Risk prediction modelling in idiopathic inflammatory myositis-associated interstitial lung disease based on seven factors including serum KL-6 and lung ultrasound B-lines

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Abstract

Objective

To develop a user-friendly nomogram-based predictive model for interstitial lung disease (ILD) in patients with idiopathic inflammatory myositis (IIM).

Methods

A retrospective study was conducted at Shantou Central Hospital, encompassing 205 IIM patients diagnosed between January 2013 and December 2022. We used the LASSO regression method in the discovery set to select features for model construction, followed by efficacy verification through AUC of ROC. Afterwards, KL-6 values and LUS B-lines number were added into this model to evaluate whether these 2 factors added to the model efficiency. Finally, a web version was constructed to make it more available.

Results

Among the 205 IIM patients, 115 (56.1%) patients were diagnosed with ILD, and 90 (43.9%) did not. The predictive model, derived from the training set, comprised four independent risk factors, including age, presence of respiratory symptoms, anti-melanoma differentiation-associated gene 5 (MDA-5) antibody positivity, and anti–aminoacyl transfer RNA synthetase (anti-ARS) antibodies positivity. Notably, anti-TIF1-γ antibody positivity emerged as a protective factor. The AUC of the ROC based on these 5 factors was 0.876 in the training set and 0.861 in the validation set. The AUC of the ROC based on the 5 factors plus KL-6 was 0.922, 5 factors plus B-line number was 0.949 and 5 factors plus both KL-6 and B-line number was 0.951. Accordingly, a nomogram and a web version were developed.

Conclusion

This predictive model demonstrates robust capability to assess ILD risk in IIM patients, particularly when augmented with serum KL-6 level or/and LUS B-line number.

Key words

idiopathic inflammatory myositis, prediction model, interstitial lung disease, KL-6, lung ultrasound, B-lines

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Introduction

Idiopathic inflammatory myositis (IIM) is an autoimmune disease characterised by multiorgan involvement, including skin, skeletal muscles, joints and lungs (1). Interstitial lung disease (ILD), in particular, is a focus due to its high morbidity and mortality rate, especially in anti-synthetase syndrome (ASS) and dermatomyositis with anti-melanoma differentiation-associated gene 5 (MDA-5) antibody positivity (2-4). Despite prompt and aggressive intervention, IIM-ILD, notably rapidly progressive-ILD (RP-ILD), significantly diminishes the quality of life and survival rates of IIM patients. Thus, early detection of ILD in IIM patients could be invaluable for improving outcomes.

Risk factors have been suggested in previous studies of IIM-ILD, including demographic features, clinical symptoms, and biomarkers. Notably, skin ulceration and older age have been linked to a higher prevalence of ILD and RP-ILD (2, 3), as have high serum ferritin, low lymphocyte count, and elevated tumour markers such as CYFRA21-1 and CEA (2, 3, 5). Our previous study also pointed out that serum level of Kreb von den Lungen-6 (KL-6), in conjunction with lung ultrasound (LUS) B-lines, seemed to help predict the onset of IIM-ILD (6). Nevertheless, there has been a scarcity of research dedicated to developing predictive models that integrate these indicators, with some models falling short in efficacy due to small sample size or its inconvenience for clinical application (7, 8). The advent of myositis autoantibodies, categorised into myositis-specific autoantibodies (MSAs) and myositis-associated autoantibodies (MAAs), has introduced new prognostic markers that aid in the early diagnosis of ILD (9, 10). Patients with MDA-5 antibody, Ro-52 antibody and anti–aminoacyl transfer RNA synthetase (anti-ARS) antibodies are at an increased risk of developing ILD and RP-ILD (3, 7, 8, 10-12). However, recent studies showed that reliance on these antibodies alone is insufficient for predicting the development of ILD (13, 14).

In this study, our objectives were twofold: firstly, to evaluate whether the inclusion of KL-6 levels and the LUS B-lines number could enhance the predictive accuracy of our model for IIM-ILD, and secondly, to explore the feasibility of developing a straightforward, user-friendly, web-based nomogram designed to facilitate the prediction of IIM-ILD.

Methods

Patients

A total of 205 IIM patients diagnosed in Shantou Central Hospital, China, from January 2013 to December 2022, were enrolled in this study. This study was approved by the Shantou Central Hospital Ethics Committee (no. 2022-037). The classification of IIM was based on published diagnostic criteria for dermatomyositis (DM), polymyositis (PM), immune-mediated necrotising myopathy (IMNM), anti-synthetase syndrome (ASS), and inclusion body myositis (IBM) (15). The presence or absence of ILD was determined for all patients using high-resolution computed tomography (HRCT) as the gold standard (16). Eligible participants were IIM patients aged 18 years or older with complete medical records. We excluded patients who were pregnant, had incomplete medical records, a history of chronic obstructive pulmonary disease (COPD) or asthma, and those without a confirmed diagnosis of IIM.

Clinical and laboratory findings

The clinical and laboratory data were extracted from the patients' medical records, as previously reported (17), including baseline demographic information, clinical signs and symptoms, and laboratory data. Specifically, MSAs and MAAs were evaluated. The MSAs included a range of antibodies such as anti-MDA5, anti-transcription intermediary factor 1γ (TIF1γ), anti-nuclear matrix protein 2 (NXP2), anti-small ubiquitin-like modifier 1 (SAE1), anti-Mi2, anti-signal recognition particle (SRP), anti-3-hydroxy 3-methylutaryl coenzyme A reductase (HMGCR) antibodies, and anti-ARS antibodies which consist of anti-EJ, anti-OJ, anti-PL-7, anti-PL-12, anti-Jo-1, anti-KS, anti-Zo, and anti-HA antibodies. The MAAs comprised anti-Ro-52, anti-polymyositis-scleroderma 75 (PMSCL 75), anti-

Table I. Demographic data of IIM patients.

Parameter	value
n	205
Age (years, IQR)	56 (44, 63.5)
Male n (%)	62 (30.2)
Course (months)	2.0 (1.0, 12.1)
Diagnosis	
DM n (%)	106 (51.7)
CADM n (%)	30 (14.6)
PM n (%)	41 (20.0)
ASS n (%)	43 (21.0)
IBM n (%)	0
IMNM n (%)	15 (7.3)
Malignancy n (%)	38 (18.5)
ILD n (%)	115 (56.1)

Table II. IIM patients' characteristics and symptoms in ILD group and non-ILD group.

Parameter	ILD	non-ILD	value	*p*-value
n	115	90		
Age (years, IQR)	58.0 (49.0, 67.0)	53.5 (33.8, 61.0)	3.565	**<0.001**
Male n (%)	22 (19.1)	40 (44.4)	15.335	**<0.001**
DM n (%)	50 (43.5)	56 (62.2)	7.104	**0.008**
Course (months)	2.0 (1.0, 12.2)	2.5 (1.0, 12.1)	-0.267	0.798
Malignancy n (%)	11 (9.6)	27 (30.0)	13.962	**<0.001**
Respiratory symptom n (%)	71 (61.7)	15 (16.7)	42.118	**<0.001**
Rash n (%)	50 (43.5)	56 (62.2)	7.104	**0.008**
Pruritus n (%)	18 (15.7)	22 (24.4)	2.485	0.115
Raynaud's phenomenon n (%)	6 (5.2)	2 (2.2)	0.541	0.462
Alopecia n (%)	2 (1.7)	1 (1.1)	0.000	1.000
Fever n (%)	10 (8.7)	5 (5.6)	0.734	0.392
Hoarseness n (%)	3 (2.6)	2 (2.2)	0.000	1.000
Dry mouth and dry eye n (%)	13 (11.3)	4 (4.4)	3.124	0.077
Dysphagia n (%)	15 (13.0)	25 (27.8)	6.979	**0.008**
Arthralgia n (%)	79 (68.7)	78 (86.7)	9.093	**0.003**
Myalgia n (%)	42 (36.5)	51 (56.7)	8.267	**0.004**
Myasthenia n (%)	58 (50.4)	76 (84.4)	25.795	**<0.001**
Oedema n (%)	5 (4.3)	2 (2.2)	0.197	0.657
Holster sign n (%)	7 (6.1)	6 (6.7)	0.029	0.866
Gottron's sign n (%)	26 (22.6)	34 (37.8)	5.612	**0.018**
V sign n (%)	18 (15.7)	34 (37.8)	13.055	**<0.001**
Shawl sign n (%)	10 (8.7)	24 (26.7)	11.786	**0.001**
Mechanic's hand n (%)	18 (15.7)	6 (6.7)	3.944	**0.047**
Periungual erythema n (%)	2 (2.6)	2 (2.2)	0.000	1.000
Cutaneous ulcer n (%)	5 (4.3)	4 (4.4)	0.000	1.000

polymyositis-scleroderma 100 (PMSCL 100), anti-RNA polymerase III (RNA-P3), anti-Th/To, anti-KU and anti-cytoplasmic 5' nucleotidase 1A (Cn1a) antibodies. Serum levels of KL-6 in IIM patients were measured using chemiluminescent enzyme immunoassay method (LUMIPULSE G2100, Japan).

Lung ultrasound

Commercially available ultrasound equipment with a 2.5-3.5 MHz cardiac sector transducer was used in this study (Siemens Medical Solutions, Erlangen, Germany). Lung ultrasound (LUS) obtained ultrasound images in a total of 50 scanning sites in IIM patients, by two senior ultrasound physicians who were unaware of demographic and clinical features of patients. The intra-reader variability was 5.6%, and the inter-reader variability was 7.1%. The sum of B-lines number yielded a total score to evaluate ILD extent (18, 19). A B-line refers to a discrete laser-like vertical hyperechoic reverberation artefact arising from the pleural line, extending to the bottom of the screen without fading, and moving synchronously with respiration (20). LUS B-lines number correlates closely with IIM-ILD severity (18).

Statistical analysis

SPSS v. 22.0 (IBM Corporation, USA) and R v. 4.21 were used for data analysis. Continuous variables with normal distribution were expressed as the mean ± standard deviation, and Student's t-test was employed for comparison between groups. The median and interquartile range (IQR) were used for presenting continuous variables with non-normal distribution, and non-parametric tests were applied for comparisons. Categorical variables were expressed as numbers (N) and percentages (%), with the Chi-square test or Fisher's exact test used for comparison. The statistical significance was considered as $p<0.05$. In this study, patients were randomly distributed into one of two groups: the training set (70%) for model development and the validation set (30%) to evaluate model performance. The least absolute shrinkage and selection operator (LASSO) regression method was employed to identify and select key features for model construction from the training set. The risk factors for IIM-ILD were quantified using odds ratios (OR) and 95% confidence intervals (95% CI) derived from multivariate logistic regression analysis. The nomogram was developed based on the results of the multivariate logistic regression analysis. The area under the receiver operating characteristic (ROC) curve was utilised to evaluate and compare the predictive capacity of the models in the training and validation sets. To test whether the KL-6 values and LUS B-lines enhanced the predictive model, we separately or simultaneously added the KL-6 values and LUS B-lines number to assess whether adding these factors enhanced the model. We also used the area under curve (AUC) value of the ROC curve to verify the predictive value of various predictive models. Finally, we developed web-based versions of these four prediction models using shinyapps.io. The prediction probability of IIM-ILD can be calculated and displayed on the website after entering clinical characteristics.

Results

Population characteristics

A total of 205 IIM patients [143 female and 62 male, mean age 56 (44, 63.5) years] were included, among which 106 (51.7%) had DM, 41 patients (20%) had PM, 43 patients (21%) had ASS, and 15 patients (7.3%) had IMNM. The presence of ILD (the ILD group) was identified in 115 patients, representing 56.1% of the study population, as detailed in Table I. The predominant ILD patterns included non-specific interstitial pneumonia in 105 cases (91.3%), organising pneumonia in 19 cases (16.5%), an overlap of non-specific interstitial pneumonia and organising pneumonia in 16 cases (13.9%), and a usual interstitial pneumonia-like pat-

tern in 17 cases (14.7%). Median age between these two groups was different (Table II), with 58.0 (49.0, 67.0) in the ILD group *vs*. 53.5 (33.8, 61.0) in the non-ILD group ($p<0.001$). Female patients were more likely to have ILD than male patients ($p<0.001$).

Clinically, patients with the following characteristics predicted ILD: respiratory symptoms ($p<0.001$) and mechanic's hand rash ($p=0.047$). Conversely, patients without ILD were more prone to present the following features: DM ($p=0.008$), malignancy ($p<0.001$), rash ($p=0.008$), dysphagia ($p=0.008$), arthralgia ($p=0.004$), myalgia ($p=0.004$), myasthenia ($p<0.001$), Gottron's sign ($p=0.018$), V sign ($p<0.001$), and shawl sign ($p=0.001$). Notably, there were no statistically significant differences observed in the disease course from onset, pruritis, Raynaud's phenomenon, alopecia, fever, dry mouth and dry eye, holster sign, periungual erythema, and cutaneous ulcer (Table II).

Among the laboratory data (Table III), patients in the ILD group had lower level of the following (all $p<0.03$): albumin, ALT, AST, CK and LDH. By contrast, the ILD group had significantly higher (all $p<0.04$): ferritin, CRP, ESR, CEA and CA125.

Among all the myositis autoantibodies profiles (Table III), anti-MDA 5 (25.2% *vs*. 3.3%, $p<0.001$), anti-ARS (42.6% *vs*. 6.7%, $p<0.001$), and anti-Ro52 (54.8% *vs*. 26.7%, $p<0.001$) showed a higher positive rate in patients with ILD than those without ILD. TIF-1γ antibody was significantly negatively associated with ILD.

Table III. Comparison of laboratory data between ILD group and non-ILD group.

Parameter	ILD	non-ILD	value	*p*-value
n	115	90		
WBC 10^9/L	8.6 ± 4.4	8.5 ± 3.8	0.220	0.826
NEU 10^9/L	5.1 (3.5, 8.6)	5.5 (3.5, 7.6)	-0.090	0.928
LY 10^9/L	1.2 (0.9, 1.8)	1.3 (1.0, 2.0)	-1.326	0.185
ALB g/L	33.9 ± 6.0	37.3 ± 6.3	-3.999	<0.001
ALT U/L	42.0 (21.0, 94.0)	66.0 (29.7, 160.0)	-2.361	0.018
AST U/L	55 (31.0, 148.0)	95.0 (45.5, 213.8)	-2.662	0.008
Cr μmol/L	55.2 (45.0, 68.6)	52.6 (43.2, 68.9)	0.605	0.545
BUN mmol/L	4.3 (3.3, 5.7)	4.6 (3.7, 5.9)	-0.796	0.426
CK U/L	354.0 (84.0, 2235.0)	1238.5 (460.5, 5921.0)	-4.202	<0.001
Ferritin ng/mL	795.5 (396.8, 1375.0)	626.6 (339.3, 971.7)	2.475	0.013
LDH U/L	425.0 (316.0, 641.0)	579.0 (357.0, 843.3)	-2.511	0.012
CRP mg/L	9.7 (3.2, 28.3)	4.5 (2.4, 12.5)	2.097	0.036
ESR mm/H	30.0 (14.0, 49.0)	15.0 (7.0, 28.0)	4.516	<0.001
CEA ng/mL	2.3 (1.4, 5.3)	1.8 (1.1, 3.1)	2.141	0.032
AFP IU/mL	1.8 (1.3, 3.1)	2.1 (1.5, 3.3)	-1.599	0.110
CA125 U/mL	18.1 (9.9, 37.4)	11.4 (7.2, 21.7)	3.254	0.001
CA199 U/mL	11.4 (6.1, 26.0)	9.3 (6.0, 18.8)	1.259	0.208
C3 g/L	0.9 (0.8, 1.0)	0.9 (0.8, 1.0)	-0.773	0.439
C4 g/L	0.2 (0.02, 0.3)	0.2 (0.2, 0.3)	0.555	0.579
ANA n (%)	86 (74.8)	64 (71.1)	0.347	0.556
Cn1a n (%)	1 (0.9)	1 (1.1)	0.030	1.000
Fibrillarin n (%)	2 (1.7)	0	1.581	0.588
TIF1γ n (%)	1 (0.9)	18 (20.0)	21.972	<0.001
HMGCR n (%)	1 (0.9)	0	0.786	1.000
KU n (%)	2 (1.7)	0	0.294	0.588
MDA5 n (%)	29 (25.2)	3 (3.3)	18.355	<0.001
Mi-2 n (%)	0	6 (6.7)	5.726	0.017
NXP2 n (%)	4 (3.5)	5 (5.6)	0.142	0.706
PM-SCL100 n (%)	1 (0.9)	0	0.786	1.000
PM-SCL75 n (%)	2 (1.7)	1 (1.1)	0.000	1.000
Ro52 n (%)	63 (54.8)	24 (26.7)	16.338	<0.001
RNA-PIII n (%)	4 (3.5)	0	1.633	0.201
Th/To n (%)	1 (0.9)	2 (2.2)	0.046	0.830
SRP n (%)	10 (8.7)	6 (6.7)	0.289	0.591
SAE1 n (%)	1 (0.9)	1 (1.1)	0.030	0.862
SAE2 n (%)	0	2 (2.2)	3.318	0.069
ARS n (%)	49 (42.6)	6 (6.7)	33.224	<0.001
KL-6 U/mL	768 (434.3, 1420.3)	270 (184.3, 339.0)	6.443	<0.001
B-lines number	146 (52.5, 250.8)	22 (10.5, 57.5)	4.532	<0.001

Identification of risk factors for ILD in IIM patients

In our study, we employed LASSO regression to identify key features within the discovery cohort, which were instrumental in the development of our predictive model (Fig. 1). In the training set, 4 predictors were identified as independent risk factors to construct the predictive model, including age (OR=1.532; 95% CI [1.191, 1.971]; $p=0.001$), respiratory symptoms (OR=3.564; 95% CI [1.547, 8.211]; $p=0.003$), anti-MDA-5 antibody (OR=9.998; 95% CI [2.663, 37.535]; $p=0.001$), and anti-ARS antibodies (OR=6.387; 95% CI [2.273, 17.942]; $p=0.001$), while anti-TIF1-γ antibody (OR=0.062; 95% CI [0.007, 0.508]; $p=0.010$) was a protective factor (Table IV). Accordingly, a nomogram based on these 5 factors was built (Fig. 2). The AUC of ROC based on these 5 factors was 0.876 in the training set and 0.861 in the validation set (Fig. 3).

Performance of KL-6 and B-lines in ILD in combination with 5 other regression-based factors

IIM-ILD patients exhibited significantly elevated levels of KL-6 levels (768.0 [434.3, 1420.3] *vs*. 270 [184.3, 339.0] U/ml, $p<0.001$) (Table III) and B-lines number (146.0 [52.5, 250.8] *vs*. 22 [10.5, 57.5], $p<0.001$) (Table III) compared to those without ILD. Among the sixty-nine patients who had both KL-6 and B-lines, these parameters were integrated into the model alongside the initial five factors. The AUC of ROC was enhanced from 0.877 to 0.922 with the addition of KL-6, to 0.949 by adding LUS B-lines, and to 0.951 with the incorporation of both (Fig. 4). Finally, to broaden the accessibility and application of the predictive model, a web version was constructed incorporating the initial five factors plus KL-6 and B-lines, allowing users to log on the website to acquire the probability of ILD occurrence in IIM patients, by entering the per patient values (Fig. 5).

Discussion

IIM are a diverse and systemic group of autoimmune disorders, with ILD emerging as the most prevalent extra-muscu-

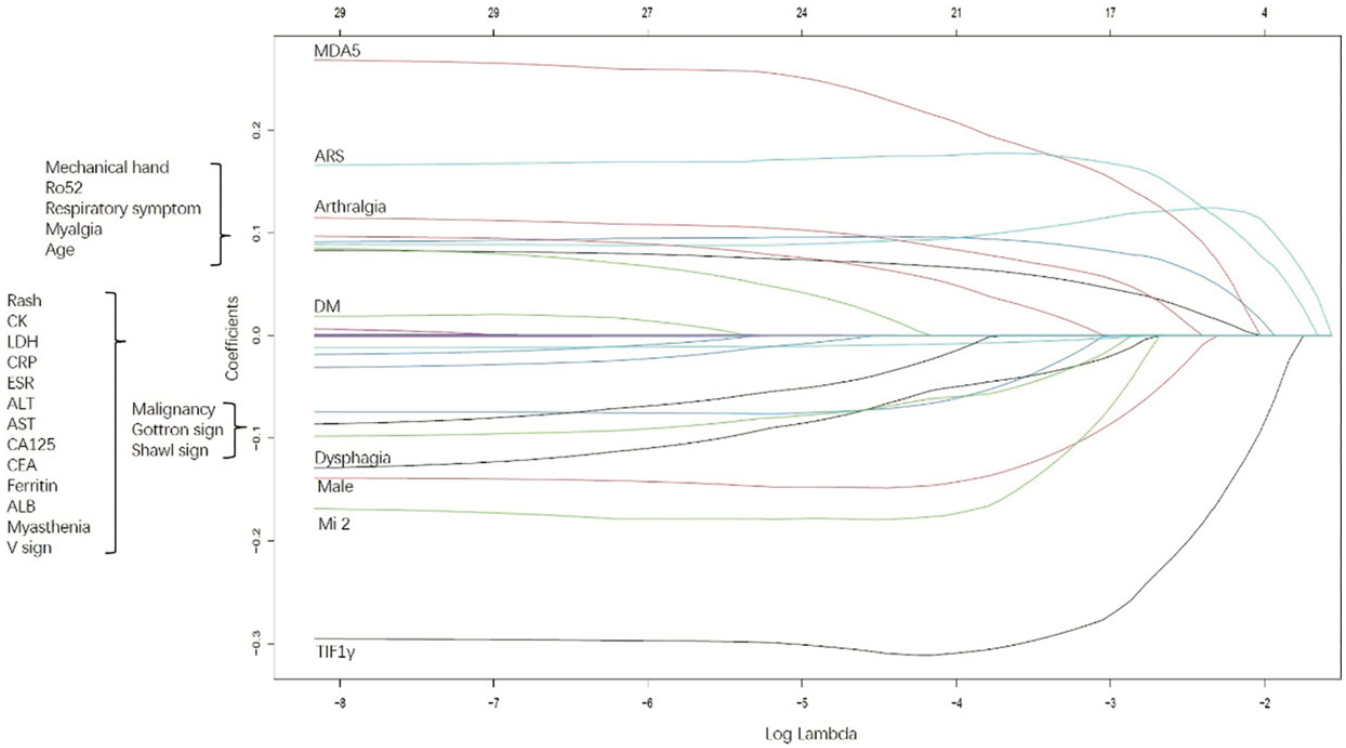

Fig. 1. LASSO coefficient profiles of the 29 valuables associated with IIM-ILD.

Table IV. Analysis of the influencing factors in a multivariate logistic regression analysis.

	B	S.E.	Wals	Sig.	OR	95% CI
Age (per 10 years)	.427	.128	11.039	0.001	1.532	1.191~1.971
Respiratory symptom	1.271	.426	8.906	0.003	3.564	1.547~8.211
TIF1γ	-2.788	1.077	6.700	0.010	0.062	0.007~0.508
MDA5	2.302	.675	11.637	0.001	9.998	2.663~37.535
ARS	1.854	.527	12.377	0.001	6.387	2.273~17.942

lar manifestation within this spectrum of illnesses. They have a high mortality rate and ILD poses a substantial risk to the quality of life and overall prognosis of IIM patients (21). Although the precise pathogenesis of ILD remains vague, studies have demonstrated that genetics (22), environment (23) and cytokines (24, 25) may play a role in the pathogenesis of IIM-ILD. The incidence of ILD in IIM patients differs across countries, with some studies reporting rates as high as 78% (1). In Chinese populations, the estimated incidence ranges from 21.9% to 74.8% (26). In our study, 56% of patients had ILD, which aligns with existing literature.

Previous studies (27, 28) focusing on the risk factors for ILD in IIM-patients have seldom offered predictive models that are readily applicable in clinical settings. In this study, 4 predictors were identified as independent risk factors, including age, respiratory symptoms, anti-MDA-5 antibody, and anti-ARS antibodies, while anti-TIF1-γ antibody was a protective factor. The nomogram prediction model and web version were established by incorporating the above-mentioned related factors in the form of a line chart, which was user friendly and accurate, as well as convenient.

The clinical manifestations of IIM-ILD patients were similar to those of other ILD patients, including cough, sputum, exertional dyspnea, haemoptysis(29). However, there still remained 29% ILD patients in our study who did not complain about respiratory symptoms. This finding underscores the importance of routine screening IIM patients for ILD, regardless of the absence of respiratory symptoms, particularly in those with other risk factors for ILD.

It is widely acknowledged that anti-MDA5 antibody serves as a specific MSA, due to its robust link to RP-ILD(30) and its role in forecasting poor patient prognosis(31). In our study, among all the MSAs, anti-MDA5 demonstrated the highest OR for ILD (OR=9.404). However, we observed three cases of anti-MDA5+ patients who did not exhibit ILD at the time of their IIM diagnosis. Importantly, these patients did not go on to develop ILD even after a two-year follow-up period, suggesting that not all MDA5+ individuals will inevitably progress to ILD within that timeframe. A study conducted by Allenbach *et al*. enrolled 121 patients with MDA5+ antibodies to identify subgroups with varying prognoses through unsupervised analysis. One subgroup experienced a universal incidence of ILD and a starkly high mortality rate, with 80% of patients succumbing within the first three months. Another subgroup, characterised by being male, with severe skin vasculopathy and frequent signs of myositis, had an 82.6% likelihood of developing ILD, but exhibited a relatively more favourable prognosis (0 death within 3 months). A third subgroup, presenting solely with

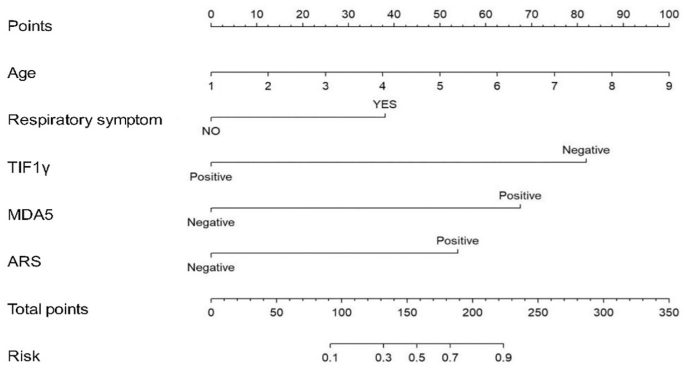

Fig. 2. The nomogram prediction model for IIM-ILD based on five factors. Determine the value of each factor based on the vertical line intersection between the variable and the point axis, and then add all variable points to calculate the total risk score, corresponding to the probability of IIM-ILD.

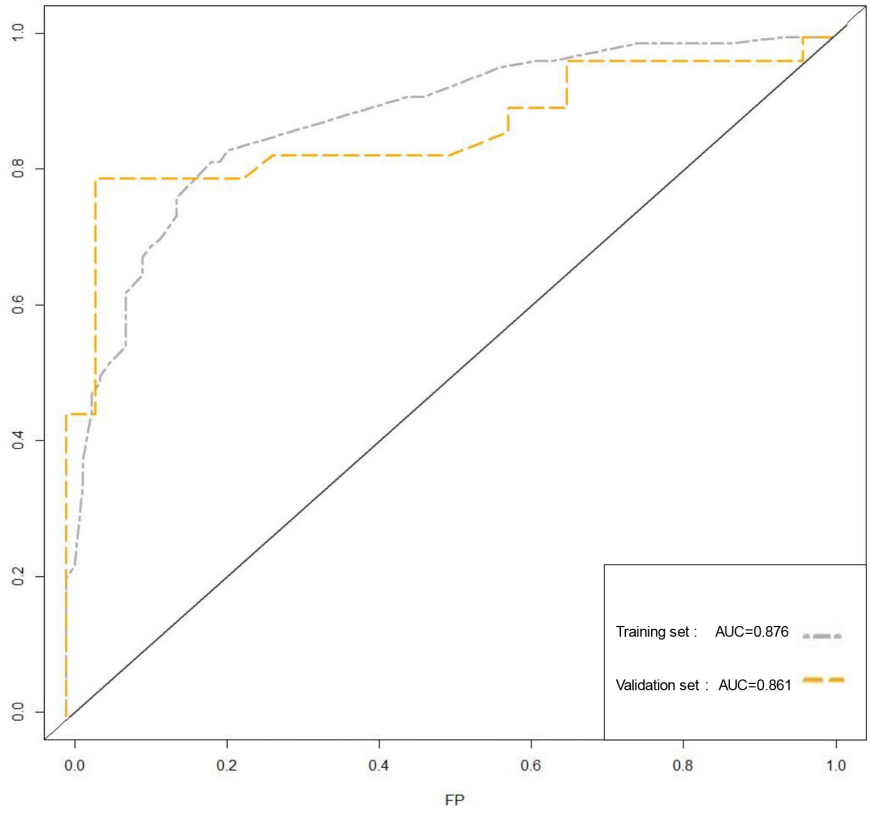

Fig. 3. ROC curve analysis of prediction model for IIM-ILD based on five factors in the training set and validation set.

pure dermato-rheumatologic symptoms (rash plus arthralgia), manifested only a 50% incidence of ILD and an intermediate prognosis (4.5% death within 3 months) (32). The algorithm showed 3 variables which distinguished the groups, including Raynaud's phenomenon, arthralgia/arthritis, and being male, the latter two factors are consistent with the findings in our study.

Furthermore, anti-ARS antibodies have been recognised for their strong correlation with the progression of chronic or acute disease and a propensity for frequent relapses among patients with IIM patients (33). ILD is a frequent complication in ASS-ILD patients with anti-Jo-1 (34). Our data corroborate this association, with 60.4% (26 out of 43) of ASS patients exhibiting anti-Jo-1 positivity. It is noteworthy that ILD can manifest as the initial clinical presentation, particularly in ASS patients with antibodies against anti-PL-7, anti-PL-12, and anti-EJ (35). This observation is mirrored in our study, where the initial presentation of ILD, rash, arthralgia and myositis presented in theses ASS patients was observed in 14 out of 15, 1 out of 15, 3 out of 15, and 2 out of 15 cases, respectively (36).

Anti-Ro-52 was well known as a myositis-associated antibody in IIM, with numerous studies highlighting a strong correlation between the presence of anti-Ro-52, particularly in the absence of anti-Ro-60, and the development of CTD-ILD (37). The coexistence of anti-Ro-52 with other antibodies, such as anti-ARS or anti-MDA5, has been suggested to exacerbate the likelihood of ILD occurrence and contribute to a poorer prognosis (38, 39). Consistently, we demonstrated anti-Ro52 is prevalent in the ILD group. However, anti-Ro52 presence did not reach statistical significance as a predictive factor, although it occurred more frequently in IIM-ILD. This discrepancy may be explained by the small sample size of patients in our study, which may have impacted the statistical power to detect a significant association.

Anti-TIF-1γ has emerged as a promising and significant predictive biomarker for the identification of IIM-associated malignancy, as evidenced by its role in our prior research (17). Notably, TIF-1γ was identified as a protective factor against ILD. This dual role of TIF-1γ might underscore the divergent clinical patterns observed in IIM patients, where ILD and malignancy represent contrasting and distinct outcomes.

A positive correlation was also found between serum tumour markers (*e.g.* CYFRA21-1 and NSE) and ILD (8). Our data also suggest higher levels of CEA and CA125 in IIM-ILD, although these two indicators were not factors in the predictive model. Nevertheless, a relationship between tumour markers and ILD remains to be explored.

KL-6 is a mucin-like, high molecular weight glycoprotein, expressed on type II alveolar epithelial cells and bronchiolar epithelial cells. Extensive studies have demonstrated the role of KL-6

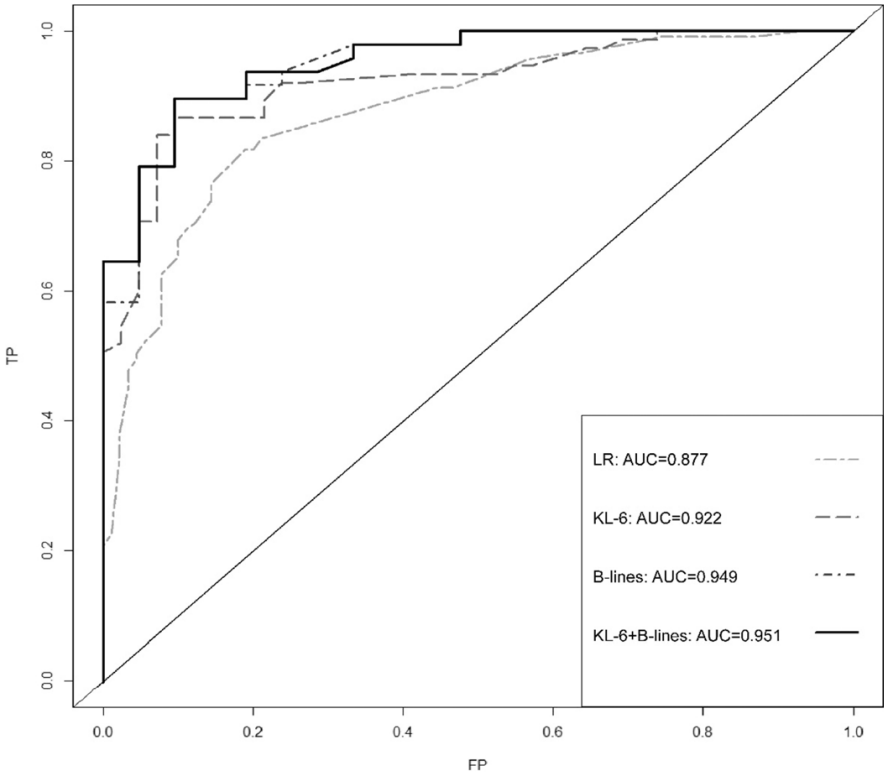

Fig. 4. ROC curve analysis of different prediction models for IIM-ILD.

Fig. 5. The web version of different prediction models for IIM-ILD.
https://huanguohai126.shinyapps.io/shiny_ild_iim/

as a biomarker of ILD occurrence and progression (18, 27, 40). Our previous work also verified that KL-6 correlated with HRCT score and pulmonary function tests in IIM-ILD patients (18). In the present study, we identified that IIM patients with ILD had significantly higher KL-6 level than those without ILD. It is noteworthy that when the KL-6 value was added into the model based on the aforementioned 5 factors, the AUC increased from 0.877 to 0.922, highlighting the usefulness of KL-6 in IIM-ILD prediction. Among our patients, eighteen patients had KL-6 values more than 1500 U/mL (ranging from 1569 to 10000), including three anti-MDA5 antibody positive patients, four patients with anti-ARS antibody positivity, one patient with anti-Ro52 antibody positivity, eight patients with anti-ARS plus anti-Ro52 antibodies positivity, and two patients without antimyositis antibody. The consistency and synchronisation of KL-6 high level and myositis specific antibody distribution further supports the major role of these variables in the model and their predictive ability for IIM-ILD. Furthermore, several other serum biomarkers were also verified to be significantly higher in IIM-ILD patients than in healthy controls, including MMP7, SPD, IL-18, and CCL18, highlighting their predictive values in IIM-ILD. Combination of these biomarkers to predict IIM-ILD warrants further research (41).

Robust data have shown the promising role of LUS in screening and diagnosing ILD in systemic sclerosis (42, 43), rheumatic arthritis (44) and IIM (18), showing B-lines' strong association with HRCT Warrick scores and pulmonary function test. The present study agrees with the previous study, showing that IIM-ILD patients had higher B-lines number than those without ILD. Additionally, our recently published case report underscores the effectiveness of LUS and the biomarker KL-6 in the successful management of a patient with anti-MDA5+ dermatomyositis-associated ILD (45). LUS offers significant advantages over HRCT, notably the elimination of radiation exposure, enhanced portability, and reduced cost, which may bolster patient compliance, particularly for high-risk individuals who do not present definitive ILD characteristics on early-stage CT scans. Furthermore, for those critical patients who cannot undergo CT scan, it is an invaluable assessment. The presence of a certain B-lines number on LUS is indicative of ILD, which means that B-lines seems to be more or less synonymous with CT findings in ILD. However, LUS couldn't replace HRCT and has its limitation for it only explores pleural and subpleural areas and does not provide detailed views of deeper deep lung zones and parenchymal structures. This restricts its ability to definitively differentiate ILD from other conditions such as pulmonary infection and oedema. For another, research on the application of LUS in IIM patients is still limited. Thus, it is not realistic to diagnose IIM-ILD merely depending on LUS. It is essential to combine it with clinical data and biomarker data. The development of the predictive model for IIM-ILD is a significant step forward. Furthermore, after entering different B-lines number in the model, the prediction probability of IIM-ILD can be calculated and displayed, increasing flexibility for ILD prediction. Additionally, the development of a user-friendly, web-based nomogram for predicting IIM-ILD is a noteworthy development, further streamlining the diagnostic process for clinicians and patients.

This study has some limitations. The inconsistencies above need to be resolved and highlight the necessity for further research to standardise protocols and achieve better consistency. It also points to the limitation of using a sin-

gle centre and using retrospective data which could lead to selection bias. Further, LUS is most sensitive and reliable in superficial areas such as the pleural and subpleural areas, not being as sensitive in the deep parenchyma. The KL-6 and B lines were only both measured in less than a third of the cohort (69 patients) because the patients who underwent this assessment were much more likely to have a specific suspicion for ILD, which is a significant limitation, and more cases are required. Finally, our data helps predict the presence but not the severity of the ILD.

The data are very encouraging, with the predictive model incorporating the 5 variables plus KL-6 level and LUS B-lines number and exhibiting rather good ability to assess ILD risk in IIM patients. Firstly, although HRCT is precise, it is not always applicable or feasible in all cases. For special groups, such as children and pregnant women, and for those difficult to undergo frequent or timely HRCT, this model can to some extent fill this gap and help doctors assess the risk. Secondly, the value of the model lies in its low-cost, convenience, radiation elimination and ability to consider multiple variables comprehensively, thereby guiding doctors to make more precise interventions and treatments. However, the existence of predictive models is not intended to completely replace HRCT but to provide an additional risk assessment tool in specific situations. HRCT remains gold standard for ILD diagnosis and could definitely provide the radiological message of ILD. Therefore, when deciding whether to use predictive models, doctors need to weigh based on the actual situation and the model's performance.

In conclusion, our data summarise the possible risk factors for IIM-ILD, encompassing age, respiratory symptoms, anti-MDA-5 antibody, and anti-ARS antibodies. Notably, the anti-TIF1-γ antibody emerged as a protective factor. A predictive model was also proposed to assess ILD risk, demonstrating robust predictive capabilities, especially when incorporating KL-6 and LUS B-lines. Nonetheless, further research is warranted to validate and refine this model for enhanced accuracy and applicability.

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