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Prevalence and clinical features of interstitial lung disease in patients with psoriasis

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Abstract

Background Despite the autoimmune nature of psoriasis, the potential association between psoriasis and interstitial lung disease (ILD) remains underexplored. This study aimed to investigate the frequency and clinical features of ILD in patients with psoriasis and propose a new conceptual framework of "ILD associated with psoriasis".

Methods A retrospective analysis of 117 patients with psoriasis was conducted, excluding those without chest imaging prior to methotrexate or biologic use and those with other comorbidities leading to ILD.

Results ILD was identified in 12 (10%) patients with psoriasis; 6/50 with psoriasis vulgaris and 6/65 with psoriatic arthritis. Three of 12 patients had no history of smoking. Serum Krebs von den Lungen-6 (KL-6) levels were elevated in patients with ILD compared to those in patients without ILD. The indeterminate for usual interstitial pneumonia (UIP) pattern was the most prevalent CT finding. A lung biopsy specimen from a representative case revealed equivalent indeterminate for UIP. Over a median 8.9-year observation period, ILD progressed in only 5 patients, with no cases of respiratory failure or death due to ILD progression, suggesting generally favourable prognoses.

Conclusions ILD associated with psoriasis would be present, and its frequency is 10% of patients with psoriasis. We propose that chest radiography and a serum KL-6 test at the initial diagnosis of psoriasis would be useful in screening for the detection of ILD. We also recommend that a physician diagnosing ILD should carefully examine the skin findings, considering if psoriasis could be associated with ILD.

Trial registration Not applicable.

Keywords interstitial lung abnormality, interstitial lung disease, interstitial pneumonia, prognosis, psoriasis

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Introduction

Psoriasis is a chronic cutaneous disorder characterised by keratotic symptoms. Among 11,631 cases studied, psoriasis vulgaris was identified as the most prevalent form of psoriasis (88.5%), followed by guttate psoriasis (3.9%), psoriatic arthritis (3.3%), generalized pustular psoriasis (1.3%), and other subtypes [1]. The development of psoriasis has been linked to abnormal immune function influenced by various external and internal factors, in addition to a genetic predisposition [2].

Interstitial lung disease (ILD) can result from factors such as dust inhalation, drug reactions, and autoimmune diseases such as rheumatoid arthritis. Given its autoimmune nature, psoriasis is potentially associated with ILD. However, there is a paucity of reports detailing the association between psoriasis and ILD [3].

If psoriasis indeed contributes to ILD, it could prompt changes in the standard medical approach to both psoriasis and ILD. For instance, a dermatologist diagnosing psoriasis may consider ordering a chest radiograph with ILD in mind, whereas a physician diagnosing ILD should carefully examine the skin findings, considering psoriasis as a potential cause. In light of this scenario, we conducted this study to explore the frequency of ILD complications in patients with psoriasis and to analyse the clinical characteristics of ILD. This study aimed to investigate prevalence and clinical features of ILD in patients with psoriasis to propose a concept of "ILD associated with psoriasis".

Methods

Patients and study design

Patients clinically diagnosed with psoriasis between 1 January 2015 and 31 December 2022 at Kagawa University Hospital were retrospectively identified, and pertinent clinical and laboratory data were extracted from their medical records. In all patients, psoriasis was diagnosed by dermatologists. No specific restrictions were imposed regarding the type of psoriasis or method of diagnosis. The diagnoses of psoriatic arthritis were made according to the CASPAR [4]. Individuals lacking chest radiographs before the initiation of treatments potentially associated with ILD (such as methotrexate and biologic agents) were excluded from the study. Additionally, patients with concurrent autoimmune diseases other than psoriasis, which are known potential causes of ILD, were excluded. Patients with suspected ILD from other known causes, including pneumoconiosis, were also excluded. This study was approved by the Research Ethics Committee of Kagawa University on 11 January 2023 (No. 2022–177). All procedures involving human participants were performed in accordance with the 1964 Declaration of Helsinki and its later amendments, covering patient data confidentiality.

Evaluation of ILDs

ILDs were diagnosed based on the patients' clinical features and radiologic findings before the initiation of treatments potentially associated with ILD to avoid drug-induced ILDs. The assessment of ILDs on high-resolution CT followed the diagnostic criteria for idiopathic interstitial pneumonia outlined in the ATS/ERS statement [5], as well as the diagnostic criteria for idiopathic pulmonary fibrosis (IPF) in the ATS/ERS/JRS/LATA statement [6]. Commonly diagnosed radiographic patterns of ILDs encompass nonspecific interstitial pneumonia (NSIP), organizing pneumonia, diffuse alveolar damage, hypersensitivity pneumonitis, and usual interstitial pneumonia (UIP) [5]. High-resolution CT patterns for diagnosing IPF include UIP, probable UIP, indeterminate for UIP, and alternative diagnosis [6]. Following the sequential reading method, a board-certified pulmonologist (N. Kanaji) and chest radiologist (M. Murota) independently reviewed all CT scans of the patients and classified the ILD patterns. In cases of discrepancy between the two evaluators, the ILD pattern was determined via consensus. ILD progression was defined as worsening findings on CT during observation period.

Statistical analysis

Overall survival (OS) was defined as the time from chest imaging (diagnosis of ILD) to death from any cause. Statistical differences between groups were assessed using Fisher's exact test, Student's *t*-test, or the chi-square test, where applicable. OS was depicted using the Kaplan-Meier method, and differences in OS were compared utilizing the log-rank test. All statistical analyses were performed using Bell Curve for Excel version 4.05 (Social Survey Research Information Co., Ltd., Japan).

Results

ILD complication rate in patients with psoriasis

A total of 149 patients with psoriasis were initially screened for eligibility, of whom 117 met the inclusion criteria. Detailed reasons for exclusion are outlined in Fig. 1. ILD was identified in 12 patients, constituting 10% of the total cohort, and 16% of the 74 patients who underwent CT examination. The types of psoriasis observed were psoriasis vulgaris in 6 patients and psoriatic arthritis in 6 patients (Table 1). While the pack-years value was higher in cigarette smokers with ILD than in smokers without ILD, it is noteworthy that the 3 patients with ILD had no history of smoking. Occupational history showed dust inhalation in one patient who was a roof manufacturer. Although silicosis was a possible occupational lung disease, CT findings did not show granular shadows typical of silicosis. Thus, no patient was clinically suspected of having pneumoconiosis. Severe psoriasis (investigator's global assessment: IGA 4) were

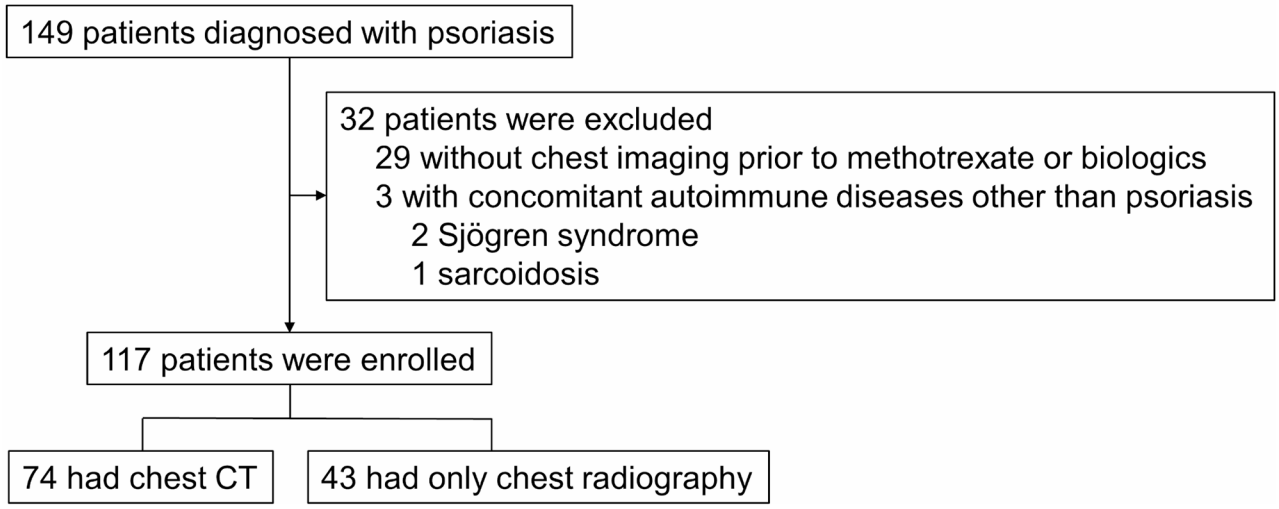

Fig. 1 The registration and exclusion flowchart

Table 1 Patients' characteristics

Characteristic	Total (*n* = 117)	ILD (+) (*n* = 12)	ILD (-) (*n* = 105)	*p*
Age at diagnosis of psoriasis, median (range)	49 (2–84)	54 (40–81)	48 (2–84)	0.07*
Man/Woman	84/33	10/2	74/31	0.51#
Smoking history				
Smoker/never smoker/unknown	58/28/31	7/3/2	51/25/29	1.00#
Pack-years in smokers, median (range)	31.5 (1.5–110)	66 (40–100)	23 (1.5–110)	< 0.01*
Type of psoriasis				
Psoriasis vulgaris	50	6	44	0.79**
Psoriatic arthritis	65	6	59	
Generalized pustular psoriasis	2	0	2	
Skin biopsy for diagnosis of psoriasis, Yes/no	50/67	5/7	45/60	1.00#
Severity of psoriasis based on IGA				
0/1/2/3/4/unknown	2/6/11/21/45/32	0/0/1/2/5/4	2/6/10/19/40/28	0.91**
Status at judgment for ILD				
Assessment with chest CT, number	74	12	62	NA
Age, median (range)	55 (2–84)	66 (45–81)	53 (2–84)	0.01*
C-reactive protein (mg/dL), average (range)	0.96 (0.01–9.54) (*n* = 114)	0.77 (0.01–5.18) (*n* = 12)	0.98 (0.01–9.54) (*n* = 102)	0.66*
LDH (U/L), average (range)	214 (133–516) (*n* = 112)	200 (144–273) (*n* = 12)	216 (133–516) (*n* = 100)	0.20*
KL-6(U/mL), average (range)	238 (74–556) (*n* = 35)	360 (226–500) (*n* = 5)	208 (74–556) (*n* = 30)	0.03*
Use of biologics after judgment for ILD				
Yes/No	80/37	7/5	73/32	0.52#

CT: computed tomography, IGA: investigator's global assessment, ILD: interstitial lung disease, KL-6: Krebs von den Lungen-6, LDH: lactate dehydrogenase, NA: not applicable, *by Student's *t*-test, #by Fisher's exact test, **by chi-square test

observed in 45 patients (38%). With the exception of 32 patients with unknown severity, no association was found between severity of psoriasis and the presence of ILD. Biologics were used in 80 patients (68%) after judgment of ILD. There was no association between the use of biologics and the presence of ILD. Serum Krebs von den Lungen-6 (KL-6) levels were elevated in patients with ILD compared to those in patients without ILD (averages 360 vs. 238 U/mL, $p = 0.03$, Table 1).

Clinical features of ILD in patients with psoriasis

The CT patterns of ILD were UIP in 1 patient, probable UIP in 1 patient, indeterminate for UIP in 6 patients, unclassifiable in 3 patients, and NSIP in 1 patient, with the most common pattern being indeterminate for UIP (50%). ILD was found in 5% of the lung fields in 6 patients, 10% in 2 patients, 20% in 2 patients, 30% in 1 patient, and 50% in 1 patient. Pulmonary function test was performed in only 5 patients with ILD: average of % vital capacity was 100%. A representative CT image illustrating the indeterminate for UIP pattern observed

in a never-smoker is presented in Fig. 2. The median follow-up periods were 4.9, 8.9, and 4.3 years for the total population, patients with ILD, and patients without ILD, respectively. During this period, three patients with ILD received prednisolone (around 5 mg per day) as treatment for psoriasis, and seven patients with ILD received biologic treatments, including anti-tumour necrosis factor (TNF)-alpha in 5, anti-interleukin (IL)-17 in 3, anti-IL-23 in 2, and anti-IL-12/23 in 1. No patient with ILD received mycophenolate. Despite ILD progression in 5 patients, including one patient treated with anti-TNF-alpha, there were no patients with respiratory failure-related deaths due to ILD. The OS from the time of chest imaging (ILD diagnosis) was not significantly different between patients with and without ILD.

Lung cancer developed in 3 patients, including 2 with ILD and 1 without. One patient with ILD died of lung cancer progression. Another 61-year-old patient with ILD and lung cancer underwent a left lower sublobar resection. The patient was a former cigarette smoker. The radiological and pathological findings of ILD in this patient are presented in Figs. 3 and 4, respectively. Over a 12-year period, ILD, characterised mainly by ground glass shadows, progressed (Fig. 3a and b). While the CT findings were classified as an NSIP pattern, pathology revealed regional fibrotic lesions just below the pleura with a relatively uniform distribution and geography. At high magnification, fibrosis, hyperplasia of type II alveolar cells (Fig. 4a), and mild lymphocytic infiltration (Fig. 4b) were observed, with pathological findings classified as indeterminate for the UIP pattern.

Discussion

This retrospective analysis of 117 patients with psoriasis revealed that (1) the incidence of ILD was 10%, (2) serum KL-6 levels were higher in patients with ILD than in those without, and (3) ILD predominantly manifests as an indeterminate for UIP pattern on CT, exhibiting a relatively stable progression. Although this study has many limitations, including lack of genetic profiling, the possibility of an association between psoriasis and ILD is conceivable, and our thoughts are discussed below.

The term "interstitial lung abnormality" (ILA) is frequently employed to characterize abnormal interstitial findings in CT scans of individuals with no prior history of ILD [7]. In the context of this study, it may be appropriate to use the term ILA. However, ILA has been linked to early or mild forms of pulmonary fibrosis [8]. Specific imaging patterns associated with an increased risk of death include both UIP and probable UIP patterns when compared to those categorised as indeterminate for UIP pattern [8]. This is a precise description of the ILD. ILA

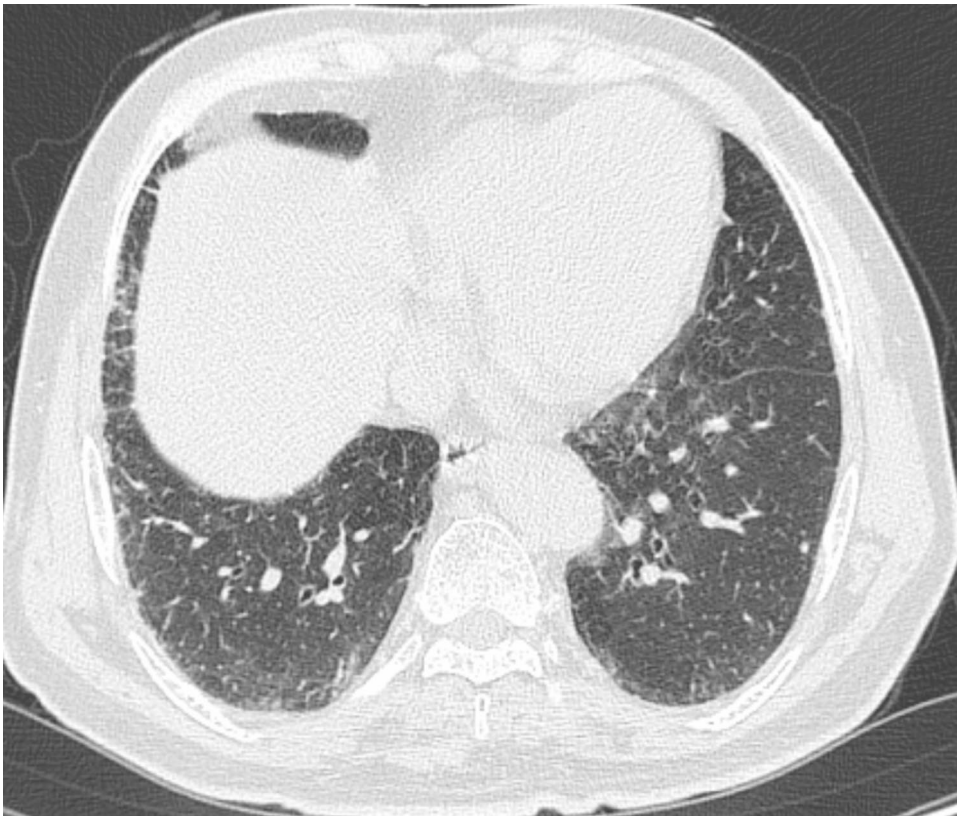

Fig. 2 Representatives of CT images of indeterminate for UIP patterns observed in a 80-year-old never-smoker man

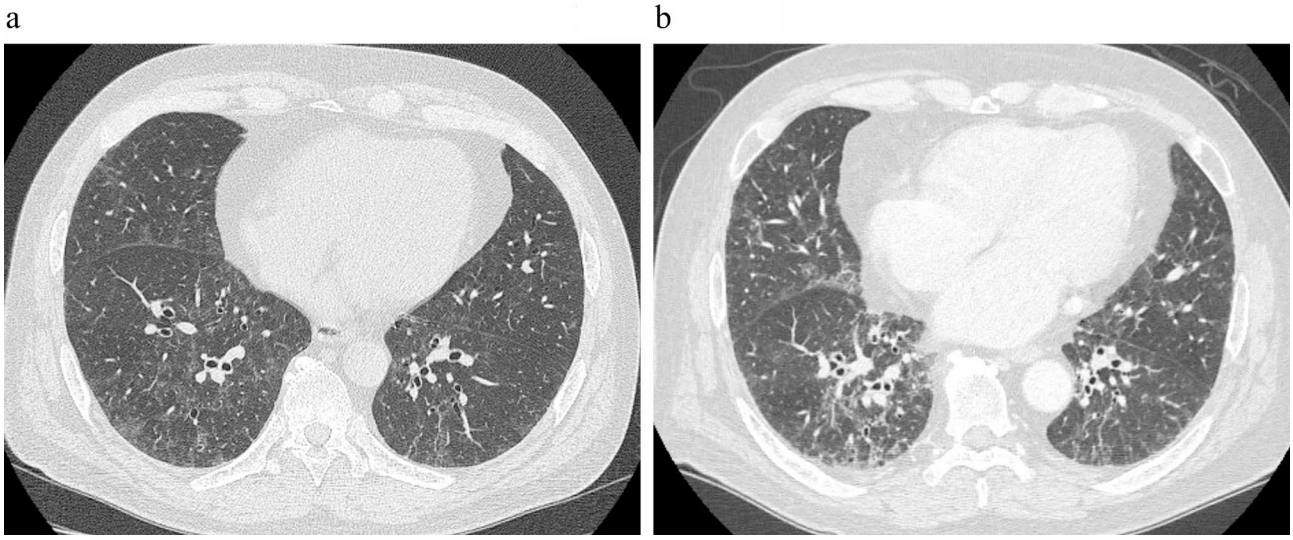

Fig. 3 CT images of ILD in a 49-year-old man. **(a)** When he was diagnosed with psoriasis vulgaris at 49 years old. The ground glass opacities are observed, mainly in the bilateral lower lobes. **(b)** Twelve years later, at age 61. ILD has progressed and is accompanied by decreased air volume in the lower lobes

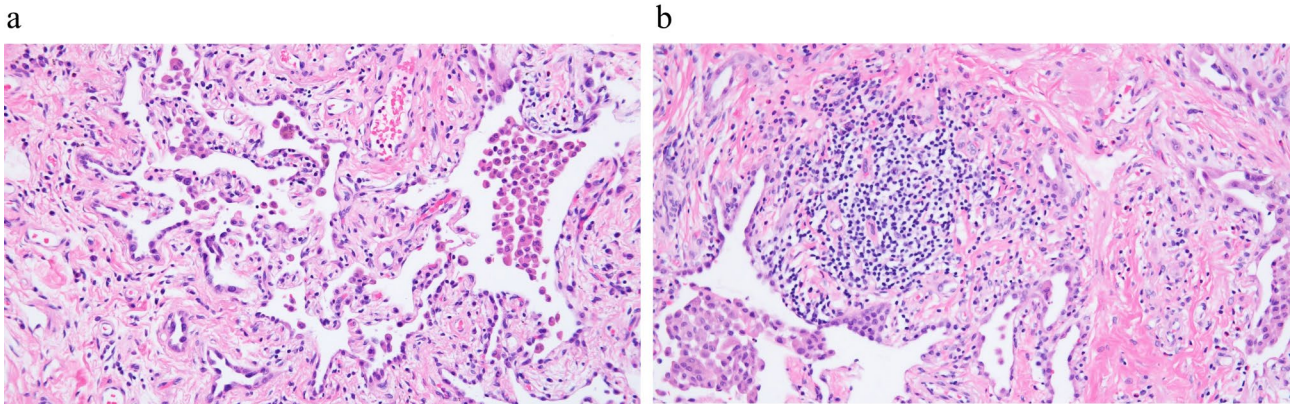

Fig. 4 Pathological findings of ILD in the 61-year-old patient shown in Fig. 3b. **(a)** Fibrosis and hyperplasia of type II alveolar cells. **(b)** Mild lymphocytic infiltration

serve as entry points for the diagnosis of ILD in radiological screening.

The frequency of ILAs varies according to patient population characteristics. In a lung cancer screening program using CT, 41 of 1,699 patients (2.4%) exhibited ILA [9]. Among a cohort of smokers, ILA was present in 194 (8%) of 2,416 high-resolution CT scans [10]. While ILA is a term rooted in imaging findings, ILD is utilized as a comprehensive clinical disease term. Although no clear distinctions in severity have been defined between ILA and ILD, some reports have defined a distinction. In the COPDGene study, 239 of 4,361 patients (5%) exhibited evidence of suspected ILD, defined as ILA, and at least one additional criterion: definite fibrosis on CT, forced vital capacity less than 80% predicted, and diffusing capacity for carbon monoxide less than 70% predicted, and 204 (5%) had ILA without suspected ILD [11]. However, we believe that the difference between the terms ILA and ILD is not important, and it is crucial to recognize ILA as ILD.

The association between ILD and various autoimmune diseases is well-established. In a Danish study, 275 of 1,869 patients with systemic sclerosis (SSc) (14.7%) were reported to have ILD [12]. Moreover, among 405 Japanese patients with SSc, 204 (50.4%) had ILD [13]. These reports did not incorporate clinical findings, such as pulmonary function, in the diagnosis of ILD. In a retrospective review of 447 ILD cases in Japan, 21 (4.7%) patients developed psoriasis complications [14]. While the causal relationship between psoriasis and ILD remains unclear, the reported frequency of 4.7% appears to be notably high. The prevalence of psoriasis varies globally, ranging from less than 1.0–2.3%, with rates of less than 1% reported in Japan [15, 16]. Thus, the reported frequency of psoriasis in the ILD population study was 4.7%, suggesting a potentially significant association between ILD

and psoriasis. The ILA rate in patients with psoriasis in this study was 10%, which surpasses the previously reported ILA rates in patients without autoimmune diseases. Considering these findings from the mentioned reports, we propose the presence of ILD associated with psoriasis. It is important to acknowledge that the 16% ILA rate, when limited to patients with CT imaging, may reflect a selection bias, even though the determination of the ILA is based on CT findings. In contrast, a study reported that only 2% of patients with psoriasis had interstitial pneumonia [17]. There may be no big differences in age and smoking history between the study and the current study. Although the causes of the discrepancy of ILD frequency are not clear, we assume that the most significant factor might be the perception of the diagnosing radiologists/physicians. They might differ in their judgment of ILD especially when on the borderline between normal and abnormal. In the current study, most ILD was mild with indeterminate for UIP pattern on CT, which might influence diagnosis of ILD.

The development of ILD involves a complex interplay among various factors. Genetic factors, environmental influences, and aging-related changes have been implicated in triggering the onset of IPF [18, 19]. While fibroblast activation by transforming growth factors is a key player in IPF progression, the involvement of other growth factors, such as platelet-derived growth factor, and cytokines, such as IL-17 and IL-23, has also been reported [19]. Bleomycin and IL-1 beta-mediated pulmonary fibrosis have shown dependence on IL-17 A [20]. IL-17 and IL-23 are recognised as pivotal players in the pathogenesis of ILD in SSc [21]. Transgenic mice overexpressing TNF develop both inflammatory arthritis and ILD resembling NSIP [22]. In these mice, the lungs exhibited an accumulation of activated monocytes, conventional dendritic cells and $CD21^{+}/CD23^{-}$ B cells [22]. Treatment with an anti-TNF agent alleviates both arthritis and ILD [22]. Some of these humoral factors have been identified as pathogenic in psoriasis, and their inhibitors have been employed in the treatment of psoriasis [23]. Given the multifaceted nature of ILD development in patients with psoriasis, it is likely that several factors contribute to its onset. However, the exact relationship between TNF and ILD remains unclear, as TNF-alpha inhibitors have been associated with ILD adverse events in the treatment of conditions like rheumatoid arthritis and psoriasis [24–26]. Although the mechanisms of ILD pathogenesis in psoriasis is unclear, this study advocates recognizing psoriasis as an autoimmune disease and noting the presence of ILD associated with psoriasis as well as ILD associated with rheumatoid arthritis and SSc. A designation of interstitial pneumonia with autoimmune features (IPAF) should be used to identify individuals with idiopathic interstitial pneumonia and features suggestive of, but no definitive for, a connective tissue disease [27]. We do not consider ILD associated with psoriasis to be IPAF. Therefore, we did not undertake the task of excluding IPAF from the inclusion criteria. In addition, none of patients with ILD met the IPAF criteria.

Prognosis is of paramount importance in patients with ILD, particularly because progressive ILD can lead to fatal outcomes. Notably, in the present study, no patient died of ILD progression during the median follow-up period of 8.9 years. Since most patients had a limited extent of ILD and the average of % vital capacity was 100%, it could be said that most patients had mild ILD. However, it is crucial to consider that patients with progressive fibrosing (PF)-ILD generally exhibit shorter survival times, irrespective of the underlying cause of ILD [28]. The prognosis of patients with IPF is closely linked to the CT findings. CT patterns such as UIP and probable UIP, which are indicative of PF-ILD, are associated with poor prognosis, whereas the indeterminate for UIP pattern is linked to a more favourable prognosis than other patterns [29, 30]. In our study, UIP and probable UIP patterns were observed in one case, with the indeterminate for UIP pattern being the most prevalent. This likely contributed to slow progression in most cases, resulting in an overall favourable prognosis. However, patients with UIP or probable UIP patterns should be closely monitored for ILD progression, even in the context of psoriasis.

Serum KL-6 levels were higher in patients with ILD than in those without although KL-6 levels were not measured in all cases. Serum KL-6 levels and chest radiography may be useful screening tools for identifying ILD. We recommend further evaluation using chest CT when abnormalities are detected in any of these tests. There was no difference in LDH levels between patients with and without ILD. Possible reasons for this include the fact that most ILDs were mild and that LDH is also produced outside the lungs. Patients with ILD were screened for several autoantibodies, including antinuclear antibody (ANA). Although ANA was positive in one patient (80-fold), there were no findings suggestive of other autoimmune diseases, including systemic lupus erythematosus. Anti-MDA5 antibodies were not examined, but no patient had dermatomyositis, polymyositis, or rapidly progressive ILD.

The present study has several limitations. First, not all the patients underwent CT. In some cases, CT was taken because of abnormalities on chest radiography. ILD cases may exist but remain undetected on chest radiography. In such instances, the actual frequency of ILD can be higher than 10%. On the other hand, we excluded patients without chest imaging prior to treatments which potentially induce ILD. If all patients were evaluated, the frequency of ILD might be lower than 10%. Second, this was a retrospective study at a single hospital, which introduced

a potential selection bias including severity of psoriasis. Exclusion criteria, such as patients without chest imaging prior to methotrexate or biologics, may have influenced the overall cohort characteristics. The fact that the study was conducted at a single institution limits the generalizability of the results, and a multi-institutional study is needed. Third, the impact of psoriasis treatment on the course of ILD cannot be discussed because we cannot exclude the possibility that treatments for psoriasis are confounding factors [26]. While it is possible that psoriasis treatment may have influenced the course of ILD, it is noteworthy that none of the patients in this study received antifibrotic drugs such as nintedanib. Fourth, the number of patients in this study is relatively small. It would be desirable to examine a larger number of patients in a multicenter setting. Fifth, the facts that not all patients were evaluated with pulmonary function test or KL-6 are also limitations of this study. Finally, we have no information on patients' genetic profiling. Ethnic differences in the genetics of ILD and genetic polymorphisms such as FAM13A, TERT, and MUC5B have been reported to be associated with the clinical course of ILD [18].

Conclusions

ILD associated with psoriasis would be present, and its frequency is 10% of patients with psoriasis. The predominant CT pattern observed in ILD associated with psoriasis was indeterminate for UIP, and the progression of ILD in these cases appeared to be relatively slow. When psoriasis is diagnosed, we recommend chest radiography and serum KL-6 levels as screening tools for identifying ILD. We also recommend that a physician diagnosing ILD should carefully examine the skin findings, considering if psoriasis could be associated with ILD.

Abbreviations

CT	computed tomography
IL	interleukin
ILA	interstitial lung abnormality
ILD	interstitial lung disease
IPAF	interstitial pneumonia with autoimmune features
KL-6	Krebs von den Lungen-6
NSIP	nonspecific interstitial pneumonia
OS	overall survival
PF	progressive fibrosing
SSc	systemic sclerosis
TNF	tumour necrosis factor
UIP	usual interstitial pneumonia

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None.

Author contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Nobuhiro Kanaji, Noriyuki Misaki, Makiko Murota, Masashi Iwata, Ryou Ishikawa, Kentaro Yamamura, Hisamu Tanaka, Naoya Yokota, Shuusuke Fujimoto, Toshiki Yajima, Hiroaki Dobashi, Hiromi Shimada, Risa Wakiya, Naoki Watanabe, Takuya Inoue, Hitoshi Mizoguchi, Yuta Komori, Kazuki Kojima, Norimitsu Kadowaki, and Teruki Dainichi. The first draft of the manuscript was written by Nobuhiro Kanaji and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Data availability

The datasets generated and analysed during the current study are not publicly available due the publication of raw data has not been approved by the Research Ethics Committee of Kagawa University (No. 2022-177) but might be available from the corresponding author (Nobuhiro Kanaji: kanaji.nobuhiro@kagawa-u.ac.jp) on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Institutional Review Board of Kagawa University (no. 2022 – 177). All procedures performed in the study involving human participants were in accordance with the ethical standards of the institutional research committee and the 1964 Helsinki declaration and its later amendments or comparable ethical standards. We obtained appropriate informed consent for the use of patient information through an opt-out form because of the retrospective nature of the study. Clinical trial number: not applicable.

Consent for publication

Not Applicable.

Competing interests

The authors declare no competing interests.

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