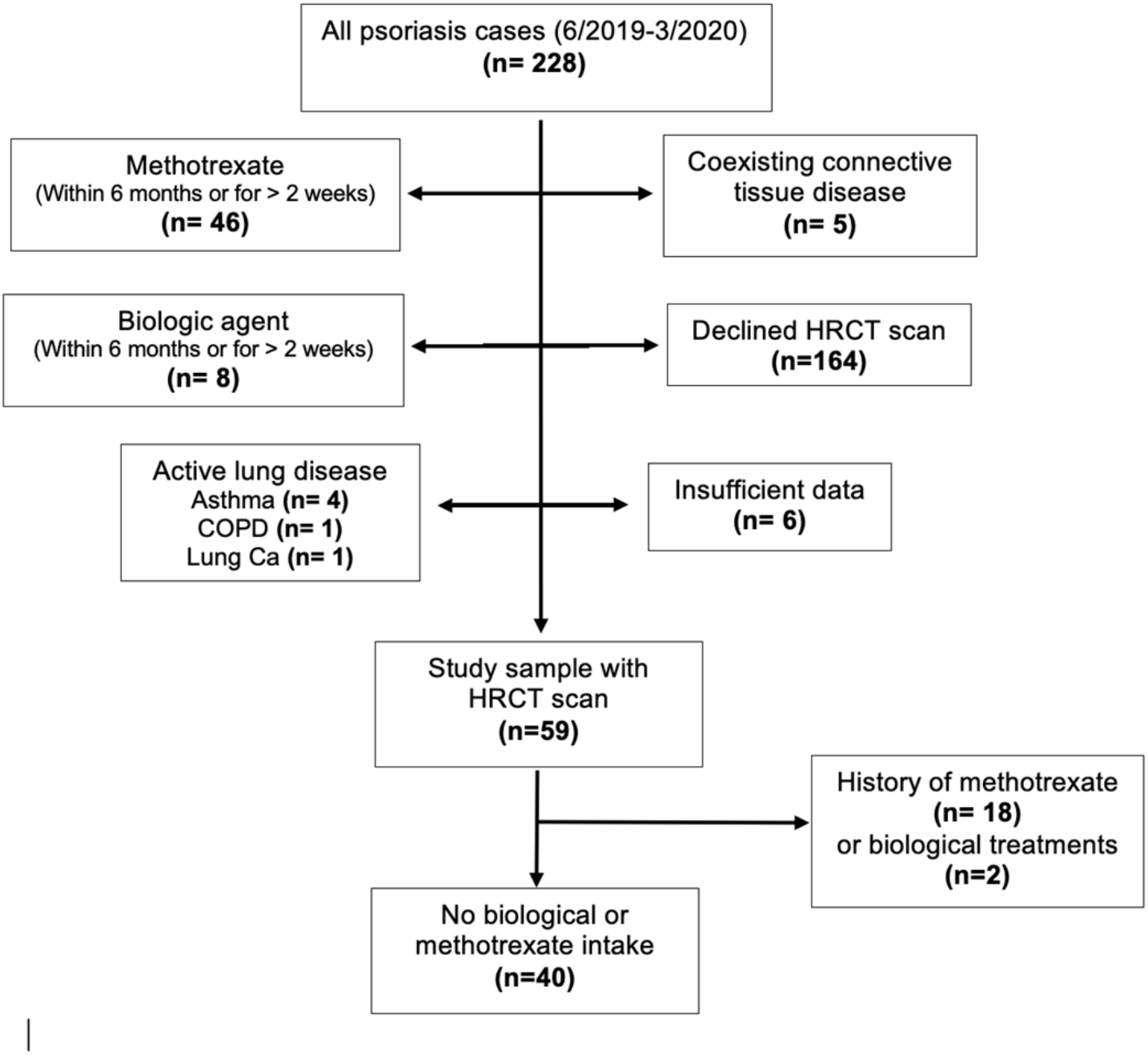

Figure 1

A Flow chart indicating the inclusion and exclusion flow.

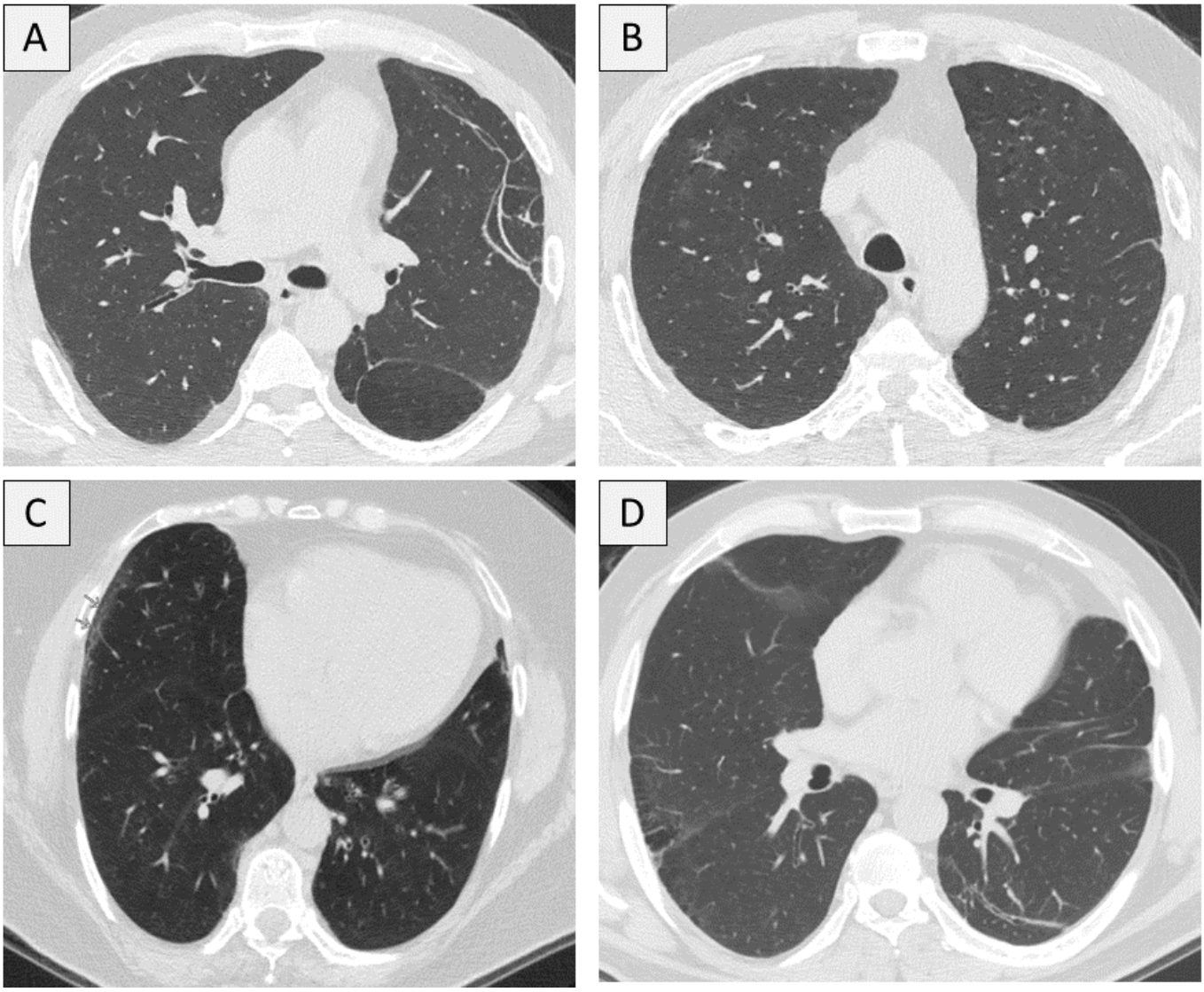

Figure 2

A, Interlobular septal thickening, prominent in the left lower lobe. **B,** Faint ground-glass opacities in the right and left upper lobes and interlobular septal thickening (irregular linear reticular opacity) in the left upper lobe periphery. **C,** Subpleural interstitial thickening, right lower lobe. **D,** Paraseptal emphysematous (subpleural) changes in the right lower lobe with Interlobular septal thickening, prominent in the left lower lobe.