



Semiquantitative HRCT scoring: a reliable predictor of rapidly progressive interstitial lung disease in patients with anti-MDA5 positive dermatomyositis

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Background: Anti-melanoma differentiation-associated gene 5 positive dermatomyositis (anti-MDA5 DM) is strongly linked to rapidly progressive interstitial lung disease (RP-ILD), which is associated with high early mortality. This study aimed to explore the feasibility of using semiquantitative visual scoring methods on high-resolution computed tomography (HRCT) to assess RP-ILD in anti-MDA5 DM patients, and to develop a risk prediction model for RP-ILD, given the poor prognosis of RP-ILD in anti-MDA5 DM.

Methods: The data of patients with anti-MDA5 DM were retrospectively analyzed. Seven HRCT-based semiquantitative scoring methods were used to assess the extent of interstitial lung disease (ILD), and the correlation of each method with the pulmonary function tests (PFTs) was analyzed. The diagnostic performance of each method for RP-ILD was also evaluated. A nomogram model was developed to predict RP-ILD risk.

Results: In total, 67 patients with anti-MDA5 DM were included in the study. Methods 1, 2, 4, 5, and 6 significantly distinguished RP-ILD from non-RP-ILD ($P < 0.05$). Method 1 showed the highest correlation with the PFTs and the best diagnostic performance for RP-ILD [area under the curve (AUC) = 0.766, $P < 0.001$]. The least absolute shrinkage and selection operator logistic regression analysis identified male sex, an advanced age at onset, fever, a decreased normal extent in the left lower lung zone, an increased consolidation extent in the left middle lung zone, and elevated C-reactive protein as predictors of RP-ILD. These six predictors were used to construct a prediction model, which had an AUC of 0.842 based on internal validation, and showed good predictive ability and clinical applicability after the calibration and clinical decision curve analyses.

Conclusions: Semiquantitative visual scoring based on HRCT can effectively assess the severity of ILD in

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anti-MDA5 DM patients. A predictive model for RP-ILD that incorporates imaging and clinical information has potential for clinical application.

Keywords: Rapidly progressive interstitial lung disease (RP-ILD); dermatomyositis (DM); anti-melanoma differentiation-associated gene 5 (anti-MDA5); high-resolution computed tomography (HRCT)

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Introduction

Myositis-specific antibodies are intricately linked to the clinical manifestations, therapeutic strategies, and prognostic outcomes of dermatomyositis (DM) patients (1). Among these antibodies, the anti-melanoma differentiation-associated gene 5 (anti-MDA5) is particularly noteworthy, as it is strongly associated with the development of rapidly progressive interstitial lung disease (RP-ILD) (2). The prevalence of RP-ILD in anti-MDA5 DM is estimated to be between 39% and 100% in East Asia (1). Notably, the 6-month all-cause mortality of RP-ILD patients is remarkably high at 40–60% (3). Patients with anti-MDA5 DM are particularly vulnerable to RP-ILD within the initial six months of disease onset, with the highest risk occurring in the first three months, after which, the risk of adverse outcomes diminishes. Consequently, it is imperative to accurately assess the characteristics and severity of interstitial lung disease (ILD) in patients with anti-MDA5 DM, and to predict the likelihood of RP-ILD development early enabling timely interventions to improve prognosis.

High-resolution computed tomography (HRCT) is a cornerstone in the diagnosis of ILD. Various semiquantitative visual scoring methods have been established to assess ILD severity and predict RP-ILD, particularly in idiopathic pulmonary fibrosis (IPF) patients (4–10). However, a standardized approach for determining severity and predicting RP-ILD in anti-MDA5 DM patients has yet to be established. It has been suggested that semiquantitative visual scoring methods employed for IPF could be adapted for anti-MDA5 DM patients (11,12). However, the clinical applicability of these methods has yet to be validated. Although predictive models have been developed to distinguish between anti-MDA5 DM-RP-ILD and anti-MDA5 DM-non-RP-ILD (12–14), there is a lack of imaging-based evaluations. This study aimed to investigate the feasibility of using various previously

established semiquantitative visual scoring methods based on HRCT to assess the severity of ILD in anti-MDA5 DM patients, predict the occurrence of RP-ILD, and identify the most suitable method for detecting ILD in patients with anti-MDA5 DM. Further, it aimed to integrate multiple factors, including imaging and clinical characteristics, to quantitatively predict the risk of RP-ILD using a nomogram prediction model. We present this article in accordance with the STROBE reporting checklist (available at <https://qims.amegroups.com/article/view/10.21037/qims-2025-1427/rc>).

Methods

Study subjects

The data of 67 patients with anti-MDA5 DM diagnosed at the Department of Rheumatology and Department of Respiratory Medicine of Tianjin Medical University General Hospital from June 2017 to March 2023 were retrospectively collected. Patients were included in the study if they met the following inclusion criteria: (I) had been diagnosed with all anti-MDA5 DM according to the 1975 Bohan/Peter or 2017 European Rheumatism/American College of Rheumatology classification criteria (15,16) and tested positive for MDA5 antibodies using a line blotting test kit (Euroimmun, Germany) (17); (II) had been diagnosed with ILD based on the 2013 American Thoracic Society/European Respiratory Society (ATS/ERS) criteria (18); and (III) had undergone chest HRCT. Patients were excluded from the study if they met any of the following exclusion criteria: (I) had other autoimmune diseases; (II) had poor-quality chest HRCT images that did not meet the diagnostic requirements; and/or (III) had lung diseases attributable to other known etiologies, such as environmental and occupational factors, medications, infections, tumors, and cardiac dysfunction. The diagnostic criteria for RP-ILD were the progressive worsening of

dyspnea over three months from the onset of pulmonary symptoms, accompanied by hypoxemia and radiologic evidence of ILD exacerbation (19). Hypoxemia was defined as a partial pressure of arterial oxygen (PaO_2) below 80 mmHg at rest. The radiologic exacerbation of ILD was strictly defined as the appearance of new, bilateral ground-glass opacities (GGOs), and/or consolidation on HRCT. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by the Ethics Committee of Tianjin Medical University General Hospital (No. IRB2021-YX-002-01), and informed consent was obtained from all the patients.

The demographic data of the enrolled patients, including sex, age of onset, smoking history, and time from onset of symptoms to diagnosis, were collected. Disease onset was defined as the point at which a patient first experienced any symptom later attributed to the disease. Clinical symptoms included cutaneous symptoms (e.g., periungual erythema and Raynaud's phenomenon), musculoskeletal symptoms (e.g., myalgia and arthritis), and constitutional symptoms (e.g., fever). Due to the myasthenia caused by DM, some patients were unable to undergo pulmonary function tests (PFTs). Those who were able to complete the PFTs had the following indices assessed: forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the ratio of the forced expiratory volume in one second to the forced vital capacity (FEV1/FVC), vital capacity (VC), and carbon monoxide diffusing capacity (DLCO).

HRCT examination

The HRCT scans were conducted using a Discovery CT 750 HD and Revolution Evo scanner (GE Healthcare, Milwaukee, WI, USA). The imaging acquisition spanned from the lung apex to the lung base, with patients instructed to hold their breath at the end of a full inspiration. The scanning parameters were set as follows: pitch: 1.375, tube voltage: 120 kV, tube current: 50–420 mA, slice thickness and interval: both 5.0 mm. For image reconstruction, a slice thickness and interval of 1.25 mm were used, and a high-resolution algorithm was employed for the lung window (window level: –700 HU and window width: 1,500 HU), and a soft-tissue reconstruction algorithm was employed for the mediastinal window (window level: 40 HU and window width: 400 HU). The time-window interval between all HRCT scans and PFTs was within the first week following diagnosis.

HRCT image analysis

Semiquantitative visual scoring of ILD

A comprehensive literature search was conducted using PubMed to retrieve articles published up to May 1, 2024 on semiquantitative visual scoring methods based on HRCT for ILD. The following search terms were used: “interstitial lung disease”, “semiquantitative scoring”, and “visual assessment”. Our systematic search yielded seven distinct semiquantitative visual assessment methods for ILD. Details of these methods were meticulously collected and are summarized in Table S1. The HRCT imaging features evaluated in these methods were assessed according to the Fleischner Society standard of chest imaging terminology (20).

After a 4-week interval, a subset of images from 12 patients (18% of the total cohort) were randomly selected and reviewed by the original observer to assess intra-observer reliability and by a different observer to assess inter-observer reliability. The radiological physicians who analyzed and processed the images were blinded to all patients' clinical information, including the final diagnosis of RP-ILD.

Type of ILD

The ATS/ERS diagnostic criteria for ILD were applied to evaluate the most appropriate ILD types (18), including (I) usual interstitial pneumonia (UIP), which is characterized by bilateral subpleural honeycombing with lower lobe predominance, with or without reticulations or traction bronchiectasis; (II) non-specific interstitial pneumonia (NSIP), which is characterized by patchy or diffuse GGO with basal distribution predominance, with or without reticulations or traction bronchiectasis, with or without honeycombing; (III) organizing pneumonia (OP), which is characterized by peribronchial or subpleural consolidation, with or without reticulations or traction bronchiectasis; and (IV) NSIP/OP, which is characterized by consolidations superimposed on a background of GGO, with or without reticulations or traction bronchiectasis.

Statistical analysis

The statistical analyses were performed using SPSS 27.0 statistical software (IBM), Prism 8.0 software (GraphPad), and R 4.1.2 software. The categorical variables are described as the number (percentage), and the continuous variables are reported as the mean $\pm$ standard deviation, or

the median (25th percentile, 75th percentile). To compare differences between groups, the Student's *t*-test, Mann-Whitney *U* test, Fisher's exact test, or chi-square test was used as appropriate. Spearman's correlation was used to detect the quantitative indexes of the semiquantitative scoring methods, and the indexes of the PFTs. The performance of the semiquantitative scoring methods in detecting RP-ILD patients was analyzed using the receiver operating characteristic (ROC) curve. The area under the curve (AUC), sensitivity, and specificity were calculated to evaluate the diagnostic performance of each scoring method. The Youden index was calculated to determine the optimal diagnostic threshold. Intra- and inter-observer agreement for visual scoring were evaluated by the intraclass correlation coefficient (ICC), with values between 0.8 and 1.0 indicating excellent agreement. The variables that were statistically significant in the univariate analysis ($P < 0.05$) were subsequently included in the least absolute shrinkage and selection operator (LASSO) logistic regression analysis to develop a robust prediction model for RP-ILD. The model was visualized and analyzed by nomogram. Finally, the performance of the predictive model was evaluated by ROC, calibration, and decision curve analyses. We performed an internal bootstrap validation with 1,000 repetitions to assess the model's generalizability and correct for overfitting optimism (Appendix 1). A *P* value < 0.05 was considered statistically significant.

Results

Basic characteristics

A total of 67 patients with anti-MDA5 DM were untimely enrolled in the study, of whom, 42 were female and 25 were male, resulting in a male-to-female ratio of 1:1.68. The median age of the patients was 54 ± 13 years. The mean time interval from disease onset to diagnosis was 2.0 (1.0–4.0) months. All the patients presented with ILD. Based on the presence or absence of RP-ILD, the patients were divided into the RP-ILD group (comprising 35 patients) and the non-RP-ILD group (comprising 32 patients). There was a statistically significant difference in disease duration between these two groups ($P < 0.05$). Clinically, the patients in the RP-ILD group were more prone to fever ($P < 0.01$); however, no significant differences were observed between the two groups in terms of smoking, muscle pain, arthritis, periungual lesions, and Raynaud's phenomenon (all $P > 0.05$).

Of the 67 patients with anti-MDA5 DM, 48 were able to complete the PFTs; however, the remaining 19 patients, 16 of whom were in the RP-ILD group, were unable to complete the PFTs due to their poor physical condition. Among those who completed the PFTs, 29 patients were in the non-RP-ILD group and 19 patients were in the RP-ILD group. The RP-ILD group had lower levels of FEV1, FVC, VC, and DLCO than the non-RP-ILD group ($P < 0.05$), but no statistically significant difference was found in the FEV1/FVC between the two groups (Table 1).

Comparison of ILD types

In terms of the ILD types, the anti-MDA5 DM patients presented with NSIP (49%), NSIP-OP (28%), OP (20%), and UIP (3%). Most non-RP-ILD patients presented with NSIP (66%), while the RP-ILD patients mainly presented with NSIP-OP (46%) ($P < 0.05$) (see Figures S1–S4).

Diagnostic performance of semiquantitative visual scoring methods for RP-ILD

Methods 1, 2, 4, 5, and 6 were found to be effective ($P < 0.05$) in distinguishing RP-ILD from non-RP-ILD, while Methods 3 and 7 were not found to be effective ($P > 0.05$) (Figure 1). The ROC curve analysis (Figure 2 and Table S2) showed that Method 1 performed best in detecting RP-ILD (AUC = 0.766, Youden index = 0.519, cut-off value = 120, sensitivity = 80%, specificity = 71.9%).

Intra- and inter-observer reproducibility of the ILD semiquantitative visual scoring methods

The intra- and inter-observer agreement of the seven ILD semiquantitative visual scoring methods was excellent, with ICC values of 0.988, 0.891, 0.975, 0.964, 0.982, 0.947, and 0.978, and 0.986, 0.889, 0.936, 0.963, 0.974, 0.904, and 0.908, respectively.

Correlation between HRCT semiquantitative visual scoring methods and PFTs

Methods 1 and 2 had a moderate negative correlation with DLCO ($r = -0.44$, $P < 0.01$; $r = -0.29$, $P < 0.05$), a moderate negative correlation with FVC ($r = -0.42$, $P < 0.01$; $r = -0.33$, $P < 0.05$), and a moderate negative correlation with VC ($r = -0.40$, $P < 0.01$; $r = -0.32$, $P < 0.05$). Method 1 was

Table 1 Basic characteristics and laboratory parameters of RP-ILD and non-RP-ILD patients

Variables	Total patients	Non RP-ILD	RP-ILD	$Z/t/\chi^2$	P value
Demographics					
Patients	67	32	35	67	0.443
Female	42 [63]	24 [75]	18 [51]	3.97	0.046*
Age, years	54±13	47±11	60±11	−4.53	<0.001***
Time interval between onset to diagnosis (months)	2.0 [1.0, 4.0]	3.0 [2.0, 4.8]	2.0 [1.0, 3.0]	−2.16	0.031*
MDA5 antibody level				2.81	0.245
+	2 [3]	2 [6]	0 [0]		
++	25 [37]	13 [41]	12 [34]		
+++	40 [60]	17 [53]	23 [66]		
Ro52 antibody level				3.515	0.319
−	26 [39]	15 [47]	11 [31]		
+	6 [9]	4 [13]	2 [6]		
++	10 [15]	4 [13]	6 [17]		
+++	25 [37]	9 [28]	16 [46]		
Clinical features					
Smoker	15 [22]	4 [13]	11 [31]	3.45	0.063
Fever	39 [58]	12 [38]	27 [77]	10.80	<0.001***
Myosalgia	33 [49]	17 [53]	16 [46]	0.37	0.544
Periungual erythema	11 [34]	7 [20]	18 [27]	1.76	0.185
Arthritis	39 [58]	21 [66]	18 [51]	1.34	0.239
Raynaud's phenomenon	3 [4]	3 [9]	0 [0]	3.44	0.064
LDH (U/L)	395 [263, 464]	365 [247, 415]	372 [275, 497]	−1.44	0.151
CRP (mg/dL)	1.3 [0.2, 1.5]	0.3 [0.2, 0.5]	1.3 [0.5, 3.1]	−4.73	<0.001***
KL-6 (u/mL)	1,146 [488, 1,314]	791 [340, 1,237]	828 [651, 1,337]	−1.17	0.243
Lym (10 ⁹ /L)	0.9 [0.5, 0.9]	0.7 [0.5, 1.1]	0.6 [0.5, 0.9]	−1.17	0.240
CK (U/L)	646 [51, 258]	97 [50, 265]	87 [49, 234]	−0.21	0.837
CK-MB (U/L)	34 [14, 27]	16 [13, 26]	19 [14, 34]	−0.84	0.400
Ferritin (ng/mL)	1,655 [376, 2,426]	716 [190, 1,535]	1,636 [704, 3,143]	−2.70	0.007**
PFT	48	29	19		
FEV1 (%)	77 [67, 88]	79 [73, 91]	69 [59, 77]	−2.57	0.010*
FEV1/FVC (%)	80 [78, 91]	82 [79, 89]	82.9 [75, 93]	−0.20	0.841
FVC (%)	80 [67, 80]	85 [73, 97]	69 [59, 82]	−2.74	0.006**
VC (%)	76 [67, 89]	82 [71, 94]	67 [61, 79]	−2.83	0.005**
DLCO (%)	53 [46, 63]	55 [49, 65]	48 [45, 55]	−2.01	0.040*

Data are presented as number, number [percentage], mean ± standard deviation, or median [25th percentile, 75th percentile]. *, P<0.05; **, P<0.01; ***, P<0.001. CK, creatine kinase; CK-MB, creatine kinase-MB; CRP, C-reactive protein; DLCO, carbon monoxide diffusing capacity; FEV1, forced expiratory volume in one second; FEV1/FVC, ratio of the forced expiratory volume in one second to the forced vital capacity; FVC, forced vital capacity; KL-6, krebs von den lungen-6; LDH, lactate dehydrogenase; PFT, pulmonary function test; RP-ILD, rapidly progressive interstitial lung disease; VC, vital capacity.

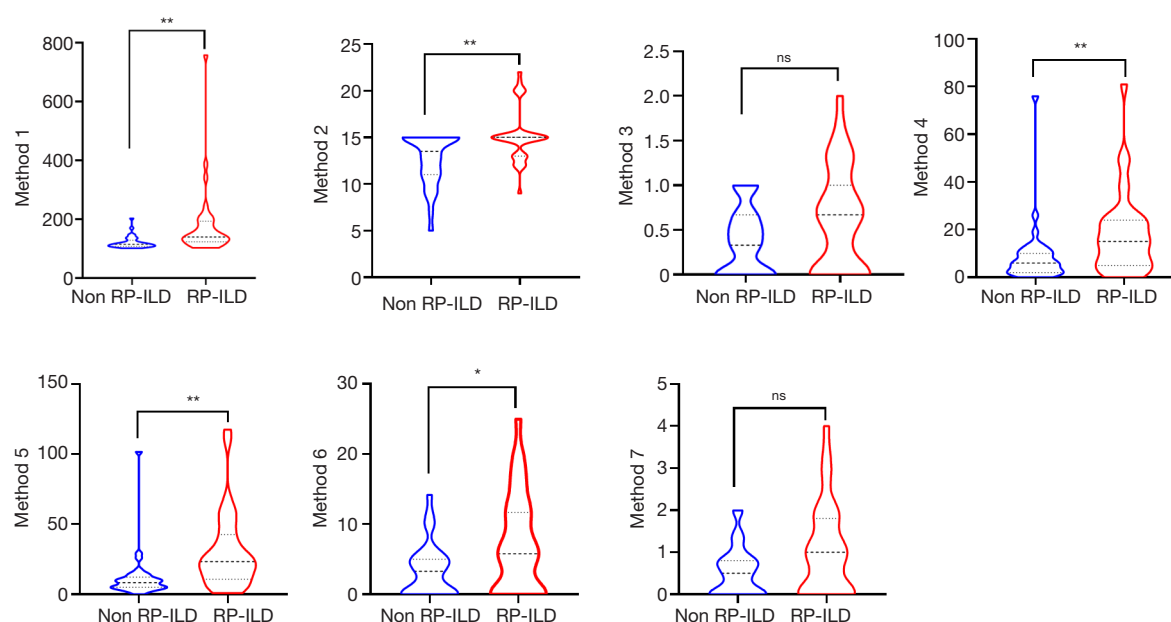


Figure 1 Differences in the seven semiquantitative visual scoring methods for RP-ILD. Details of seven methods are summarized in [Table S1](#). ns, no significance; *, $P < 0.05$; **, $P < 0.01$. RP-ILD, rapidly progressive interstitial lung disease.

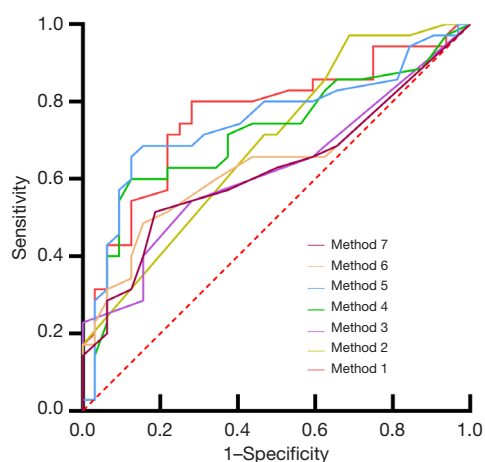


Figure 2 ROC curves for the diagnosis of RP-ILD by semiquantitative scores based on HRCT. Details of seven methods are summarized in [Table S1](#). HRCT, high-resolution computed tomography; ROC, receiver operating characteristic; RP-ILD, rapidly progressive interstitial lung disease.

moderately negatively correlated with FEV1 ($r = -0.36$, $P < 0.05$), and Method 2 was not significantly associated with FEV1 ($r = -0.27$, $P > 0.05$). Methods 3 to 7 were not correlated with any of the PFT parameters ([Table 2](#)).

Establishment of the RP-ILD prediction model

Following the univariate analysis, a total of 30 indicators that exhibited statistically significant differences, including ILD type, demographic variables, clinical features, and HRCT scores from Method 1 (all with P values < 0.05 ; [Table S3](#)) were selected for inclusion in the LASSO logistic regression analysis for further selection for establishing the RP-ILD prediction model ([Figure S5](#)). The categorical variables were assigned values as follows: sex (0: male; 1: female), fever (0: present; 1: absent), and ILD type (1: NSIP; 2: OP; 3: NSIP + OP; 4: UIP). All the continuous variables were introduced into the model using their original values. The variables that were finally included in the model were gender, age, the normal range in the left lower lung area, the consolidation range in the left middle lung area, fever, and C-reactive protein (CRP). A nomogram model was then constructed to predict the risk of patients with anti-MDA5 DM developing RP-ILD ([Table 3](#) and [Figure 3A](#)). This model demonstrated strong discrimination and accuracy for anti-MDA5 DM RP-ILD in the development cohort, with an AUC of 0.920 (0.859, 0.980) and a cut-off value of 0.585 ([Figure 3B](#)). The bootstrap internal validation yielded a mean AUC of 0.842 on the test set. The calibration curve ([Figure 3C](#)) and decision curve ([Figure 3D](#)) showed the good

Table 2 Correlation between the seven semiquantitative scoring methods for ILD and the PFT parameters

Title	FEV1	FEV1/FVC	FVC	VC	DLCO
Method 1	−0.36*	0.03	−0.42**	−0.40**	−0.44**
Method 2	−0.27	0.18	−0.33*	−0.32*	−0.29*
Method 3	−0.16	0.17	−0.23	−0.20	−0.20
Method 4	−0.12	0.08	−0.15	−0.11	−0.16
Method 5	−0.22	0.09	−0.30	−0.21	−0.26
Method 6	−0.13	0.24	−0.25	−0.15	−0.13
Method 7	−0.18	0.16	−0.26	−0.21	−0.23

Details of seven methods are summarized in [Table S1](#). *, P<0.05; **, P<0.01. DLCO, carbon monoxide diffusing capacity; FEV1, forced expiratory volume in one second; FEV1/FVC, ratio of the forced expiratory volume in one second to the forced vital capacity; FVC, forced vital capacity; ILD, interstitial lung disease; PFT, pulmonary function test.

Table 3 Multivariable logistic regression analysis performed after LASSO variable selection

Variable	β	Standard error	Odds ratio (95% CI)	P value
Gender	−0.11	1.24	0.89 (0.02–1.00)	0.040*
Age of onset	0.04	0.05	1.04 (1.00–1.20)	0.014*
Nor LLZ	−0.01	0.05	0.99 (0.95–1.00)	0.009**
Con LMZ	0.03	0.07	1.02 (1.00–1.24)	0.002**
Fever	0.40	1.11	1.45 (1.00–43.15)	0.037*
CRP	0.27	1.28	1.31 (1.00–70.78)	0.001**

*, P<0.05; **, P<0.01. Con LMZ: consolidation range in the left middle lung zone; Nor LLZ: normal range in the left lower lung zone. CI, confidence interval; CRP, C-reactive protein; LASSO, least absolute shrinkage and selection operator.

clinical applicability of the nomogram, indicating that the use of this predictive model resulted in excellent net clinical benefits ([Figure S6](#)).

Discussion

The present study showed that semiquantitative visual scoring based on HRCT was an effective method for assessing the initial severity of ILD in patients with anti-MDA5 DM. Four methods (Methods 1, 2, 4, and 5) were able to detect RP-ILD, of which, Method 1 exhibited the best diagnostic performance. Notably, Method 1 showed a significant negative correlation with the PFTs (FEV1, FVC, VC, and DLCO), which suggests that Method 1 reflects the clinical presentation and prognosis of anti-MDA5 DM patients. By focusing on each potential imaging sign in a specific lung zone and integrating it with other critical clinical and laboratory data, the nomogram prediction

model revealed that the severity of RP-ILD in anti-MDA5 DM patients was associated with multiple initial indicators, including male sex, an older age at onset, fever, a decrease in the normal area in the left lower lung zone, an increase in the extent of consolidation in the left middle lung zone, and an elevated CRP level.

Performance of semiquantitative visual scoring methods based on HRCT for the assessment of disease severity

Semiquantitative HRCT scoring systems represent the most widely used method for assessing the severity of ILD. In IPF, these scoring systems have been shown to be robust independent predictors of DLCO and mortality. However, to date, no specific HRCT scoring method for evaluating ILD in patients with anti-MDA5 DM has been established. We found that the HRCT patterns of ILD in anti-MDA5 DM patients were the same as those observed in IPF (14,21),

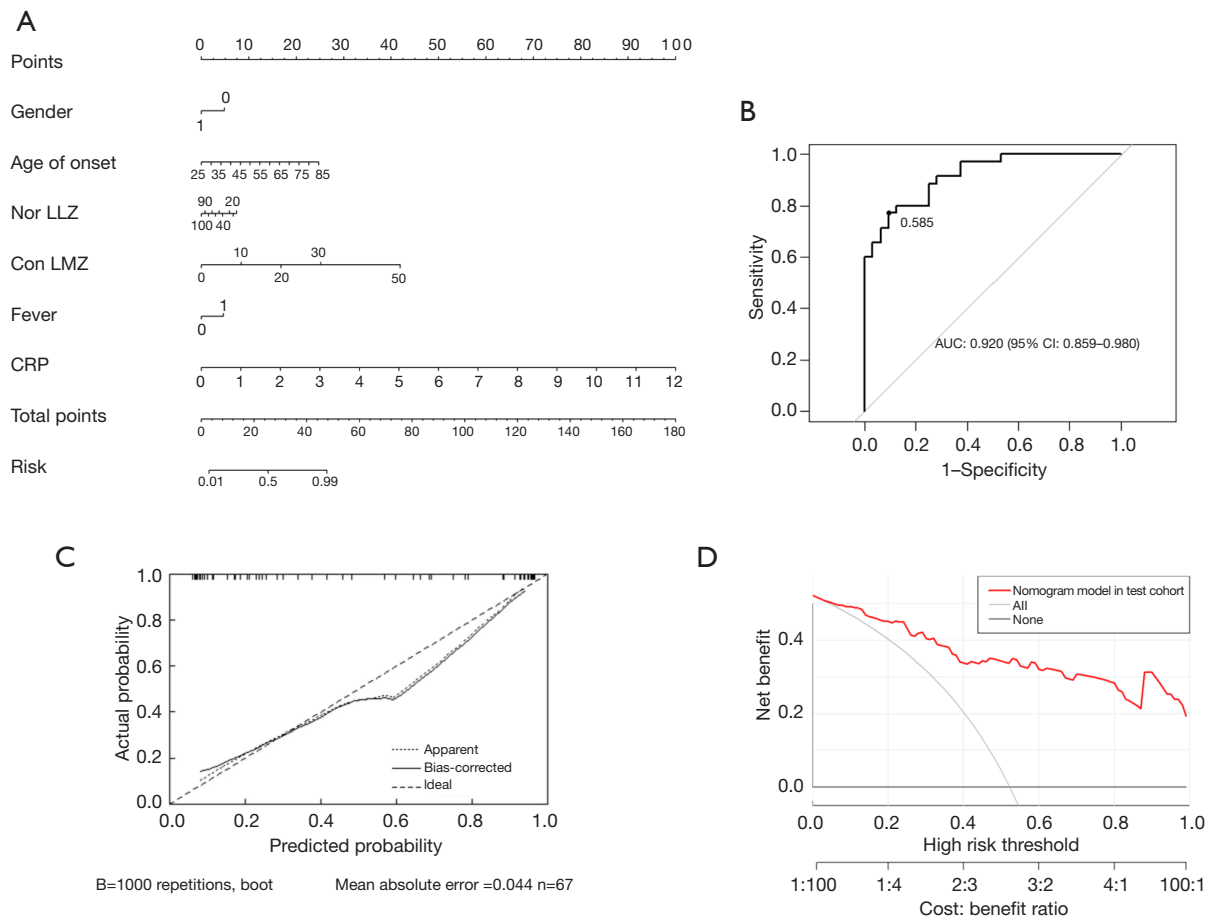


Figure 3 Efficacy of the nomogram in predicting RP-ILD. (A) Nomogram for predicting the occurrence of RP-ILD in patients with anti-MDA5 DM. (B) AUC of the ROC curve of the nomogram model. Patients with a predicted probability over 0.585 were classified as high risk for RP-ILD. (C) Calibration curve of the nomogram model. The calibration curve demonstrated that the model was well-calibrated, closely matching the ideal model with a mean absolute error of 0.044. The Hosmer-Lemeshow test confirmed its reliability with $\chi^2=2.570$ and $P=0.96$, which suggested that the model had a good calibration. (D) Clinical decision curve of the nomogram model. The predictive model for RP-ILD offers a more significant net clinical benefit than both all-intervention and no-intervention strategies. Higher net benefits further enhance its clinical utility. Con LMZ: consolidation range in the left middle lung zone; Nor LLZ: normal range in the left lower lung zone. anti-MDA5 DM, anti-melanoma differentiation-associated gene 5 positive dermatomyositis; AUC, area under the curve; CI, confidence interval; CRP, C-reactive protein; ROC, receiver operating characteristic; RP-ILD, rapidly progressive interstitial lung disease.

with subtypes including NSIP (49%), NSIP-OP (28%), OP (20%), and UIP (3%). Therefore, we deemed it theoretically feasible to use semiquantitative HRCT scoring methods to assess the severity of ILD in patients with anti-MDA5 DM.

Some studies have attempted to evaluate the severity of ILD in anti-MDA5 DM patients using various semiquantitative HRCT scoring methods (10,12). In the present study, the result showed that four HRCT semiquantitative scoring methods (Methods 1, 2, 4, and 5) yielded significantly higher scores in the RP-ILD group than the non-RP-ILD group,

with Method 1 demonstrating the most superior diagnostic performance. As the results of the present study showed, the RP-ILD group predominantly presented with OP and NSIP-OP (62%), while the non-RP-ILD group primarily presented with NSIP (65%), indicating a propensity for progression in NSIP-OP and OP. Zuo *et al.* (14) found that both OP and NSIP-OP patterns were associated with an increased risk of rapid progression, with a relatively mild or chronic clinical course more commonly observed in patients with NSIP during follow-up (odds ratio: 4.08, $P<0.001$).

Studies (22,23) have also suggested that consolidation in the lower lung area is an independent predictor of death within 90 days after onset in ILD in anti-MDA5 DM, highlighting the importance of consolidation in assessing the severity of ILD. Although Methods 2, 4, and 5 can be used to evaluate the severity of ILD in anti-MDA5 DM patients, Methods 2 and 4 may not provide a comprehensive assessment of ILD severity due to the lack of consolidation assessment, which may lead to an incomplete assessment of ILD severity, which may explain the relatively lower diagnostic performance of these models. The AUC of Method 1 was slightly higher than that of Method 5, which may be due to the different scopes of the lesions assessed. Method 5 evaluated only six levels, whereas Method 1 assessed the entire lung, providing more comprehensive information. The Method 1 assessment not only included GGO and consolidation, but also assessed whether these were combined with tractional bronchiectasis, and assigned weights of different HRCT patterns to calculate the total score. Thus, this method differentiated the role of each HRCT pattern in the comprehensive assessment, providing a more objective and precise method for assessing the clinical presentation and prognosis of patients.

PFTs are a staple in clinical practice for monitoring respiratory function. In a multicenter study, Wu *et al.* (24) found that the baseline FVC was the most important prognostic factor for predicting six-month all-cause mortality in anti-MDA5 DM. However, obtaining accurate PFT results can be challenging, and completing PFTs may be particularly difficult for some patients with RP-ILD, especially anti-MDA5 DM patients with severe muscle damage. Unlike PFTs, HRCT does not require patients to take multiple deep breaths, and can directly visualize the phenotype and the degree of ILD.

The findings of this study revealed that Method 1 was negatively correlated with the FEV1, FVC, VC, and DLCO, effectively reflecting the status of pulmonary function. Therefore, it is more feasible and practical to use Method 1 to assess the severity of ILD in anti-MDA5 DM patients. Methods 3, 6, and 7 primarily focus on the extent of reticulation and honeycombing, which are the main manifestations of pulmonary fibrosis. Pulmonary fibrosis is less common in patients with DM-RP-ILD (25), which may account for the poor performance of Methods 3, 6, and 7 in assessing DM-RP-ILD. Fathi *et al.* (26) also found that the pulmonary fibrosis scores of patients with DM-ILD did not differ significantly during the follow-up period, which is consistent with the results of this study. Our findings

suggest that assessing the extent of fibrosis alone has a limited role in indicating the progression of DM-RP-ILD.

Risk factors in clinical features

Anti-MDA5 DM is a rare disease, predominantly affecting females (1). However, the results of this study suggest that male sex is a significant risk factor for the development of RP-ILD in anti-MDA5 DM patients. Studies have reported a higher risk of RP-ILD and a reduction in the overall survival time in male anti-MDA5 DM patients compared to female anti-MDA5 DM patients, which is consistent with our findings (27,28). Sex hormones have been shown to play a critical role in lung injury, allergic airway response, and immune response (29), leading to the hypothesis that sex hormone levels might account for the different incidences of RP-ILD between males and females. Additionally, in occupations that are male-dominated, there is a relatively higher prevalence of smoking and exposure to other habitual, occupational, or environmental factors, which may also contribute to pulmonary deterioration in male patients.

The multifactorial analysis of this study revealed an increased likelihood of RP-ILD risk in patients with an advanced age, high CRP levels, and fever. Previous studies suggest that older DM patients, particularly those over 50 years old, exhibit increased inflammation markers and are at a higher risk of RP-ILD. The mortality risk of anti-MDA5 DM patients increases significantly with age, particularly in those aged over 60 years (28,30). CRP levels, which can be a sensitive indicator of various inflammatory responses and tissue damage, have also been found to be increased during the acute exacerbation of pulmonary fibrosis (31). Our study showed that the RP-ILD patients had a higher incidence of fever than the non-RP-ILD patients, and that the febrile anti-MDA5 DM patients were prone to develop RP-ILD (14). Fever is typically associated with increased inflammation, which promotes macrophage and neutrophil activation and proliferation, thereby increasing disease activity and exacerbating the systemic inflammatory response. Consequently, low or normal CRP levels and an absence of fever may indicate reduced inflammatory activity and a more balanced immune status, potentially leading to improved patient outcomes.

In our study, although serum ferritin was found to be statistically significant in the univariate analysis, it was not included in the LASSO regression model due to the redundancy in the predictive information it provided compared to stronger, more specific predictors such as

characteristic HRCT features. Further, while anti-Ro52 antibody has been associated with a poor prognosis in certain patient cohorts (32), no significant association between anti-Ro52 and RP-ILD was observed in our cohort, which aligns with recent reports on anti-MDA5 DM (33). This discrepancy underscores the clinical and immunological heterogeneity of the disease and suggests that the prognostic relevance of anti-Ro52 may be context-specific; however, these findings need to be clarified and validated in future studies.

Risk factors in HRCT characterizations

Several preliminary studies have outlined the imaging features of ILD in anti-MDA5 DM patients, with some suggesting that consolidation in the middle and lower lung zones on HRCT is associated with RP-ILD (22,34,35). Chino *et al.* (36) showed that perilobular opacity on HRCT, which evolves into consolidation, corresponds pathologically to diffuse alveolar damage (DAD). These studies observed a rapid expansion of perilobular opacity and consolidation, accompanied by a reduction in lung volume, a pattern indicative of anti-MDA5 DM-RP-ILD and DAD (36,37). A decreased normal area in the left lower lung zone and an increased extent of consolidation in the left middle lung zone were identified as risk factors for RP-ILD in this study. Our findings indicated that the RP-ILD group had higher consolidation scores in the middle and lower lung zones bilaterally, which may reflect the progression of consolidation in these lung zones with a tendency to spread upward and forward. Chino *et al.* identified perilobular opacity as the predominant imaging feature, which is relatively common in patients with OP (38). The pathological correlation further supports this finding, showing that areas of perilobular opacity progressed rapidly to consolidation, corresponding to membranous organization and fibrosis with alveolar collapse (37). The presence of consolidation often signifies advanced stages of DAD in pulmonary pathology (5,39,40), which is of significant clinical utility for patient management.

This study had some limitations. First, as a single-center study, its findings need to be validated in a multicenter study to enhance the generalizability of the results. The assessment of inter-observer reliability was conducted on a random subset of 12 cases, which might limit the precision of the reliability estimates. Second, the absence of lung tissue biopsies limited our ability to more precisely examine the correlations between radiological patterns observed on

HRCT and the corresponding histopathological types of ILD. However, Kang *et al.* reported that the DAD, UIP, and NSIP patterns identified in biopsies often present as the OP pattern on HRCT (41), and the absence of details of the pathological type did not affect the assessment of disease progression. In addition, some of the patients in this study could not undergo the PFTs due to muscle damage caused by DM, which is a common clinical issue. Finally, although CRP served as a strong predictor in our model, it is a non-specific acute-phase reactant susceptible to rapid fluctuation due to infections or other inflammatory conditions. This characteristic may compromise the stability and generalizability of the model across diverse clinical settings.

Conclusions

Semiquantitative visual scoring based on HRCT is a validated method for assessing ILD and monitoring the progression of RP-ILD in anti-MDA5 DM patients. A predictive model, incorporating both semiquantitative visual scoring and clinical information, could delay and reduce the development of RP-ILD, thereby improving patient prognosis, which is essential in guiding patient management.

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Footnote

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coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki and its subsequent amendments. The study was approved by Ethics Committee of Tianjin Medical University General Hospital (No. IRB2021-YX-002-01) and informed consent was taken from all the patients.

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