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Serum carbohydrate antigen 153 as a predictor of interstitial lung disease associated with rheumatoid arthritis is positively correlated with serum Krebs von den Lungen-6

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Abstract

Objective The objective of this study was to evaluate the clinical significance of carbohydrate antigen (CA) 153 and its correlation with Krebs von den Lungen-6 (KL-6) in the prediction and determination of the severity of interstitial lung disease (ILD) in rheumatoid arthritis (RA) patients.

Methods Data was collected retrospectively on a cohort of 357 RA patients who were admitted to our hospital from January 2018 to December 2020. The classification of patients into subgroups was based on high-resolution computed tomography (HRCT) of the chest, resulting in 135 patients with RA but no ILD, 107 patients with RA and indeterminate ILD, 91 patients with RA and mild ILD, and 24 patients with RA and advanced ILD. The levels of CA153 and KL-6 were determined by chemiluminescence analysis.

Results The serum levels of CA153 were found to be significantly higher in both the RA-mild ILD group and the RA-advanced ILD group compared to the RA-no ILD group (8.00 vs. 6.40, q = 0.039; 20.30 vs. 6.40, q < 0.001). Multivariate analysis demonstrated that CA153 was an independent risk factor for RA-ILD (RA-mild ILD + RA-advanced ILD) [odds ratio (OR) = 1.124, 95% confidence interval (CI) = (1.060–1.191), $p < 0.001$] and RA-advanced ILD (OR = 1.583, 95% CI = 1.247–2.010, $p < 0.001$). Furthermore, the receiver operating characteristic (ROC) analysis indicated that CA153 had diagnostic value for both RA-ILD (RA-mild ILD + RA-advanced ILD) and RA-advanced ILD. The best area under ROC curve (AUC) of CA153 for RA-ILD (RA-mild ILD + RA-advanced ILD) was 0.66 ($p < 0.001$; sensitivity = 57.27%; specificity = 72.03%). The AUC of CA153 for RA-advanced ILD was 0.95 ($p < 0.001$; sensitivity = 95.65%;

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specificity = 83.05%). Moreover, CA153 was negatively correlated with forced vital capacity percent predicted (FVC% pred) (r = -0.383, p = 0.037) but positively related to KL-6 (r = 0.762, p < 0.001).

Conclusion It was concluded that CA153 was positively associated with KL-6 and might be a significant and clinical availably measurable serum marker to predict the diagnosis and severity of ILD in RA patients.

Keywords Rheumatoid arthritis, Interstitial lung disease, Tumor markers, Carbohydrate antigen 153, Krebs von Den Lungen-6

Background

Rheumatoid arthritis (RA) is a chronic systemic autoimmune disorder accompanied by the existence of rheumatoid nodules, pulmonary involvement, vasculitis and additional systemic comorbidities [1]. Among the various extra-articular manifestations of RA, lung involvement is the most common complication, including interstitial lung disease (ILD), rheumatoid nodules, pleural involvement and pulmonary vasculature complications [2]. ILD is a critical cause of morbidity and mortality in patients with RA, which can be detected in 60% of RA patients with high-resolution computed tomography (HRCT) imaging [3–5]. A recent study also revealed that the rates of death caused by rheumatoid arthritis-associated interstitial lung disease (RA-ILD) increased 28.3% in women and fell 12.5% in men [5]. Despite HRCT being the primary method for early detection of pulmonary pathological changes, early diagnosis of ILD remains challenging.

Circulating tumor markers have been employed as a practical and economical diagnostic tool for various malignant or non-malignant disease [6–8]. There was a significantly higher proportion of ILD patients in abnormal values of carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9 and CA125 compared to individuals in the control group [9]. Moreover, the levels of tumor markers CA153, CA125 and CA19-9 were statistically elevated in RA-ILD patients as opposed to RA patients without ILD, in particular, higher CA125 levels increased the susceptibility to ILD [10, 11]. The predictive value of serum Krebs von den Lungen-6 (KL-6) for the development and progression of ILD is widely acknowledged, which indicates the extent of alveolar epithelial injury [12–14]. Previous studies have shown that CA153 is encoded by the same the mucin 1 (MUC1) gene as KL-6. Both CA153 and KL-6 belong to the MUC1 family, which covers the surface of various epithelial cells, such as alveolar, breast and gastrointestinal cells [15–17]. Most importantly, Ricci et al. found that increased CA153 levels were related to decreased total lung capacity (TLC), decreased diffusing capacity of the lung for carbon monoxide (DLCO) and advanced pulmonary fibrosis according to HRCT findings [18]. Although some studies have focused on the positive correlation between CA153 and KL-6 in fibrotic lung diseases, whether CA153 can distinguish RA-ILD patients and be a biomarker for the presence of RA-ILD is still unclear [19, 20]. Also, the relationship between KL-6 and CA153 in RA-ILD has rarely been reported.

The objective of this study was to assess the predictive value of CA153 in RA-ILD and explore the correlation between CA153 and KL-6, thereby offering clinical application value for early identification and screening of RA-ILD.

Materials and methods

Study population

We reviewed 676 patients diagnosed with Rheumatoid arthritis according to the 1987 American College of Rheumatology (ACR) and/or the 2010 European League against Rheumatism (EULAR)/ACR classification criteria for RA and recruited from the Department of Rheumatology and Immunology at the First Affiliated Hospital of Xiamen University between January 2018 and December 2020 [21, 22]. Patients with cancer, other autoimmune diseases, other pulmonary disease and incomplete medical records were excluded from the study. Finally, 357 patients were eligible for inclusion (Fig. 1). Reference groups including systemic sclerosis-associated ILD (SSc-ILD), idiopathic pulmonary fibrosis (IPF) and healthy control were also enrolled, which met the diagnosis criteria of corresponding disease [23, 24]. This study adhered to the principles of the Declaration of Helsinki and received approval from the Clinical Research Ethics Committee of the First Affiliated Hospital of Xiamen University (2023031).

HRCT ILD classification

Chest HRCT imaging abnormalities indicative of the severity of ILD were classified into four categories—no ILD, indeterminate ILD (focal or unilateral ground-glass attenuation, focal or unilateral reticulation, or patchy ground-glass abnormality involving < 5% of the lung), mild ILD (changes affecting > 5% of any lobar region with nondependent ground-glass or reticular abnormalities, diffuse centrilobular nodularity, nonemphysematous cysts, honeycombing, or traction bronchiectasis) and advanced ILD (bilateral fibrosis in multiple lobes associated with honeycombing and traction bronchiectasis in a subpleural distribution) [25–27]. Patients with ILD were detected in this study by chest HRCT imaging

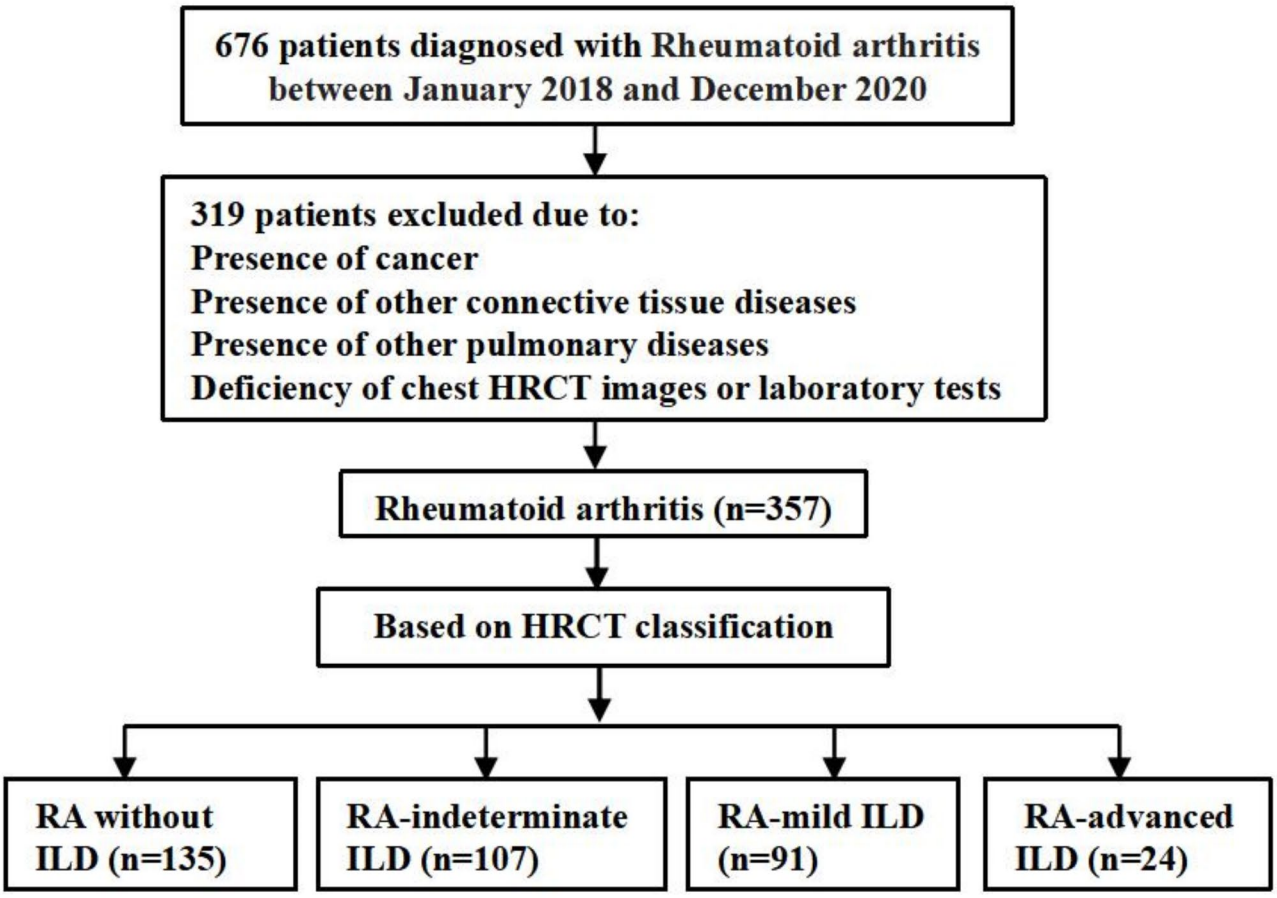

Fig. 1 Flowchart of the population included in the study. RA, rheumatoid arthritis; ILD, interstitial lung disease; HRCT, high-resolution computed tomography

abnormalities suggestive of either mild or advanced ILD [27]. The extent of ILD was calculated as follows: three images at the level of the aortic arch, the carina and 1 cm above the diaphragm were taken, and the percentage of imaging abnormalities in each field was scored as follows: 1 (1–25% involvement), 2 (26–50% involvement), 3 (51–75% involvement) and 4 (76–100% involvement). The six lung field scores were added to obtain the final score [28–30]. The interpretation of all images was conducted independently and in a blinded manner by two radiologists and one pulmonologist. The final assessment was achieved by consensus if there were discrepancies.

Clinic data collection

Clinical data collected included general clinical information, pulmonary function and laboratory indexes such as rheumatoid factor (RF), anti-cyclic citrullinated peptide (anti-CCP), serum tumor markers and KL-6 were extracted from the medical records. Additionally, the concentrations of tumor markers were tested by chemiluminescence analysis in the Department of Nuclear Medicine of the First Affiliated Hospital of Xiamen University, including CA125, CA153, CA19-9, CA242, CA50, CEA, cytokeratin 19 fragment (CYFRA21-1), neuron-specific enolase (NSE) and squamous cell carcinoma antigen (SCCA). CA724 and pro-gastrin-releasing peptide (proGRP) were measured by electrochemiluminescence analysis. The following are the normal ranges: CA125 < 35.00 U/ml, CA153 < 32.40 U/ml, CA19-9 < 37.00 U/ml, CA242 < 20.00 IU/ml, CA50 < 25.00 U/ml, CA724 < 8.20 U/ml, CEA < 5.00 ng/ml, CYFRA21-1 0.10–3.39 ng/ml, NSE < 10.00 ng/ml, proGRP 25.30–69.20 pg/ml and SCCA < 2.50 ng/ml. The concentration of KL-6 was determined by the LumipulseG1200 kit through chemiluminescence analysis in the Department of Laboratory Medicine. About 107 participants were measured with KL-6. Pulmonary function was tested in 29 participants through spirometry. The American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations for the standardization of lung function tests were followed when performing spirometry [31]. Data collection was carried out by two independent authors.

Statistical analysis

Statistical analysis was conducted using SPSS 24.0 and GraphPad Prism 9. Continuous variables were presented as mean ± standard deviation or median and interquartile range, while categorical variables were expressed as frequency with percentage. Differences in categories were evaluated using the chi-square test, Fisher's exact test, Mann-Whitney U test and Student's t-test. When conducting multiple comparisons, False Discovery Rate adjustment was applied and q-value < 0.05 was considered statistically significant. Logistic regression analysis was conducted through the Forward: LR method to analyze the risk factors of different severity of ILD in patients with RA. The receiver operating characteristic (ROC) curve analysis was applied to assess the sensitivity and specificity of CA153 for predicting the severity of RA-ILD. Internal validation of the ROC analysis was conducted through the method of bootstrapping by R-Project package "fbroc". Spearman's correlation was utilized to establish correlations, with "r" representing the correlation coefficient, which ranges from − 1 to + 1. Two-sided p-value < 0.05 was considered statistically significant.

Results

Clinical characteristics of different severity of RA-ILD patients

A total of 357 RA patients were included in this study: 135 (37.82%) patients had no ILD, 107 (29.97%) patients had indeterminate ILD, 91 (25.49%) patients had mild ILD, and 24 (6.72%) patients had advanced ILD (Fig. 1). The study participants' basic characteristics were summarized in Table 1. The prevalence of RA-ILD, which includes both mild and advanced cases, was 32.21% in our cohort.

The mean age of RA-ILD (RA-mild ILD + RA-advanced ILD) patients was 62.47 ± 9.54 years and that of RA-no ILD patients was 54.94 ± 10.92 years. RA-ILD patients were significantly older than those without ILD (q < 0.001). The average age in different severity of RA-ILD presented an upward trend with increasing severity of ILD. Most patients of our RA cohort were female (n = 258, 72.27%). However, most RA-advanced ILD patients were male (n = 14, 58.33%) and had a higher proportion of smoking (n = 10, 41.67%), which demonstrated statistically significant differences when compared to patients with RA alone. Also, body mass index (BMI) in RA-ILD (RA-mild ILD + RA-advanced ILD) patients was higher than that of RA-no ILD patients (23.30 ± 3.86 vs. 21.77 ± 3.41, q = 0.002) and the value of BMI in RA-mild ILD was higher compared with RA-no ILD patients (23.51 ± 3.92 vs. 21.77 ± 3.41, q = 0.002).

There was no significant difference in the duration of the disease process, and clinic symptoms, such as morning stiffness, joint deformity among each group. In addition, compared with RF levels in the RA-no ILD group, increased levels of RF were observed both in the RA-ILD (RA-mild ILD + RA-advanced ILD) group and in the RA-advanced ILD group (144.00 vs. 82.80, q = 0.023; 437.50 vs. 82.80, q < 0.001, respectively). However, anti-CCP and disease Activity Score (DAS) 28 showed no significant difference among each group. Approximately 62.5% (n = 15) of patients showed cough and 58.33% (n = 14) of patients had dyspnea in RA-advanced ILD. Velcro rale presented in 54.17% (n = 13) of patients when ILD advanced. Meanwhile, no statistically significant difference was observed in percent predicted forced vital capacity (FVC% pred) among each group. Diffusing capacity of the lung for carbon monoxide percent predicted (DLCO% pred) of RA-ILD (RA-mild ILD + RA-advanced ILD) patients was lower than that of RA-no ILD patients (58.28 ± 17.72 vs. 97.00 ± 18.39, q = 0.036) with the increase of respiratory symptoms in frequency. Similarly, RA-advanced ILD patients and RA-mild ILD patients also had lower DLCO% pred (55.83 ± 18.08 vs. 97.00 ± 18.39, q = 0.043; 59.50 ± 18.22 vs. 97.00 ± 18.39, q = 0.039, respectively) with more respiratory manifestations as compared with RA-no ILD patients.

Further analysis showed that there were no evident differences in inflammatory markers (C-reactive protein and erythrocyte sedimentation rate) among each group. Besides, the values for pulmonary arterial pressure were significantly elevated in the RA-ILD (RA-mild ILD + RA-advanced ILD) group and in the RA-advanced ILD group than in the RA-no ILD group (30.64 ± 6.59 vs. 27.60 ± 5.30, q = 0.037; 33.10 ± 5.24 vs. 27.60 ± 5.30, q = 0.019, respectively). RA-ILD (RA-mild ILD + RA-advanced ILD) patients were more susceptible to developing osteoporosis (n = 65, 56.52%) and fragility fracture (n = 16, 13.91%) than RA-no ILD patients (n = 48, 35.56%, q = 0.002; n = 5, 3.70%, q = 0.008, respectively). The proportion of RA-mild ILD patients complicating with osteoporosis was 58.24%, and fragility fracture was 14.29%, which were significantly greater compared with RA patients with no ILD (q = 0.002; q = 0.008, respectively). And the proportion of RA patients receiving corticosteroid therapy or immunosuppressant therapy showing no significant difference among each group.

The laboratory results are shown in supplementary Tables 1–3, including hematological parameters, coagulation markers and immunological parameters.

The levels of tumor markers and KL-6 in different severity of RA-ILD

We investigated the levels of tumor markers and KL-6 in different severity of RA-ILD. Serum CA125, CA153, CA19-9, CA242, CA50, CA724, CEA, CYFRA21-1, NSE, proGRP, SCCA and KL-6 were measured among

Table 1 Basic characteristics of the rheumatoid arthritis patients

	RA-no ILD (*n* = 135)	RA-indeterminate ILD (*n* = 107)	RA-mild ILD (*n* = 91)	RA-advanced ILD (*n* = 24)	RA-ILD (RA-mild ILD + RA-advanced ILD) (*n* = 115)
Demographic features					
Age(years)	54.94 ± 10.92	59.19 ± 9.09**	61.97 ± 8.80***	64.38 ± 11.97***	62.47 ± 9.54***
Male, n(%)	33(24.44)	32(29.91)	20(21.98)	14(58.33)**	34(29.57)
BMI(kg/m^2)	21.77 ± 3.41	21.96 ± 3.06	23.51 ± 3.92**	22.48 ± 3.57	23.30 ± 3.86**
Current/ever smoking, n(%)	16(11.85)	17(15.89)	12(13.19)	10(41.67)**	22(19.13)
RA associated clinical features					
Duration of RA(years)	7.00(2.00,11.00)	7.00(1.00,15.00)	6.00(1.00,13.00)	5.00(2.00,10.00)	5.00(2.00,11.00)
Morning stiffness, n(%)	99(73.33)	80(74.77)	63(69.23)	16(66.67)	79(68.70)
Joint deformity, n(%)	50(37.04)	43(40.19)	31(34.07)	8(33.33)	39(33.91)
RF, IU/ml	82.80(18.00,268.00)	105.00(29.80,429.00)	125.00(22.40,491.00)	437.50(111.00,1077.25)***	144.00(23.70,541.00)*
Anti-CCP, RU/ml	83.60(16.70,200.00)	79.80(34.10,200.00)	81.90(12.60,200.00)	184.00(48.55,200.00)	99.10(18.70,200.00)
DAS28(CRP)	4.11 ± 1.50	4.21 ± 1.73	4.14 ± 1.64	3.73 ± 1.45	4.06 ± 1.61
DAS28(ESR)	4.67 ± 1.52	4.87 ± 1.72	4.78 ± 1.66	4.66 ± 1.46	4.76 ± 1.62
Respiratory manifestations					
Cough, n(%)	0(0.00)	2(1.87)	5(5.49)*	15(62.50)***	20(17.39)***
Dyspnea, n(%)	1(0.74)	1(0.93)	3(3.30)	14(58.33)***	17(14.78)***
Velcro rale, n(%)	0(0.00)	0(0.00)	2(2.20)	13(54.17)***	15(13.04)***
Pulmonary function test					
FVC%pred	92.00 ± 7.07	86.11 ± 9.18	81.33 ± 13.22	77.67 ± 20.05	80.11 ± 15.31
DlCO%pred	97.00 ± 18.39	74.22 ± 31.29	59.50 ± 18.22*	55.83 ± 18.08*	58.28 ± 17.72*
CT pattern					
UIP				16(66.67)	
NSIP				8(33.33)	
Inflammatory markers					
CRP, mg/l	15.30(3.49,43.30)	13.30(4.07,39.80)	15.20(4.93,57.00)	9.29(4.04,32.08)	14.50(4.48,46.90)
ESR, mm/h	40.00(19.00,74.00)	40.00(22.00,65.00)	44.00(25.00,81.00)	55.50(38.00,74.25)	45.00(26.00,80.00)
Pulmonary arterial pressure, **mmHg**	27.60 ± 5.30	28.91 ± 5.25	30.01 ± 6.81	33.10 ± 5.24*	30.64 ± 6.59*
Comorbidities					
Hypertension, n(%)	26(19.26)	25(23.36)	27(29.67)	4(16.67)	31(26.96)
Diabetes, n(%)	11(8.15)	16(14.95)	12(13.19)	3(12.50)	15(13.04)
Osteoporosis, n(%)	48(35.56)	42(39.25)	53(58.24)**	12(50.00)	65(56.52)**
Osteopenia, n(%)	29(21.48)	28(26.17)	17(18.68)	6(25.00)	23(20.00)
Fragility fracture, n(%)	5(3.70)	7(6.54)	13(14.29)**	3(12.50)	16(13.91)**
Joint replacement, n(%)	6(4.44)	13(12.15)	4(4.40)	1(4.17)	5(4.35)
Medication					
Corticosteroid, n(%)	45(33.33)	31(28.97)	32(35.16)	13(54.17)	45(39.13)
Immunosuppressant, n(%)	63(46.67)	49(45.79)	40(43.96)	16(66.67)	56(48.70)

Note: 29 participants were tested pulmonary function, 6 participants of RA-advanced ILD, 12 participants of RA-mild ILD, 9 participants of RA-indeterminate ILD, 2 participants of RA-no ILD; 125 participants were measured pulmonary arterial pressure, 10 participants of RA-advanced ILD, 39 participants of RA-mild ILD, 34 participants of RA-indeterminate ILD, 42 participants of RA-no ILD

Abbreviations: RA: rheumatoid arthritis; ILD: interstitial lung disease; BMI: body mass index; RF: rheumatoid factor; anti-CCP: anti-cyclic citrullinated peptide; DAS28, 28-joint Disease Activity Score; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; FVC% pred: forced vital capacity percent predicted; DLCO% pred: diffusing capacity of the lung for carbon monoxide percent predicted; UIP: usual interstitial pneumonia; NSIP: non-specific interstitial pneumonia

*q < 0.05, **q < 0.01, ***q < 0.001 compared with RA-no ILD

the different groups. As shown in Table 2, the results indicated that the RA-ILD group (RA-mild ILD + RA-advanced ILD) had significantly higher levels of CA153, CA19-9, CA50, CEA and CYFRA21-1 compared with the RA-no ILD group. Besides, the RA-advanced ILD group displayed significantly elevated levels of KL-6 and tumor markers, namely CA125, CA153, CA19-9, CEA, CYFRA21-1 and NSE, in comparison to the RA-no ILD group. Moreover, higher levels of CA153, CA50 and CYFRA21-1 distinguished the RA-mild ILD group from

Table 2 Tumor markers of the study participants

	RA-no ILD (*n* = 135)	RA-indeterminate ILD (*n* = 107)	RA-mild ILD (*n* = 91)	RA-advanced ILD (*n* = 24)	RA-ILD (RA-mild ILD + RA-advanced ILD) (*n* = 115)
CA125,U/ml	9.10(6.73,12.95)	8.90(6.55,12.50)	9.10(6.45,13.95)	18.90(10.35,30.75)***	10.65(7.00,17.30)
CA153,U/ml	6.40(4.68,10.50)	7.05(5.60,10.90)	8.00(4.80,12.70)*	20.30(15.40,30.10)***	10.35(6.08,17.23)***
CA19-9,U/ml	14.16(8.66,21.02)	15.25(9.21,22.97)	16.57(10.54,25.28)	26.43(11.68,73.37)*	17.48(10.57,28.00)*
CA242,IU/ml	3.68(2.64,5.86)	3.25(2.29,5.69)	4.27(3.07,6.28)	3.99(2.21,25.37)	4.25(3.03,6.58)
CA50,U/ml	4.75(2.81,7.73)	4.78(2.96,8.44)	5.89(4.04,10.52)*	7.04(4.63,16.75)	6.54(4.06,10.65)*
CA724,U/ml	1.47(0.89,3.24)	1.93(0.92,3.47)	1.58(0.94,3.26)	2.05(1.14,5.42)	1.61(0.94,3.53)
CEA, ng/ml	0.95(0.50,1.50)	0.99(0.50,1.61)	1.32(0.51,1.90)	1.37(1.17,2.87)**	1.34(0.64,1.95)*
CYFRA21-1,ng/ml	2.14(1.54,2.97)	2.13(1.66,2.97)	2.53(1.74,3.67)*	3.70(2.49,5.77)***	2.71(1.91,4.31)***
NSE, ng/ml	3.11(2.56,3.98)	3.19(2.43,4.08)	3.39(2.72,4.49)	4.30(3.41,5.38)**	3.59(2.78,4.62)
proGRP, pg/ml	30.99(23.33,43.67)	34.90(26.46,45.63)	34.13(27.62,46.30)	32.96(18.99,43.40)	34.13(25.16,45.15)
SCCA, ng/ml	1.03(0.69,1.59)	0.91(0.63,1.36)	1.02(0.67,1.52)	1.36(0.96,1.73)	1.11(0.69,1.53)
KL-6,U/ml	229.00(163.00,311.00)	185.00(161.00,268.00)	248.00(154.50,338.00)	1190.50(654.25,1637.00)***	287.00(167.00,531.00)

Abbreviations: *CA*: carbohydrate antigen; *CEA*: carcinoembryonic antigen; *CYFRA21-1*: cytokeratin 19 fragment; *NSE*: neuron-specific enolase; *proGRP*: pro-gastrin-releasing peptide; *SCCA*: squamous cell carcinoma antigen; *KL-6*, Krebs von den Lungen-6

107 participants were tested KL-6, 8 participants of RA-advanced ILD, 37 participants of RA-mild ILD, 35 participants of RA-indeterminate ILD, 27 participants of RA-no ILD

*q < 0.05, **q < 0.01, ***q < 0.001 compared with RA-no ILD

Table 3 Risk factors related to different severity of RA-ILD assessed by logistic regression analysis. (A) logistic regression analysis performed to assess the risk factors associated with RA-ILD (RA-mild ILD + RA-advanced ILD). (B) logistic regression analysis performed to assess the risk factors associated with RA-advanced ILD

Variate	OR	95% CI	*p*-value
Age	1.061	1.020–1.104	0.003
BMI	1.248	1.125–1.383	< 0.001
RF	1.001	1.000-1.002	0.029
Osteoporosis	3.093	1.486–6.436	0.003
CA153	1.124	1.060–1.191	< 0.001
Variate	**OR**	**95% CI**	***p*-value**
Age	1.156	1.031–1.297	0.013
smoking history	23.087	2.587-206.024	0.005
CA153	1.583	1.247–2.010	< 0.001

Abbreviations: OR, odds ratio; CI, confidence interval

the RA-no ILD group. Especially, the levels of CA153 were significantly increased in the RA-ILD (RA-mild ILD + RA-advanced ILD) group compared with those in the RA-no ILD group (10.35 vs. 6.40, q < 0.001). Compared with the RA-no ILD group, increased levels of CA153 were observed both in the RA-advanced ILD group and in the RA-mild ILD group (20.30 vs. 6.40, q < 0.001; 8.00 vs. 6.40, q = 0.039, respectively). Moreover, the value of KL-6 in RA-advanced ILD patients was 1190.50 U/ml, significantly higher than the value of KL-6 in RA-no ILD patients (q < 0.001).

Multivariate analyses of risk factors of different severity of RA-ILD

To further identify the risk factors related to different severity of RA-ILD, multivariate logistic regression analyses through the Forward: LR method were performed. The Forward: LR method helped the selection of significant variables from the variables with q-value < 0.05 in univariate analysis to participate in modeling. We included these variables (Age, BMI, RF, Osteoporosis, Fragility fracture, CA153, CA199, CA50, CEA and CYFRA21-1) into the first multivariate logistic regression analysis. And the five variables, age, BMI, RF, osteoporosis and CA153 were selected by the Forward: LR method to participate in modeling. We found that age [odds ratio (OR) = 1.061, 95% confidence interval (CI) = (1.020–1.104), $p = 0.003$], BMI [OR = 1.248, 95% CI = (1.125–1.383), $p < 0.001$], the serum levels of RF [OR = 1.001, 95% CI = (1.000–1.002), $p = 0.029$], complicating with osteoporosis [OR = 3.093, 95% CI = (1.486–6.436), $p = 0.003$] and the serum levels of CA153 [OR = 1.124, 95% CI = (1.060–1.191), $p < 0.001$] were significantly associated with RA-ILD (RA-mild ILD + RA-advanced ILD) (Table 3A). We also conducted an assessment of the risk factors associated with RA-advanced ILD. We included these variables (Age, Sex, smoking history, RF, CA125,

CA153, CA199, CEA, CYFRA21-1 and NSE) into the second multivariate logistic regression analysis. And the three variables, age, smoking history and CA153 were selected by the Forward: LR method to participate in modeling. We found that age [OR = 1.156, 95% CI = (1.031–1.297), $p = 0.013$], smoking history [OR = 23.087, 95% CI = (2.587–206.024), $p = 0.005$] and the serum levels of CA153 [OR = 1.583, 95% CI = (1.247–2.010), $p < 0.001$] were independent predictors of RA-advanced ILD (Table 3B).

Predictive role of CA153

Next, we further compared the CA153 levels among different groups. The levels of CA153 were apparently increased in mild, advanced and mild + advanced RA-ILD compared with the RA-no ILD group (q = 0.039; q < 0.001; q < 0.001, respectively) (Fig. 2). Moreover, we made a breakdown of the CT pattern of RA-advanced ILD into usual interstitial pneumonia (UIP) and non-specific interstitial pneumonia (NSIP). We found that the levels of CA153 were elevated both in UIP and NSIP compared with RA-no ILD (q < 0.001; q < 0.001, respectively). However, there was no significant difference of CA153 level between UIP and NSIP (Fig. 3). We further estimated the extent of ILD in RA-advanced ILD patients and found a positive correlation between CA153 and ILD extent ($r = 0.525$, $p = 0.01$) (Fig. 4). Furthermore, we compared the levels of CA153 of RA-ILD and of other fibrotic diseases such as SSc-ILD and IPF with healthy control. The results showed that CA153 levels were elevated in RA-ILD, SSc-ILD and IPF compared with healthy control (q = 0.024; q < 0.001; q < 0.001, respectively) (Supplementary Table 4).

Additionally, a ROC curve was constructed to assess the ability of CA153 to predict RA-ILD (RA-mild ILD + RA-advanced ILD) (Fig. 5A). In Table 4, the best CA153 cutoff value was 9.00 (U/ml), yielding a sensitivity of 57.27% and a specificity of 72.03%, with the best area under ROC curve (AUC) of 0.66 (95% CI = (0.59–0.74), $p < 0.001$). Moreover, the ROC curve analysis using CA153 to predict RA-advanced ILD indicated an optimal cutoff CA153 of 11.45 (U/ml), AUC of 0.95 [95% CI = (0.91–0.98), $p < 0.001$], sensitivity of 95.65% and specificity of 83.05% (Fig. 5B; Table 4). Meanwhile, internal validation of ROC analyses was conducted through the method of bootstrapping (Supplementary Fig. 1). Notably, four indicators, age, BMI, RF and CA153 were identified as risk factors by logistic regression analysis and joint prediction combining the four risk factors to predict RA-ILD (RA-mild ILD + RA-advanced ILD) was conducted. The ROC curve for the combination of age, BMI, RF and CA153 to predict RA-ILD exhibited an AUC of 0.81. The ROC of age, CA153 and their combination were also

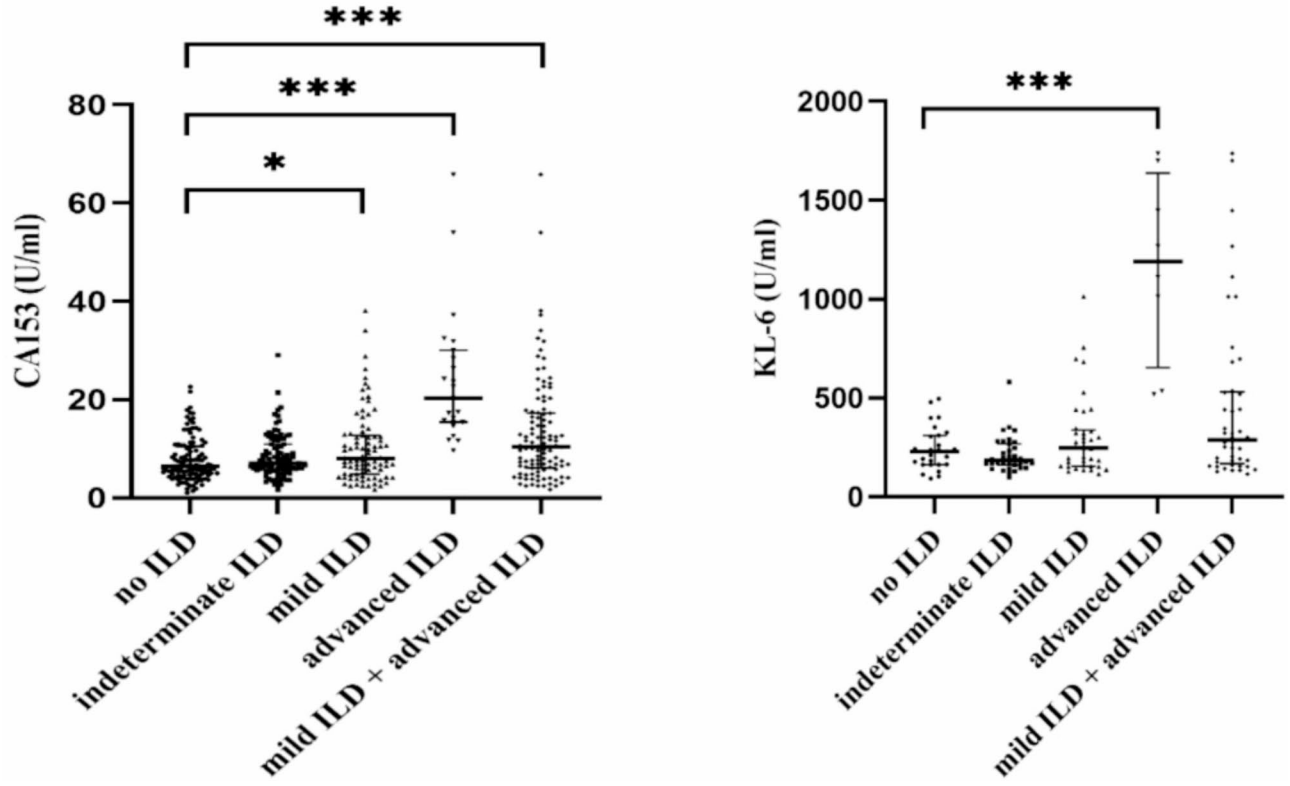

Fig. 2 Serum CA153 and KL-6 levels were measured in each RA group. Note: *q < 0.05, **q < 0.01, ***q < 0.001

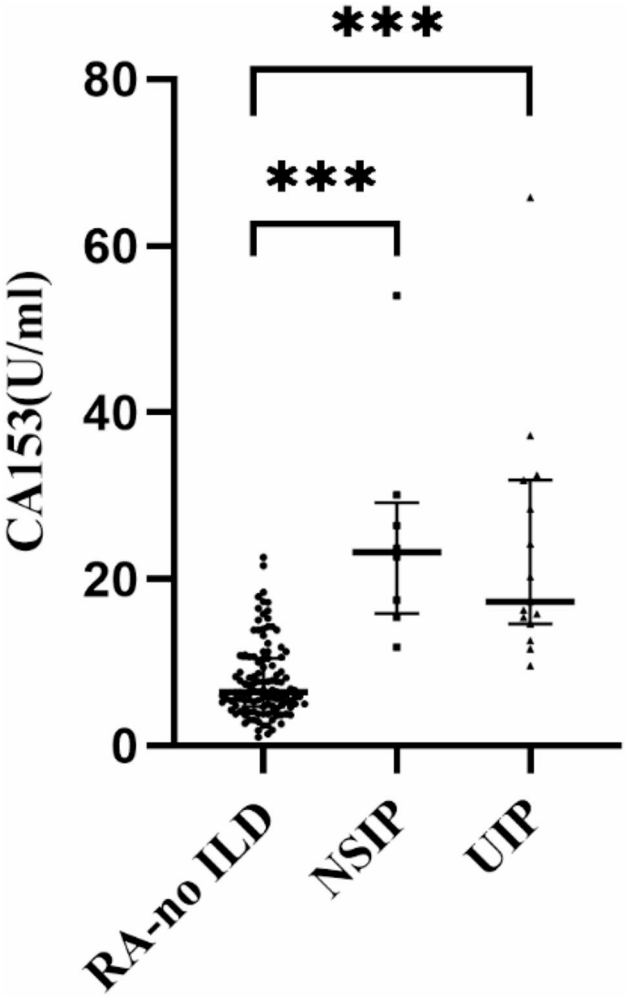

Fig. 3 Serum CA153 levels were measured in different CT pattern. Note: *q < 0.05, **q < 0.01, ***q < 0.001

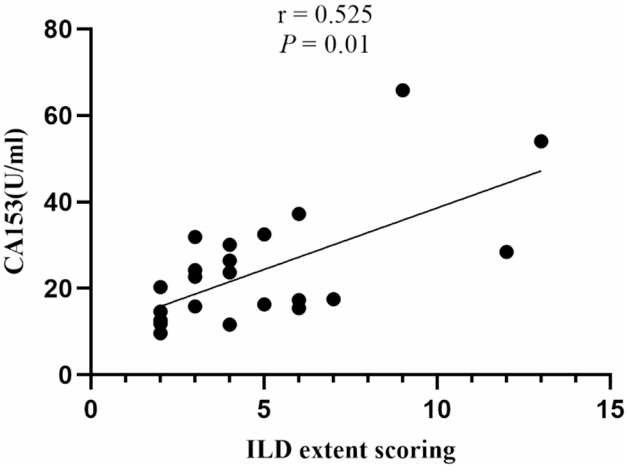

Fig. 4 Correlation of CA153 with ILD extent in patients with RA-advanced ILD

plotted to differentiate RA-advanced ILD from RA-no ILD, exhibiting an AUC of 0.97 (Supplementary Fig. 2).

We also analyzed the correlation between CA153 and other indexes by Spearman analysis and a positive pertinence was observed between CA153 and age ($r = 0.161$, $p = 0.004$) as well as RF ($r = 0.123$, $p = 0.027$) in Table 5. Conversely, CA153 was negatively correlated with forced vital capacity percent predicted (FVC% pred) and DLCO% pred ($r = -0.383$, $p = 0.037$; $r = -0.365$, $p = 0.052$, respectively), but the DLCO% pred showed no statistical significance.

To further investigate the association between CA153 and lung fibrosis markers in RA-ILD patients, we tested the concentration of KL-6 in the serum of 107 RA participants, which is an important indicative marker of ILD, and explored the relationship between CA153 and KL-6. The findings revealed a positive correlation between serum CA153 and KL-6 in RA-ILD patients ($r = 0.762$, $p < 0.001$) (Fig. 6).

Discussion

In this retrospective study, we aimed to assess the predictive value of CA153 in RA patients with ILD, as well as its relationship with KL-6. The results suggested that serum CA153 levels were notably elevated in RA-mild and RA-advanced ILD. CA153 was also an independent predictor of RA-advanced ILD. The ROC curve demonstrated that CA153 might serve as a potential biomarker for assessing ILD severity in RA patients. Further, the increased CA153 level in patients with RA-ILD was positively correlated with the KL-6 level.

Previous studies have shown that serum CA153 levels are increased in dermatomyositis-associated ILD and can assess the disease severity of dermatomyositis [32]. It is also reported that CA153 compared with other tumor markers has the best diagnostic value for primary Sjögren's syndrome-associated ILD [33]. Additionally, CA153 is significantly elevated in IPF patients but decreases after lung transplantation and has a significant correlation with survival [34]. Sofia et al. demonstrates that increased CA153 levels are inversely associated with FVC% pred and DLCO% pred in IPF [35]. In general, CA153 is not only a tumor-associated biomarker, but also associated with fibrotic ILDs such as hypersensitivity pneumonitis (HP), SSc-ILD and RA-ILD [11, 19, 36–40].

In our research, RA-advanced ILD patients were older in comparison to the general RA population with a greater proportion of males and an increase in tobacco exposure. No differences were found in RA associated clinical symptoms. Consistent with previous reports, high levels of RF were reported to be associated with increased risk of advanced ILD in patients of RA. Comorbidities commonly associated with RA-ILD included osteopenia and fragility fracture. Additionally,

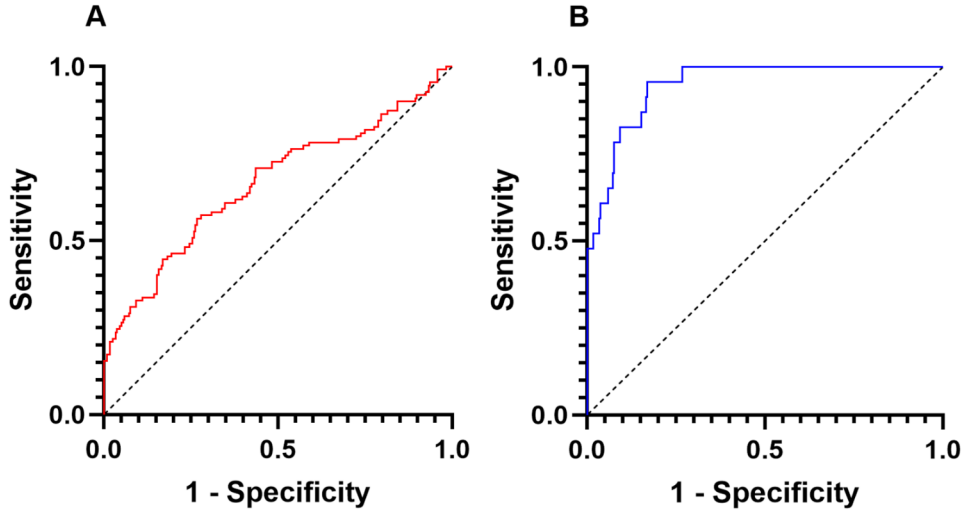

Fig. 5 Predictive capacity of CA153 in the presence of ILD in RA. (**A**) Predictive capacity of CA153 in the presence of ILD in RA (RA-mild ILD + RA-advanced ILD). (**B**) Predictive capacity of CA153 in the presence of advanced ILD in RA

Table 4 AUC, optimal cut-off value, sensitivity, specificity, Youden's index and p-value of CA153 for different severity of RA-ILD using a ROC curve

Variate	RA-no ILD vs. RA-ILD (RA-mild ILD + RA-advanced ILD)	RA-no ILD vs. RA-advanced ILD
CA153		
AUC (95% CI)	0.66(0.59–0.74)	0.95(0.91–0.98)
Cut-off value, U/ml	9.00	11.45
Sensitivity	57.27%	95.65%
Specificity	72.03%	83.05%
Youden's index	0.2930	0.7870
p-value	< 0.001	< 0.001

Table 5 Correlation of CA153 with other clinical indexes in patients with RA

	CA153	
Variate	r	p
Age	0.161	0.004
BMI	0.009	0.870
RF	0.123	0.027
Anti-CCP	0.004	0.942
FVC%pred	-0.383	0.037
DLCO%pred	-0.365	0.052
KL-6	0.762	< 0.001
Pulmonary arterial pressure	0.139	0.134

DLCO% predict value was inversely associated with RA-mild and RA-advanced ILD. Our results also further indicated the serum CA153 levels were elevated in RA-mild and RA-advanced ILD patients compared with RA patients. Logistic regression analysis revealed that higher levels of CA153 were independently related to a raised risk of advanced ILD in RA patients. It was suggested that the tumor marker CA153 was likely to have a significant role in predicting ILD for RA patients. In the

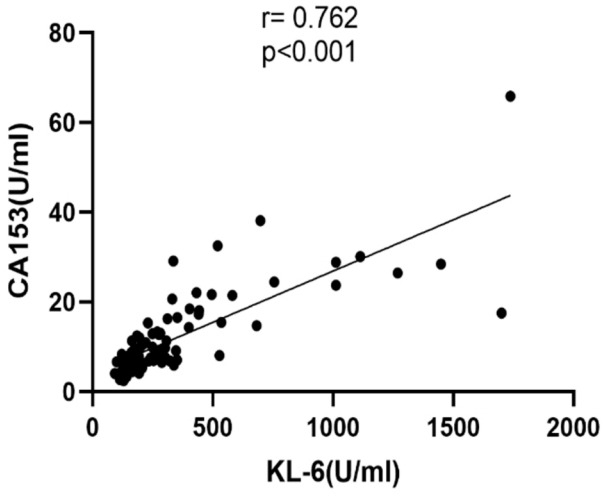

Fig. 6 Correlation of CA153 with KL-6 in patients with RA. *N*=107, 8 participants of RA-advanced ILD, 37 of RA-mild ILD, 35 of RA-indeterminate ILD and 27 of RA-no ILD

research, RA-ILD accounted for 32.21% of all RA patients who were measured with HRCT. Interestingly, we have found that the level of CA153 positively correlated with the severity of ILD as assessed by HRCT, which was not reported before. To determine the appropriate cut-off values for CA153, statistical analyses using Youden index values were conducted. The optimal cut-off value for CA153 in RA-mild ILD + RA-advanced ILD was identified as 9.00 U/ml. ROC analyses also demonstrated that serum CA153 levels exceeding 11.45 U/ml were able to accurately predict the presence of advanced ILD in RA patients, with a sensitivity of 95.65% and specificity of 83.05%. It can be seen the predictive value of serum CA153 in RA to identify patients with higher risk of ILD progression.

Although CA153 as an alternative marker for KL-6 in fibrotic lung diseases, few researches have investigated the association with characteristics in RA-ILD [20]. Moreover, of particular interest was the observation that CA153 exhibited a positive correlation with KL-6 in RA-ILD patients in our study. The possible reason could be that CA153 and KL-6 both belong to the mucin 1 (MUC1) family which is a transmembrane glycoprotein of the mucin family, covers the surface of all epithelial cells and overexpresses in various epithelial adenocarcinomas such as breast and lung cancer [15–17]. Other study found a positive correlation between the serum levels of KL-6 and CA153 in 20 female patients with interstitial pneumonia associated with collagen diseases, which include seven RA patients, and its correlation coefficient is 0.74 [19]. Gyokuto et al. also indicates the pertinence of KL-6 and CA153 in the general population with a correlation coefficient of 0.84 [41]. In accordance with these results, our study has showed the relationship between KL-6 and CA153 with a correlation coefficient of 0.762. Therefore, the level of serum CA153 has a positive correlation with that of serum KL-6 in RA-ILD patients.

Finally, the limitations of the present study need to be discussed. First, because of the retrospective observational design of the study, we were unable to follow up the dynamic change of the CA153 level and survival data. Second, not all participants were measured KL-6 and spirometry, which might cause bias and also limit the value of the study. Third, the number of RA-advanced ILD patients was small in our study, which might cause a lack of insight into the characteristics of RA-advanced ILD patients. Therefore, more studies have to be performed in order to establish the clinical utility, sensitivity and specificity of CA153 in RA-ILD, assist ILD severity assessment and predict disease prognosis.

Conclusions

In conclusion, our study identified that tumor marker CA153, positively correlated with KL-6, might assist early diagnosis and severity assessment of RA-ILD.

Abbreviations

CA	carbohydrate antigen
KL-6	Krebs von den Lungen-6
ILD	interstitial lung disease
RA	rheumatoid arthritis
HRCT	high-resolution computed tomography
OR	odds ratio
CI	confidence interval
ROC	receiver operating characteristic
AUC	area under the receiver operating characteristic curve
FVC% pred	forced vital capacity percent predicted
RA-ILD	rheumatoid arthritis-associated interstitial lung disease
CEA	carcinoembryonic antigen
MUC1	mucin 1
TLC	total lung capacity
DLCO% pred	diffusing capacity of the lung for carbon monoxide percent predicted
ACR	American College of Rheumatology
EULAR	European League against Rheumatism
RF	rheumatoid factor
anti-CCP	anti-cyclic citrullinated peptide
CYFRA21-1	cytokeratin 19 fragment
NSE	neuron-specific enolase
SCCA	squamous cell carcinoma antigen
proGRP	pro-gastrin-releasing peptide
ATS	American Thoracic Society
ERS	European Respiratory Society
BMI	body mass index
DAS	Disease Activity Score
UIP	usual interstitial pneumonia
NSIP	non-specific interstitial pneumonia
IPF	idiopathic pulmonary fibrosis
HP	hypersensitivity pneumonitis
SSc-ILD	systemic sclerosis-associated ILD
CRP	C-reactive protein
ESR	erythrocyte sedimentation rate

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03558-4.

Supplementary Material 1: **Table S1**. Hematological parameters of the study participants. **Table S2**. Coagulation markers of the study participants. **Table S3**. Immunological parameters of the study participants. **Table S4**. Serum CA153 levels were measured in different population. **Figure S1**. Internal validation of the ROC analysis. **Figure S2**. Joint prediction combining risk factors.

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Author contributions

Jiaxi Guo and Aiping Ma drafted the manuscript. Guangdong Wang and Fengbei Cen collected the associated clinical data. Heqing Huang and Shaowei Lin contributed to the data statistical analyses. Shenhui Huang prepared the figures and tables. Dehao Liu and Yikai Lin interpreted HRCT images and assisted ILD classification. Aiping Ma, Sien Shi and Xinhua Yu conceptualized the framework for this research. All authors read and approved the final manuscript.

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Data availability

The raw data supporting the conclusions of this article are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was reviewed and approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University. The participants provided their written informed consent to participate in this study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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