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Predictive factors of fibrotic interstitial lung abnormality on high-resolution computed tomography scans: a prospective observational study

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Abstract

Background Fibrotic types of interstitial lung abnormalities seen on high-resolution computed tomography scans, characterised by traction bronchiolectasis/bronchiectasis with or without honeycombing, are predictors of progression and poor prognostic factors of interstitial lung abnormalities. There are no reports on the clinical characteristics of fibrotic interstitial lung abnormalities on high-resolution computed tomography scans. Therefore, we aimed to examine these clinical characteristics and clarify the predictive factors of fibrotic interstitial lung abnormalities on high-resolution computed tomography scans.

Methods Clinical and paraclinical data of 164 patients enrolled in the initial year of a multicentre prospective observational study (Kumamoto interstitial lung abnormalities study in Japan) involving over 62,000 examinees during routine health examinations were analysed. Clinical laboratory evaluations are expressed as medians and interquartile ranges for each evaluation time point, and boxplots were created for graphical representation. The percentages of abnormal clinical laboratory results were compared between the groups using chi-square or Fisher's exact tests. Univariate or multivariate logistic regression analyses were performed to analyse the relationship between fibrotic interstitial lung abnormalities and other clinical factors.

Results Fibrotic interstitial lung abnormalities were observed on high-resolution computed tomography scans in 135 (82%) patients at the time of diagnosis. Multivariate analysis showed that older age (Odds ratio, 1.06; 95% confidence interval, 1.01–1.12; $p=0.021$), auscultatory fine crackles (Odds ratio, 3.39; 95% confidence interval, 1.33–8.65; $p<0.01$), and elevated serum surfactant protein-D (Odds ratio, 2.68; 95% confidence interval, 1.02–8.64; $p=0.045$) were independent predictive factors of fibrotic interstitial lung abnormalities. The predicted area under the curve of the fibrotic interstitial lung abnormalities based on these three factors was 0.77 (95% confidence interval, 0.68–0.86). The

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proportion of undecided diagnoses in the fibrotic interstitial lung abnormalities group (14%) was significantly lower than that in the non-fibrotic interstitial lung abnormalities group (41%) ($p = 0.0027$).

Conclusions Fine crackles on auscultation and elevated serum surfactant protein-D levels are predictors of fibrotic interstitial lung abnormalities in older patients with interstitial lung abnormalities. These findings may assist non-radiological physicians in referring patients to specialists for early intervention in progressive fibrotic interstitial lung diseases.

Trial registration number/date UMIN000045149/2021.12.1.

Keywords Interstitial lung abnormality, Idiopathic pulmonary fibrosis, Progressive pulmonary fibrosis, High-resolution CT, Fine crackles, Multidisciplinary discussion, Working diagnosis

Background

Interstitial lung abnormalities (ILAs) are defined as the incidental identification of non-dependent abnormalities on computed tomography (CT), including ground glass or reticular abnormalities, lung distortion, traction bronchiectasis/bronchiolectasis, honeycombing, and non-emphysematous cysts involving ≥ 5% of the lung zone in individuals in whom interstitial lung disease is not suspected [1–3]. ILAs also comprise the asymptomatic phases of interstitial lung disease, such as idiopathic pulmonary fibrosis (IPF) and progressive pulmonary fibrosis (PPF), and have recently gained clinical importance [4, 5]. The types of ILA findings on high-resolution CT (HRCT) scans are radiologically subcategorised into three patterns: non-subpleural, non-fibrotic subpleural, and fibrotic subpleural [1, 2]. The subpleural fibrotic type of ILA presenting with traction bronchiolectasis/bronchiectasis with or without honeycombing has been described as a predictor of ILA progression and poor prognostic factor [1, 2, 5–9]. In a similar health screening cohort study [7] of Asians followed up for over 12 years, fibrotic ILA was independently associated with ILA progression, disease-specific mortality, and all-cause mortality compared with no ILA.

Furthermore, fibrotic ILA is associated with a higher risk of lung cancer occurrence and death [10–13]. Axelsson et al. [11] found that fibrotic ILA showed a higher risk of lung cancer occurrence and death compared to non-fibrotic ILA in 5,764 patients in the AGES-Reykjavik study.

Reports describing the clinical characteristics of patients with fibrotic ILA on HRCT scans are not available. Apart from radiological findings, many clinical questions involving fibrotic ILA have been raised, including the background risk factors for fibrotic ILA, the frequency of fibrotic ILA exhibiting fine auscultatory crackles, and potential serum markers appropriate for diagnosing fibrotic ILA.

The Kumamoto ILA study (KILA-J study), a prospective multicentre observational study, was conducted to clarify the frequency of IPF or PPF progression from ILAs, the natural course from preclinical status, and outcomes after treatment based on a large general population health check-up in Japan [14]. This was the first study that aimed to examine the clinical characteristics and clarify the predictive factors of fibrotic ILA on HRCT scans. We present our findings based on 164 cases registered in the first year of the KILA-J study.

Methods

The KILA-J study is a multicentre prospective observational study.

Study population

Details of the study population of the multicentre prospective observational are provided in Additional file 1 [14]. Patients with suspected ILAs in screening health check-up facilities were referred for further examination to any of the three teaching hospitals. Patients diagnosed with ILA confirmed by HRCT who provided informed consent were enrolled in the study. The final diagnosis of ILA based on HRCT screening by pulmonologists was strengthened by concordance of the diagnosis by expert chest radiologists or more than two pulmonologists who reviewed the records of each eligible patient. The first patient was registered on 20 June 2022, and 164 patients were eventually enrolled in the first year of the study, of whom 91% were referred from two check-up centres with a total of 62,280 annual attendances. Three patients who consented to registration withdrew their consent due to the time and cost of testing because they were asymptomatic.

Data collection

The following data were collected and registered at enrolment: (i) age, sex, date of birth, height, weight, and body mass index; (ii) reason for referral from screening facilities; (iii) smoking history, environmental history (presence or absence of dust exposure, contact with birds, and occupational history), and family history of interstitial pneumonia; (iv) comorbidities, including diabetes mellitus, coronary artery disease, gastroesophageal reflux, cardiovascular diseases other than coronary artery disease, and lung cancer; and (v) presence of fine crackles

on auscultation, chest radiographic findings, and HRCT findings and patterns based on the Idiopathic Pulmonary Fibrosis International Guidelines and the Hypersensitivity Pneumonitis International Guidelines [14]. The following physical examination variables were collected: oxygen saturation (SpO_2) levels and dyspnoea scale score (modified Medical Research Council), pulmonary function tests, blood gas analysis, and 6-minute walk test results. Other tests with results include biological assessments (including blood count, renal, and hepatic functions), autoantibody screening blood sampling, serum interstitial pneumonia markers (Krebs von den Lungen-6 [KL-6], surfactant protein-D [SP-D]), interstitial lung disease (ILD)-GAP index, and echocardiography results. Suspected diagnosis and diagnostic accuracy of IPF based on ontology were recorded after discussing the multidisciplinary diagnosis (MDD) via a web conference involving the three institutions (Inter-facility MDD diagnosis) and each institution's diagnosis.

Evaluation of auscultation

The presence of fine crackles on auscultation at enrolment was assessed by each board-certified respiratory physician for reproducibility, by having the patient take at least five adequate inhalations.

Evaluation of HRCT findings

HRCT images were evaluated independently by two experienced chest radiologists (T. J. and K. F.) for the first 100 cases at the start of enrolment to check the concordance rate of HRCT findings. The agreement rate between the two readers was assessed. The results of the first 100 cases were discussed between the readers, and the consensus results were registered in the EDC database. If the two radiologists did not agree on the HRCT patterns or scores; one of the patterns or scores was adopted by consensus. From the 101st case, each patient's finding was assessed by one radiologist.

The presence and extent of areas of subpleural ground-glass attenuation, subpleural reticulation, non-emphysematous cysts, traction bronchiolectasis/bronchiectasis, and honeycombing were assessed. Air-space consolidation with volume loss from the apex to the upper lobes, suspicious of PPFE, was also assessed.

The criteria for fibrotic ILA or non-fibrotic ILA are the presence or absence of traction bronchi and bronchiectasis, with or without honeycombing and those for fibrotic ILA were defined by the presence of architectural distortion with traction bronchiectasis or honeycombing (or both) [1].

Statistical analysis

Continuous variables are expressed as averages and standard deviations or medians and interquartile ranges (IQRs), and categorical variables for each group are expressed as the number of participants and percentages. Clinical laboratory evaluations are expressed as a median and IQR for each evaluation time point, and boxplots were created for graphical representation. In addition, percentages of abnormal clinical laboratory results were compared between the groups using chi-squared or Fisher's exact tests. For continuous variables, the Mann–Whitney test was used without assuming normality. Potentially important confounding factors were determined based on previous reports of the progression of interstitial pneumonia and early lesions of pulmonary fibrosis. Univariate or multivariate logistic regression analyses were performed to analyse the relationship between fibrotic ILA and other clinical factors. A graphical representation of the odds ratio and confidence interval for logistic regression was shown in a forest plot. We employed receiver operating characteristic curve analysis to examine the area under these clinical factors' curve extracted from adjusted logistic regression analyses for the fibrotic ILA. Missing data were not imputed. Three patients with fibrotic ILA had missing data. The missing data included the lowest value of the 6-minute walk test in one patient and serum SP-D values in two patients.

Results

Patient characteristics

Fibrotic ILAs were observed on HRCT scans in 135 (82%) of the 164 cases at the time of ILA diagnosis. A comparison of the background factors for positive and negative fibrotic ILA findings on HRCT is shown in Table 1.

Background factors and fibrotic ILA

Patients with positive fibrotic ILA on HRCT scans (median [IQR] age, 70 [65,74] years) were significantly older than those with negative findings (median [IQR] age, 66 [62,71] years) ($p = 0.005$) (Fig. 1a). A total of 103/164 (63%) patients had fine auscultatory crackles at the time of ILA diagnosis; this proportion was higher in the fibrotic ILA (94/138, 70%) than in the non-fibrotic group (29, 31%) ($p < 0.001$). Cough symptoms were significantly more frequent in the fibrotic ILA group (25%) than in the non-fibrotic ILA group (7%) ($p = 0{,}045$), whereas the modified MRC scale scores were not significantly different between the two groups. No significant differences were observed in sex, family history of interstitial pneumonia, smoking history, Brinkman index, or comorbidities.

Functional impairment and fibrotic ILA

The difference in percent forced vital capacity (%FVC) and percent vital capacity (%VC) were not significantly different between the two groups. Similarly, the difference in the distance from the 6-min walk test (6MWT)

Table 1 Characteristics of the fibrotic and non-fibrotic ILA groups

	Entire cohort	Fibrotic ILA	
		Positive	Negative
Subjects, n (%)	164 (100)	135 (82.3)	29 (17.6)
Age	69 [65, 73]	70 [65, 74]	66 [62, 71]
Sex (%)			
Female	38 (23.2)	29 (21.5)	9 (31.0)
Male	126 (76.8)	106 (78.5)	20 (69.0)
Family history of interstitial pneumonia			
No	148 (90.2)	123 (91.1)	25 (86.2)
Yes (One person)	10 (6.1)	8 (5.9)	2 (6.9)
Unknown	6 (3.7)	4 (3.0)	2 (6.9)
Body mass index	24.5 [22.3, 26.6]	24.1 [22.2, 26.3]	25.9 [24.1, 27.4]
Smoking history			
never	47 (28.7)	40 (29.6)	7 (24.1)
ex-smoker	81 (49.4)	65 (48.1)	16 (55.2)
current smoker	36 (22.0)	30 (22.2)	6 (20.7)
Brinkman index	400 [0.0, 810.0]	460 [0, 880]	245 [37.5, 485]
Cormorbidity			
Diabetes mellitus	34 (20.7)	30 (22.2)	4 (13.8)
Coronary disease	16 (9.8)	15 (11.1)	1 (3.4)
Non-coronary heart disease	29 (17.7)	27 (20.0)	2 (6.9)
Gastro-esophageal reflex disease (GERD)	47 (28.7)	36 (26.7)	11 (37.8)
modified MRC			
0	112 (68.3)	90 (66.7)	22 (75.9)
1	50 (30.5)	44 (32.6)	6 (20.7)
2	2 (1.2)	1 (0.7)	1 (3.4)
Cough			
positive	36 (22.0)	34 (25.2)	2 (6.9)
negative	128 (78.0)	101 (74.8)	27 (93.1)
Fine crackles			
positive	103 (62.8)	94 (69.6)	9 (31.0)
negative	61 (37.2)	41 (30.4)	20 (69.0)
PaO2	89.5 [83.0, 97.0]	90.0 [83.0, 96.5]	89.0 [85.0, 98.9]
%Forced vital capacity (%FVC)	97.7 [88.7, 106.7]	97.7 [87.8, 106.7]	98.5 [90.8, 105.7]
%Vital capacity (%VC)	93.1 [84.3, 103.0]	92.8 [83.8, 102.1]	94.8 [88.6, 105.5]
% DLco	89.1 [73.4, 106.1]	86.9 [70.5, 106.1]	95.0 [82.9, 104.7]
ILD GAP score	2.0 [1.0, 3.0]	2.0 [1.0, 3.0]	1.0 [1.0, 2.0]
ILD GAP stage	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
6 min walk test distance	463.5 [420.0, 505.0]	480.0 [440.0, 505.0]	460.0 [420.0, 502.5]
initial SpO2 at 6 min walk test	98.0 [97.0, 98.0]	98.0 [97.0, 98.0]	98.0 [97.0, 98.0]
Lowest SpO2 at 6 min walk test ($n=163$)	95.0 [92.0, 96.0]	94.0 [91.2, 96.0]	96.0 [94.0, 97.0]
Decline SpO2 during 6 min walk test ($n=163$)	3.0[1.0, 5.0]	3.0 [2.0, 5.7]	1.0 [1.0, 3.0]
WBC	5900 [5200, 7200]	6000 [5200, 7200]	5800 [5000, 6900]
LDH (IU/L)	193 [173, 224]	193 [175, 224]	184 [168, 218]
KL-6	409 [291, 616]	424 [313, 631]	252 [216, 466]
SP-D ($n=162$)	116 [79, 197]	128.1 [84.4, 206.2]	85.9 [64.3, 112.7]
Elevated SP-D ($\geqq$ 110 ng/ml)($n=162$)	87 (53.0)	79 (59.4)	8 (28.6)

HRCT: high-resolution CT, ILA: interstitial lung abnormality, IPF: idiopathic pulmonary fibrosis, The number of missing data is three all from the fibrotic ILA cases: one was the lowest value of the 6-minute walk

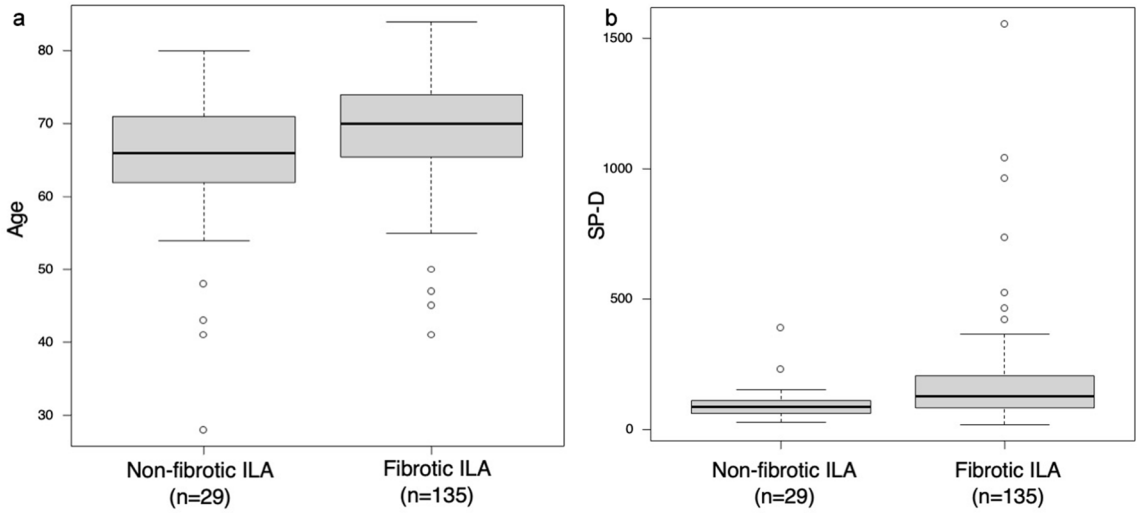

Fig. 1 **a** Comparison of age between fibrotic and non-fibrotic ILA. **b** Comparison of serum SP-D value between fibrotic and non-fibrotic ILA

and initial SpO_2 at the beginning of the 6MWT did not differ significantly between the groups. However, the lowest SpO_2 during the 6MWT in the fibrotic ILA group was significantly lower than that in the non-fibrotic group ($P = 0.012$), and the decrease in SpO_2 during the 6MWT differed significantly between the groups ($p = 0.003$).

Serum markers and fibrotic ILA

Both serum KL-6 and SP-D were significantly higher in the fibrotic ILA group than in the non-fibrotic group. However, the median KL-6 level in the fibrotic ILA group was within the normal range, whereas the median SP-D level was above the normal range (> 110 ng/mL) (Fig. 1b). Furthermore, the frequency of elevated SP-D levels was significantly higher in the fibrotic ILA group (59.4%) than in the non-fibrotic group (28.6%) ($p = 0.003$).

HRCT findings

Comparisons of HRCT findings between fibrotic and non-fibrotic ILA are shown in Table 2.

HRCT findings in fibrotic ILA

CT abnormalities were significantly more extensive in the fibrotic ILA group (median [IQR], 20% [15, 25]) than in the non-fibrotic group (median [IQR], 10% [10.15]). Traction bronchiolectasis was observed in 98% of patients in the fibrotic ILA compared to 0% in the non-fibrotic ILA group, with a significant difference in frequency. Honeycombing was positive in 16% of cases of fibrotic ILA, whereas there were no cases of non-fibrotic ILA. Subpleural reticular shadows and non-emphysematous cysts were more frequent in the fibrotic ILA than in the non-fibrotic ILA group. The subpleural attenuation of the ground glass was similar in both groups.

HRCT patterns according to the International guidelines

According to the HRCT pattern classification based on the IPF International Guidelines, the frequency of definite, probable, and indeterminate usual interstitial pneumonia (UIP) patterns was significantly higher in cases of fibrotic ILA, whereas the frequency of ILA was significantly higher in cases of non-fibrotic ILA.

Based on the classification of HRCT patterns for International Guidelines on Hypersensitivity Pneumonitis, fibrotic hypersensitivity pneumonitis (HP) patterns were significantly more frequent in the fibrotic ILA than in the non-fibrotic ILA group ($p < 0.001$), whereas non-fibrotic HP patterns were less frequent in the fibrotic ILA group than in the non-fibrotic ILA group ($p < 0.001$).

Correlation between fibrotic ILA in HRCT scans and working diagnoses on MDD

Table 3 shows the correlation between fibrotic or non-fibrotic ILA patterns and working diagnoses of interfacility MDD. Undecided diagnoses were made in 31 (18.9%) of the 164 patients enrolled in this ILA study, and specific working diagnoses were made in more than 80% of the cases during the first year of this study. In the fibrotic ILA group, IPF (23.0%), hypersensitivity pneumonitis (21.5%), smoking-related interstitial pneumonia (13.3%), unclassifiable interstitial pneumonia (11.9%), and autoimmune interstitial pneumonia (8.9%) accounted for approximately 80% of the working diagnoses, whereas undecided diagnoses accounted for only 14%. Conversely, undecided diagnoses accounted for 41% of the non-fibrotic ILA group, and specific working diagnoses accounted for 60%. The proportion of undecided diagnoses in the fibrotic ILA group (14.1%) was significantly lower than that in the non-fibrotic ILA group (41.4%) ($p = 0.0027$).

Table 2 High-resolution CT findings of Fibrotic and non-fibrotic ILA

	Entire cohort	Fibrotic ILA		
		Positive	Negative	p-value
Subjects, n (%)	164 (100)	135 (82.3)	29 (17.6)	
High-resolution CT findings				
Extent of abnormalities	20.0 [10.0, 25.0]	20.0 [15.0, 25.0]	10.0 [10.0, 15.0]	< 0.001
5%	9 (5.6)	4 (3.0)	5 (17.2)	
10%	34 (20.7)	19 (14.1)	15 (51.7)	
15%	33 (20.1)	29 (21.5)	4 (13.8)	
20%	39 (23.8)	37 (27.4)	2 (6.9)	
25%	13 (7.9)	13 (9.6)	0 (0.0)	
30%	20 (12.2)	19 (14.1)	1 (3.4)	
35%	5 (3.0)	5 (3.7)	0 (0.0)	
40%	2 (1.2)	2 (1.5)	0 (0.0)	
45%	2 (1.2)	2 (1.5)	0 (0.0)	
50%	3 (1.8)	1 (0.7)	2 (6.9)	
55%	1 (0.6)	1 (0.7)	0 (0.0)	
60%	3 (1.8)	3 (2.2)	0 (0.0)	
Subpleural ground-glass attenuation				1
positive	153 (93.2)	126 (93.3)	27 (93.1)	
negative	11(6.8)	9 (6.7)	2 (6.9)	
Subpleural reticular shadows				< 0.001
positive	148 (90.2)	128 (94.8)	20 (69.0)	
negative	16 (9.8)	7 (5.2)	9 (31.0)	
Non-emphysematous cysts				< 0.001
positive	58 (35.6)	58 (43.0)	0 (0.0)	
negative	106 (64.4)	77 (57.0)	29 (100.0)	
Traction bronchiolectasis				< 0.001
positive	133 (81.1)	133 (98.5)	0 (0.0)	
negative	31 (18.9)	2 (1.5)	29 (100.0)	
Honeycombing				0.015
positive	22 (13.4)	22 (16.3)	0 (0.0)	
negative	142 (86.5)	113 (83.7)	29 (100.0)	
IPF guideline HRCT pattern				
UIP pattern	20 (12.2)	20 (14.8)	0 (0)	0.026
Probable UIP pattern	27(16.4)	27 (20.0)	0 (0)	0.005
Indeterminate for UIP pattern	42 (25.6)	41(30.4)	1 (3.4)	0.002
Alternative diagnosis	34 (20.7)	28 (20.7)	6 (20.7)	1
ILA	41(25.0)	19 (14.1)	22 (75.9)	< 0.001
HP guideline HRCT pattern				
Non-fibrotic HP	10 (6.1)	2 (1.5)	8 (4.9)	< 0.001
Typical	1 (0.6)	0 (0.0)	1 (0.6)	
Compatible with HP	9 (5.5)	2 (1.5)	7 (4.2)	
Fibrotic HP	154 (93.9)	133 (81.1)	21 (12.8)	< 0.001
Typical	3 (1.9)	3 (1.9)	0 (0.0)	
Compatible with HP	24 (14.6)	21 (12.8)	3 (1.9)	
Indeterminate for HP pattern	127 (77.4)	109 (65.8)	18 (10.9)	

HRCT: high-resolution CT, ILA: interstitial lung abnormality, IPF: idiopathic pulmonary fibrosis, HP: hypersensitivity pneumonitis

Implementation of clinical factors with fibrotic ILA on HRCT scans

Univariate and multivariate logistic regression analyses of clinical predictive factors for fibrotic ILA on HRCT are shown in Table 4. Univariate regression analyses showed that age (odds ratio [OR], 1.070; 95%confidence interval [CI], 1.030–1.120), Brinkman index (OR, 1.000; 95%CI, 1.000–1.000), auscultatory crackles (OR, 5.090; 95%CI, 2.140–12.100), decreased SpO_2 during the 6MWT (OR, 1.330; 95%CI, 1.080–1.630), serum SP-D (OR, 1.010; 95%CI, 1.000–1.020), and elevated serum SP-D (≥ 110 ng/

Table 3 Working diagnoses of Fibrotic and non-fibrotic ILA

	Entire cohort	Fibrotic ILA		
		Positive	Negative	p-value
Subjects, n (%)	164 (100)	135 (82.3)	29 (17.6)	
Age	69 [65, 73]	70 [65, 74]	66 [62, 71]	0.005
Working diagnosis by inter-facility MDD				NA
Idiopathic pulmonary fibrosis (IPF)	31 (18.9)	31 (23.0)	0 (0.0)	
Nonspecific interstitial pneumonia (NSIP)	0 (0.0)	0 (0.0)	0 (0.0)	
Organizing pneumonia	1 (0.6)	1 (0.6)	0 (0.0)	
Pleuroparechymal pulmonary fibroelastosis (PPFE)	3 (1.8)	2 (1.5)	1 (3.4)	
Unclassifiable interstitial pneumonia	20 (12.2)	16 (11.9)	4 (13.8)	
Hypersensitivity pneumonitis	35 (21.3)	29 (21.5)	6 (20.7)	
Autoimmune interstitial pneumonia	13 (7.9)	12 (8.9)	1 (3.4)	
Smoking related interstitial pneumonia	20 (12.2)	18 (13.3)	2 (6.9)	
Sarcoisosis	0 (0.0)	0 (0.0)	0 (0.0)	
Drug-induced interstitial pneumonia	0 (0.0)	0 (0.0)	0 (0.0)	
Pneumoconiosis	0 (0.0)	0 (0.0)	0 (0.0)	
Others	10 (6.1)	7 (5.2)	3 (10.3)	
Diagnosis undecided	31 (18.9)	19 (14.1)	12 (41.4)	

HRCT: high-resolution CT

MDD: multidisciplinary discussion diagnosis

mL; OR, 3.660; 95%CI, 1.500–8.910) were significantly associated with fibrotic ILA (Fig. 2).

After adjusting covariables by multivariate regression analyses, age (OR 1.060, 95%CI 1.010–1.120), auscultatory fine crackles (OR 3.390, 95%CI 1.330–8.640), and elevated serum SP-D (≥110 ng/mL) (OR, 2.680; 95%CI, 1.020–8.640) were independent predictive factors of fibrotic ILA on HRCT scans (Fig. 2). The predicted AUC of fibrotic ILA based on these three factors was 0.77 (95%CI, 0.68–0.86) (Fig. 3).

Discussion

Our study demonstrated for the first time that regarding the clinical characteristics of patients with fibrotic ILA on HRCT, older age, fine auscultatory crackles, and elevated serum SP-D are predictive factors of fibrotic ILA in a multicentre prospective observational study of patients screened during health examinations. Furthermore, fibrotic ILAs are frequently associated with a specific working diagnosis.

Ageing, pulmonary fibrosis, and ILA

Older age is a common risk factor for progressive fibrosing ILDs, including IPF in 2,746 patients enrolled in the Canadian Registry [16]. Similarly, age is a predictive factor for ILA in 327 patients with ILA [17]. In the present study, older age was independently associated with fibrotic ILA in HRCT. Lung ageing is associated with molecular and physiological changes that decrease pulmonary remodelling and regenerative capacity and increase susceptibility to pulmonary fibrosis [18]. In the future, the effects of early intervention with anti-fibrotic drugs in progressive cases of fibrotic ILA should be examined.

Fine auscultatory crackles and ILA

Auscultation is a physical examination essential for the initial assessment of lung disease. Fine auscultatory crackles can be discerned before radiologic abnormalities are detected and are considered an early sign of pulmonary impairment [19]. Furthermore, they have been closely associated with findings suggestive of the extent of lung fibrosis in HRCT patterns defined by former

Table 4 Univariate and Multivariate analyses of predictive factors of fibrotic ILA

	Univariate for Fibrotic ILA			Multivariate for Fibrotic ILA		
Variable	**Odds Ratio**	**95%CI**	***P* value**	**Odds Ratio**	**95%CI**	***P* value**
Age	1.07	1.030 – 1.120	0.001	1.06	1.010–1.120	0.021
Sex	0.608	0.250–1.480	0.272			
Brinkman Index	1	1.000–1.000	0.043			
Fine crackles	5.09	2.140–12.100	< 0.001	3.39	1.330–8.640	< 0.010
%FVC	0.984	0.958–1.010	0.262			
%DLco	0.987	0.969–1.000	0.151			
Decline of SpO2 at 6-minute walk test	1.33	1.080–1.630	0.007			
Serum KL-6	1	1.000–1.000	0.294			
Serum SP-D	1.01	1.000–1.020	0.01			
Serum SP-D elevation (≧110ng/mL)	3.66	1.500–8.910	0.004	2.68	1.020–8.640	0.045

%FVC: %forced vital capacity, %DLco: %diffusing capacity of lung for carbon monoxide, KL-6: Krebs von den lungen-6, Sialylated carbohydrate antigen, SP-D: surfactant protein-D

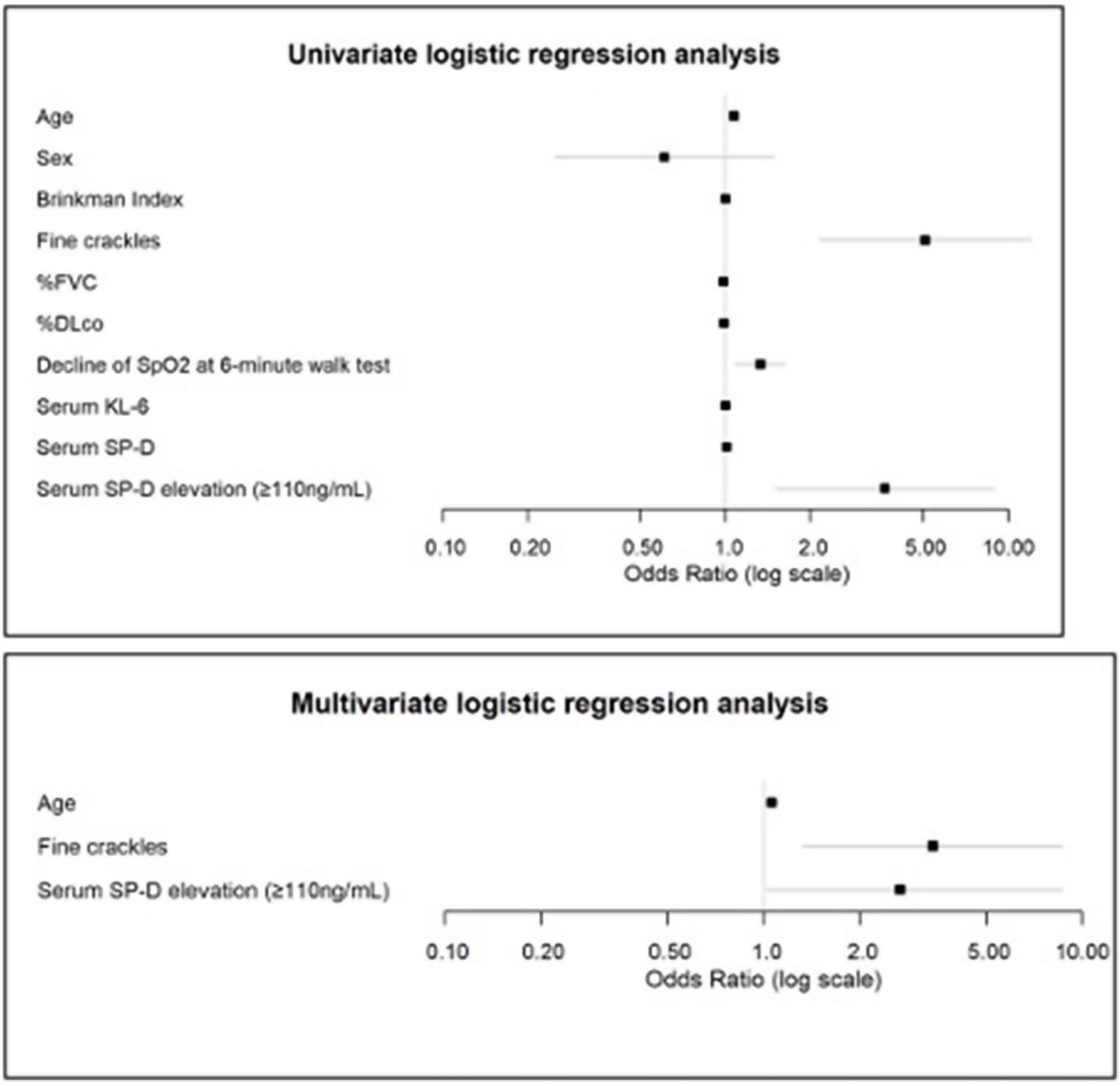

Fig. 2 Forest plots of univariate and multivariate logistic regression analysis

international IPF guidelines [20] (definite UIP pattern: OR [95%CI], 19.8 [5.28–74.25]; possible UIP pattern: OR [95%CI], 13.09 4.87–35.2). Auscultatory fine crackles were present in 103 (63%) of 164 cases at the time of ILA diagnosis and were detected more frequently in fibrotic ILA (70%) than in non-fibrotic ILA (31%) in our study, which was evaluated for the first time in a prospective ILA study. Furthermore, fine auscultatory crackles were independent predictive signs of fibrotic ILA, with a high OR of 3.390 (95%CI, 1.330–8.640). Each HRCT pattern in the latest international guidelines for IPF or HP in our patients with fibrotic ILA was mainly categorised into definite, probable, or indeterminate for UIP in the IPF guidelines, and fibrotic HP in the HP guidelines. Although the presence of auscultatory fine crackles and HRCT patterns in the IPF guidelines corresponded to those described previously [21], the relationship between fine crackles and fibrotic HP patterns was first elucidated in this study. Our results may help doctors during health check-up screening or primary care physicians make referrals to specialists.

Serum markers and ILA

Serum markers such as KL-6 and SP-D have a diagnostic and prognostic value in ILDs. Although KL-6 and SP-D are two of the most promising biomarkers in ILD, KL-6 showed a higher sensibility and specificity as well as a diagnostic accuracy compared to SP-D and other biomarkers [22]. However, there are no reports on the relationship between these markers and ILA. Serum SP-D levels are elevated early in interstitial pneumonias [23–25]. Kashiwabara [23] reported that serum levels of SP-D and KL-6 were significantly higher in seven patients, who showed incidental parenchymal abnormalities in the

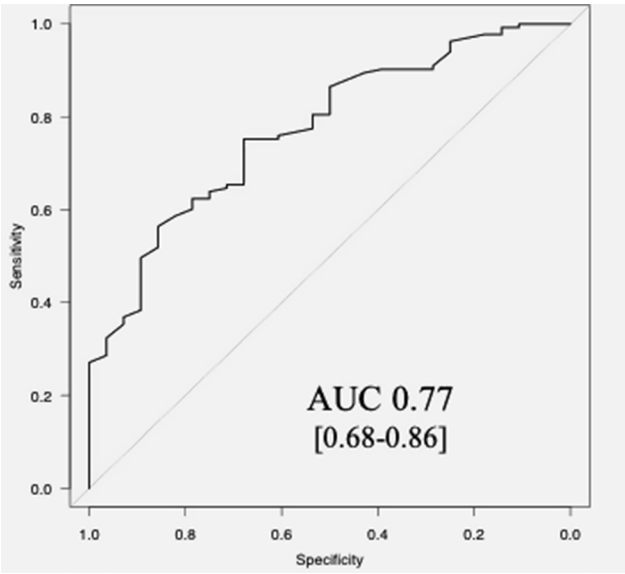

Fig. 3 ROC curve: predicting value of age, auscultatory fine crackles, and elevated SP-D for fibrotic ILA ROC, Receiver operator characteristic; ILA, interstitial lung abnormality

posterior subpleural aspect of the lung on CT performed for health checks, than that in 14 control participants. The report was the first to point out the relationship between ILA and serum markers [23]. Our study demonstrated that serum SP-D levels were significantly higher in fibrotic ILA than in non-fibrotic ILAs. An elevation above normal was an independent predictor of fibrotic ILA, with an OR of 2.680 (95%CI, 1.020–8.640).

Other factors of ILA

Individuals with ILA have an increase in symptoms such as decreased total lung capacity [26]. A recent meta-analysis [27] also showed that older age, male sex, and lower FVC are risk factors associated with increased risk of ILA. We found that cough symptoms were significantly more frequent in the fibrotic ILA group (25%) than in the non-fibrotic ILA group (7%) ($p = 0.045$), while the difference in %FVC and %VC were not significantly different between the fibrotic ILA and non-fibrotic groups. The reason for this, even though the fibrotic ILA group had a higher cough frequency, and the reason why there was no gender difference, was thought to be the small number of non-fibrotic ILA and female cases.

Predictors of fibrotic ILA

Studies on the clinical characteristics and predictors of patients with fibrotic ILA using HRCT are lacking. We found that age, fine auscultatory crackles, and elevated serum SP-D levels were independent predictive factors for fibrotic ILA. Using these three factors, the predicted AUC for fibrotic ILA was 0.77 (95%CI, 0.68–0.86). Hoyer et al. [28] reported that early diagnosis in 264 patients with IPF led to a better prognosis than a diagnostic delay of more than one year. However, delayed diagnosis of IPF from recognition of symptoms has been problematic worldwide [29, 30]. In the primary care setting, early symptoms of IPF may be diagnosed as an acute condition or knowledge of fibrotic ILD is scarce [30, 31]. Brereton et al. [31] reported that the length of time spent in healthcare systems before referral to ILD specialist centres reflected the disease severity, duration of antifibrotic therapy, and impact on survival in patients with IPF. Therefore, it is of critical value for doctors involved in health check-up screening and for primary care physicians to ensure timely referral to ILD specialist centres. Our results could help these clinicians consult specialists.

Working diagnoses for ILA and fibrotic ILA

The proportion of ILDs remained unclassifiable after the initial MDD. This requires potential diagnostic confidence for different types of ILDs, as suggested by a working group led by Ryerson et al. [33]. When there is no clear diagnosis, patients can be managed based on a working diagnosis in which a non-definite diagnosis is made with a certain confidence based on clinical reasoning [34]. Since ILA does not necessarily progress to extensive ILD [1], there have been no data on the significance of a working diagnosis in patients with ILA. Spagnolo et al. [31] recommended that ILA might need continued surveillance or focused investigations, especially if it is the fibrotic type, in addition to awareness of increasing risk factors, such as older age, smoking history, and genetic elements. In our study, the proportion of specific working diagnoses in the fibrotic ILA group was significantly higher than that in the non-fibrotic ILA group. Once a specific working diagnosis is made, the elimination of risk factors, such as smoking cessation or antigen avoidance, could lead to more proactive guidance, and is the first step in non-medicinal therapeutic intervention.

Study limitations

Our study has several limitations. First, this study is ongoing, and a relatively small number of patients were enrolled during the first year. However, these preliminary findings are worth reporting because there is a lack of data on the clinical characteristics of patients with fibrotic ILA screened from a healthy population. Second, our study was based on data at the time of ILA diagnosis and did not include disease progression; therefore, our patients with fibrotic ILA should be closely followed up if they show a similar progressive course of fibrotic ILA reported in previous studies. This course may change due to the proactive elimination of risk factors. Third, because of the small number of patients with non-fibrotic ILA, only three predictors that are commonly observed

and relatively objective even when diagnosed by non-specialists, were extracted. However, using the three factors, the predicted AUC of fibrotic ILA was 0.77 (95%CI, 0.68–0.86), which was fairly specific. Fourth, the working diagnoses in this study were determined by more than five specialists because of interfacility MDD. The boundary between ILA and ILD remains controversial, and some argue that it is appropriate to give ILA cases a working diagnosis of ILD. As discussed previously, making potential working diagnoses could lead to the proactive elimination of causative elements.

Conclusions

This study evaluated the clinical characteristics of patients with fibrotic ILA who were enrolled in a multicentre prospective cohort study of a health check-up population. Older age, fine crackles on auscultation, and elevated serum SP-D levels were found to be independent predictors of fibrotic ILA. The combination of these three factors was predictable for fibrotic ILA and may act as an indicator for referral to specialists of patients with early potentially progressive fibrotic lesions.

Abbreviations

6-MWT	6-minute walk test
AUC	Area under the curve
CI	Confidence interval
FVC	Forced vital capacity
VC	Vital capacity
DLco	Diffusing capacity of lung for carbon monoxide
HP	Hypersensitivity pneumonitis
HRCT	High-resolution computed tomography
ILA	Interstitial lung abnormality
IQR	Interquartile range
IPF	Idiopathic pulmonary fibrosis
KL-6	Krebs von den Lungen-6
UIP	Usual interstitial pneumonia
MDD	Multidisciplinary discussion diagnosis
OR	Odds ratio
PPF	Progressive pulmonary fibrosis
ROC	Receiver operator characteristic
SP-D	Surfactant protein D

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03520-4.

Supplementary Material 1

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Author contributions

KI, HI, KI, KK, YY, KA, HO, KA, NH, TJ, KF, TS, JM, MY, KM, and TS were involved in study conception, data analysis, and drafting and revision of the manuscript. All authors are accountable for the accuracy and integrity of the research output.TS and JM are biostatisticians and were in charge of the statistical analysis.

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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.

Declarations

Ethics approval and consent to participate

This study complied with the Helsinki Declaration and the protocol, and the informed consent forms were approved by the Institutional Review Boards of Kumamoto University Hospital (approval number: 2368), Saiseikai Kumamoto Hospital (approval number: 809), and Kumamoto Red Cross Hospital (approval number: 464). Written informed consent was obtained from all participants. Patient recruitment commenced on 20 June 2022.

Consent for publication

Consent for publication was obtained from all participants and authors.

Competing interests

KI, HI, TJ, and TS received lecture fees from Nippon Boehringer Ingelheim Co. Ltd. Boehringer Ingelheim had no role in the design, analysis, or interpretation of the results in this study. Boehringer Ingelheim was given the opportunity to review the manuscript for medical and scientific accuracy as it relates to Boehringer Ingelheim substances, as well as intellectual property considerations.KI, KK, YY, KA, HO, KA, NH, KF, TS, JM, MY, and KM declare no conflict of interest.

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