Progression prediction in idiopathic inflammatory myopathy-associated interstitial lung disease: a combination of initial high attenuation areas and anti-melanoma differentiation-associated gene 5-positive

X. Fang[1,2], L. Zou[2], H. Zhao[2], B. Liu[1]

[1]Department of Radiology, The First Affiliated Hospital of Anhui Medical University, Anhui; [2]Department of Radiology, The Second Affiliated Hospital of Anhui Medical University, Anhui, China.

Abstract

Objective

To analyse quantitative lung densitometry and clinical baseline data of individuals with idiopathic inflammatory myopathy (IIM) and identify risk factors capable of predicting the progression of interstitial lung disease (ILD).

Methods

We utilised quantitative lung densitometry and clinical baseline data as explanatory variables. Univariate and multivariate Cox regression analyses were employed to pinpoint effective risk factors for predicting ILD progression in IIM patients.

Results

The findings from the Cox univariate regression analysis indicate that elevated carcinoembryonic antigen levels (HR=1.036, 95% CI 1.004-1.069) are connected to an elevated risk of ILD progression in patients with IIM (P=0.027), while PO_2 (HR=0.980, 95% CI 0.962-0.997) , forced vital capacity (HR=0.551, 95% CI 0.320-0.946) are protective factors for ILD progression in patients with IIM (p=0.025, p=0.031, respectively), anti-EJ positivity (HR=0.399, 95% CI 0.175-0.912) and anti-Ro52 positivity (HR=0.437, 95% CI 0.199-0.960) are risk factors for ILD progression in patients with IIM (p=0.029, p=0.039, respectively). Furthermore, the results of Cox multivariate regression analysis reveal that high attenuation areas (HAA) (>465.745 cm^3) (HR=5.007, 95% CI 1.773-14.144) and anti-melanoma differentiation-associated gene 5 (Anti-MDA5) positivity (HR=0.127, 95% CI 0.041-0.396) are autonomous prognostic risk factors for ILD progression in individuals with IIM (p=0.002, p<0.001, respectively).

Conclusion

Among IIM patients, those who are anti-MDA5-positive, and exhibit HAA (>465.745cm^3) are more likely to experience ILD progression.

Key words

idiopathic inflammatory myopathy, interstitial lung disease, high attenuation areas, anti-melanoma differentiation-associated gene 5

Xianjing Fang, MD
Liwei Zou, MD
Hong Zhao, MD
Bin Liu, MD

Please address correspondence to:
Bin Liu
The First Affiliated Hospital of Anhui Medical University, 218 Jixi Road, Hefei 230022 Anhui, China.
E-mail: Lbhyz32188@126.com

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Introduction

Idiopathic inflammatory myopathies (IIMs) constitute a diverse group of connective tissue disorders characterised by differing degrees of acquired skeletal muscle inflammation. This group includes conditions such as polymyositis (PM), dermatomyositis (DM), and clinically amyopathic dermatomyositis (CADM) (1, 2). IIM can involve multiple systems and organs throughout the body, influencing the patient outcomes, with interstitial lung disease (ILD) emerging as a significant comorbidity. A meta-analysis conducted by Sun in 2021 revealed that among individuals globally diagnosed with PM/DM, the incidence of ILD is reported to reach as high as 41%, with an even more pronounced occurrence in Asian populations (3).

Some individuals with IIM-ILD may develop rapidly progressive ILD within one to two months of symptom onset, and this condition often proves resistant to immunosuppressive treatment, presenting considerable challenges in clinical management (4, 5). Notably, a study has revealed that within a few months after diagnosis of IIM, ILD accounted for the mortality of 71% of CADM patients and 60% of individuals with primary DM (6). Although ILD findings may manifest before, during, or after the diagnosis of IIM, the clinical course remains variable. Therefore, early assessment of the unknown risk of IIM-ILD progression is essential to optimise patient management.

High-resolution computed tomography (HRCT) plays a crucial and integral role in the identification and description of alterations in the lung's interstitial space (7, 8). However, the inconsistencies among various observers and even within the same observer make HRCT lack reliable and quantitative evaluation for ILD diagnosis (9). To address this challenge and enhance the accuracy of predicting IIM-ILD, a more objective and dependable approach to assessment is required.

Quantitative lung densitometry is a method that employs computer algorithms to provide a quantitative assessment of lung tissue density. It utilises HRCT images to evaluate lung diseases based on density values, usually represented in Hounsfield units (HU). This approach allows for the quantification of density changes in lung tissue, thereby assisting doctors in detecting and diagnosing lung diseases, particularly ILD. Through quantitative lung densitometry, clinicians can achieve more precise assessments of lung lesions, providing improved guidance for clinical treatment (10-13).

Currently, there is a lack of relevant research on quantitative lung densitometry in forecasting the progression of ILD in individuals with IIM. Hence, this study strives to investigate predictive markers for ILD progression among patients with IIM, leveraging baseline quantitative lung densitometry alongside pertinent clinical data.

Methods

Study subjects and diagnostic criteria

Between May 2018 and December 2022, we gathered comprehensive data from a cohort of 126 patients diagnosed with IIM by utilising the electronic medical records system of the Second Affiliated Hospital of Anhui Medical University. All enrolled patients had complete medical records, chest HRCT images acquired at the time of initial diagnosis, and follow-up records (with the final follow-up time point set as March 30, 2023). The time duration commencing from the initial diagnosis of IIM and extending until either ILD progression, or the conclusion of the final follow-up period was designated as the "survival time". ILD progression was identified when the follow-up period showed the presence of two or more of the following conditions: worsening respiratory symptoms (*e.g.* dyspnoea upon exertion), decreased lung parenchymal opacity observed on chest HRCT, a decline of more than 10% in forced vital capacity (FVC), or a drop of more than 10 mmHg in arterial oxygen tension (PaO_2).

This study obtained endorsement from the Ethics Committee of the Second Affiliated Hospital of Anhui Medical University and strictly adhered to ethical standards. All participants provided written informed consent.

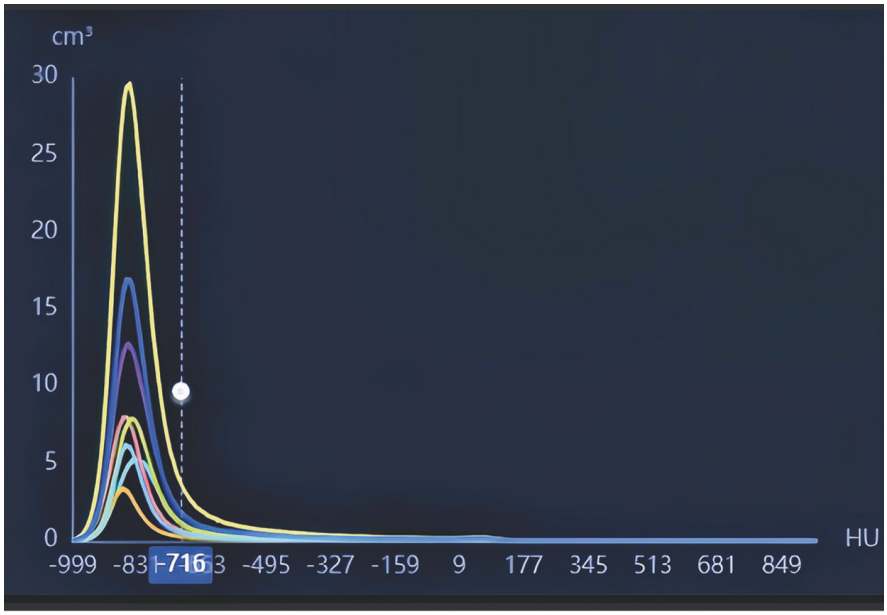

Fig. 1. Density plot.

Quantitative lung densitometry analysis

To ensure accuracy, all chest HRCT scans were carefully examined for potential complications, including pleural effusions, oedema, haemorrhages, and bacterial or viral infections. Any scan with such complications was excluded from the final analysis. Fortunately, no examination was deemed ineligible in this series. Importantly, all CT examinations were performed without the use of contrast enhancement.

In this study, we conducted pulmonary parenchymal analysis using the InferRead CT Lung software provided by InferVision (Fig. 1). The software automatically segmented the lung images and analysed the following parameters: total lung volume (TLV; -1024 HU to -250 HU), normal lung density (NLD; -950 HU to -700 HU), high attenuation areas (HAA; -700 HU to -250 HU), and mean lung attenuation (MLA). Normal lung index (NLI) and HAA% represent the proportions of TLV occupied by NLD and HAA, respectively (Fig. 2). These methods were based on literature reports (14, 15).

Data collection

The patients' clinical baseline data were extracted from their initial electronic medical records and follow-up visits (Table I).

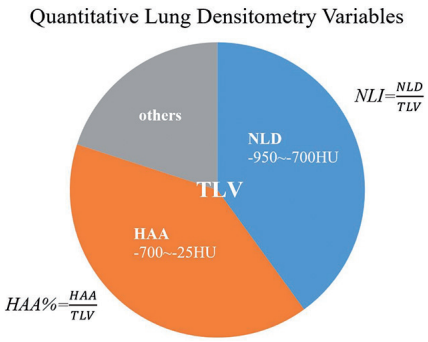

Fig. 2. Quantitative lung densitometry variables.

Statistical analysis

We conducted the statistical analysis using SPSS 23.0 software. Quantitative data were expressed as $\bar{x} \pm s$, while categorical data were displayed as frequency and percentage. To compare the advanced ILD group with the non-advanced ILD group, we employed the t-test or Mann-Whitney U-test for continuous data, and the χ^2 test or Fisher's exact test for categorical data.

To identify meaningful predictors of ILD progression, we employed receiver operating characteristic (ROC) analysis along with the Youden's index to determine the optimal cut-off values and groupings. COX univariate and multivariate regression analyses were utilized to identify independent predictors of ILD progression in patients with IIM. A p-value of <0.05 was considered significant.

Results

Among the 126 IIM patients, 35 were males, average age was 53.1±14.6 years, ranging from 13 to 88 years. Based on diagnostic criteria, 93 (73.81%), 26 (20.63%), and 7 (5.56%) cases were classified under DM, PM, and CADM groups, respectively. The patients were monitored for an average of 23.5 months, with a range of 0.5 to 56 months.

Comparison of ILD progressors and non-ILD progressors

Table I provides the variables' comparison between the ILD progressors and non-ILD progressors. Out of 126 patients, 37 (29.4%) experienced ILD deterioration, the median age was 58.5 years. It is worth noting that variables such as male sex, height, weight, body mass index (BMI), smoking status, IIM diagnosis, procalcitonin (PCT), interleukin (IL)-6, Krebs von den Lungen-6 (KL-6), rheumatoid factors (RF), creatine kinase (CK), aspartate aminotransferase (AST), alanine aminotransferase (ALT), triglyceride (TG), anti-cyclic citrullinated peptide antibody (anti-CCP), positron emission tomography-computed tomography (PET-CT) score, PCO_2, total lung capacity (TLC), diffusing lung capacity (DLCO), DLCO% predicted, and forced expiratory volume in one second (FEV1) did not exhibit statistically significant differences between ILD progressors and non-ILD progressors. However, older age, ILD, elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), peak ferritin and carcino-embryonic antigen (CEA), higher A-aDO_2, higher FEV1/FVC ratio, and complications such as CMV infection and EB infection were associated with ILD progressors. Moreover, progressors had lower FVC and PO_2 values than non-progressors. With respect to the utilisation of myositis-specific antibodies (MSAs) and Muscle-specific autoantibodies (MAAs), anti-glycyl tRNA synthetase (anti-EJ), anti-melanoma differentiation-associated gene 5 (anti-MDA5), and Anti-Ro52 were more significant for ILD progressors, while Anti-histidyl-tRNA synthetase (anti-Jo-1) and Anti-transcription intermediary factor-gamma

Table I. Baseline characteristics of patients with IIM.

Variables	ILD progressors (n=37)		Non-ILD progressors (n=89)		*p*
	Value	Available data per outcome	Value	Available data per outcome	
Demographics					
Age at onset, years	58.49±12.18	37 (100%)	50.82±15.01	89 (100%)	*0.007*
Male	14 (37.84%)	37 (100%)	21 (23.60%)	89 (100%)	*0.104*
ILD	37 (100%)	37 (100%)	63 (70.79%)	89 (100%)	*<0.001*
height, cm	159.85±8.13	34 (91.9%)	160.82±8.38	88 (98.9%)	*0.566*
weight, kg	54.50 (51.00, 62.00)	34 (91.9%)	58.00 (50.00,64.00)	88 (98.9%)	*0.459*
BMI, kg/m^2	22.00±2.64	34 (91.9%)	22.41±3.01	88 (98.9%)	*0.482*
current/former smoker	9 (24.32%)	37 (100%)	12 (13.48%)	89 (100%)	*0.112*
CMV	1 (3.23%)	31 (83.78%)	1 (1.92%)	52 (58.43%)	*0.009*
EB	6 (19.35%)	31 (83.78%)	7 (14.29%)	49 (55.06%)	*0.007*
PJP	3 (100%)	3 (8.11%)	3 (100%)	3 (3.37%)	*0.24*
Diagnosis					
PM	6 (16.22%)	37 (100%)	20 (22.47%)	89 (100%)	*0.429*
DM	29 (78.38%)	37 (100%)	64 (71.91%)	89 (100%)	*0.452*
CADM	2 (5.41%)	37 (100%)	5 (5.62%)	89 (100%)	*0.664*
Laboratory parameters					
CRP, mg/dL	12.50 (2.85,35.60)	37 (100%,3.20)	1.20 (10.50)	89 (100%)	*0.001*
PCT, ng/ml	0.06 (0.03,0.11)	26 (70.3%,0.06)	0.03 (0.11)	35 (39.3%)	*0.994*
IL-6, pg/ml	15.70 (4.70,34.00)	27 (73.0%,18.30)	6.25 (69.10)	41 (46.1%)	*0.581*
ESR, mm/h	29.00 (14.75,48.25)	36 (97.3%,18.50)	7.00 (33.25)	86 (96.6%)	*0.008*
KL-6, U/mL	887.00 (479.00,1635.00)	27 (73.0%,624.00)	364.00 (1167.00)	39 (43.8%)	*0.094*
RF (IU/ml)	16.25 (10.55,336.45)	6 (16.2%,24.55)	15.25 (34.80)	12 (13.5%)	*0.820*
Ferritin, ng/mL	756.25 (275.75,1432.00)	36 (97.3%,220.00)	115.00 (448.00)	77 (86.5%)	*<0.001*
CK, U/L	388.00 (73.50,993.00)	37 (100%,345.00)	67.00 (1584.00)	89 (100%)	*0.533*
AST, U/L	60.00 (33.50,147.00)	37 (100%,54.00)	31.50 (118.50)	89 (100%)	*0.541*
ALT, U/L	54.00 (30.50,84.00)	37 (100%,49.00)	28.00 (85.50)	89 (100%)	*0.750*
TG (mmol/L)	1.52 (1.14,2.63)	34 (91.9%)	1.36) (1.00,1.99)	87 (97.8%)	*0.237*
CEA, ng/ml	3.52 (2.08,6.90)	35 (94.6%)	1.67) 0.94,2.50)	78 (87.6%)	*<0.001*
anti-CCP (RU/ml)	9.20 (3.43,18.93)	24 (64.9%)	5.55) 2.78,11.18)	56 (62.9%)	*0.250*
PO_2, L mmHg	73.40 (63.10,84.93)	32 (86.5%)	86.80) 75.70,102.80)	51 (57.3%)	*0.004*
PCO_2	35.12±5.35	30 (81.1%)	36.64±5.80	51 (57.3%)	*0.246*
A-aDO_2	36.25 (25.78,48.73)	30 (81.1%)	23.35) 7.63,31.43)	50) 56.2%)	*0.004*
PET-CT score	19.50 (8.50,30.75)	28 (75.7%)	28.00) 7.50,40.00)	57) 64.0%)	*0.203*
PFTs					
TLC	3.50 (2.83,3.92)	8 (21.6%)	4.09 (3.22,4.86)	32 (36.0%)	*0.197*
FVC%predicted, %	69.76 (56.38,80.89)	33 (89.2%)	77.08 (69.23,94.59)	59 (66.3%)	*0.011*
DLCO%predicted, %	46.50 (39.62,85.16)	9 (24.3%)	61.47 (42.46,76.28)	32 (36.0%)	*0.297*
FVC	2.07±0.70	33 (89.2%)	2.39±0.72	60 (67.4%)	*0.045*
DLCO	3.59 (3.04,6.50)	9 (24.3%)	5.19 (3.33,6.36)	32 (36.0%)	*0.410*
FEV1	1.71 (1.39,2.18)	32 (86.5%)	1.87 (1.52,2.39)	59 (66.3%)	*0.125*
FEV1/FVC	86.06±7.72	32 (86.5%)	82.97±6.58	59 (66.3%)	*0.047*
MSA					
Anti-SRP	0 (0%)	36 (97.3%)	4 (4.65%)	86 (96.6%)	*0.242*
Anti-Jo-1	5 (13.89%)	36 (97.3%)	26 (30.23%)	86 (96.6%)	*0.045*
Anti-PL-7	6 (16.67%)	36 (97.3%)	5 (5.81%)	86 (96.6%)	*0.063*
Anti-PL-12	3 (8.33%)	36 (97.3%)	3 (3.49%)	86 (96.6%)	*0.243*
Anti-EJ	7 (19.44%)	36 (97.3%)	4 (4.65%)	86 (96.6%)	*0.015*
Anti-OJ	1 (2.78%)	36 (97.3%)	2 (2.33%)	86 (96.6%)	*0.653*
Anti-SAE1	0 (0%)	36 (97.3%)	1 (1.16%)	86 (96.6%)	*0.705*
Anti-SAE2	0 (0%)	36 (97.3%)	1 (1.16%)	86 (96.6%)	*0.705*
Anti-Mi-2	2 (5.56%)	36 (97.3%)	4 (4.65%)	86 (96.6%)	*0.574*
Anti-TIFγ	2 (5.56%)	36 (97.3%)	17 (19.77%)	86 (96.6%)	*0.038*
Anti-MDA5	15 (41.67%)	36 (97.3%)	11 (12.79%)	86 (96.6%)	*0.001*
Anti-NXP2	1 (2.78%)	36 (97.3%)	2 (2.33%)	86 (96.6%)	*0.653*
Anti-Ku	0 (0%)	36 (97.3%)	4 (4.65%)	86 (96.6%)	*0.242*
MAA					
Anti-PMScl75	2 (5.56%)	36 (97.3%)	3 (3.49%)	86 (96.6%)	*0.463*
Anti-PMScl100	3 (8.33%)	36 (97.3%)	1 (1.16%)	86 (96.6%)	*0.077*
Anti-Ro52	28 (77.78%)	36 (97.3%)	47 (54.65%)	86 (96.6%)	*0.013*
Quantitative Lung Densitometry					
TLV	2513.64 (1941.35,3332.00)	37 (100%)	2904.57 (2173.37,3723.04)	89 (100%)	*0.109*
NLD	1489.03 (1074.66,2185.62)	37 (100%)	1929.13 (1397.56,2513.66)	89 (100%)	*0.018*
NLI, %	59.43±8.78	37 (100%)	65.86±10.27	89 (100%)	*0.001*
HAA	645.85±177.27	37 (100%)	513.35±173.00	89 (100%)	*<0.001*
HAA, %	25.36 (20.13,34.60)	37 (100%)	17.49 (11.07,28.63)	89 (100%)	*0.002*
MLA, HU	– 699.03(–742.45,–647.63)	37 (100%)	–759.90 (–805.24,–696.63)	89 (100%)	*<0.001*
Type of ILD					
NSIP	27 (72.97%)	37 (100%)	49 (55.06%)	89 (100%)	*0.061*
OP	2 (5.41%)	37 (100%)	5 (5.62%)	89 (100%)	*0.664*
NSIP/OP	3 (8.11%)	37 (100%)	4 (4.49%)	89 (100%)	*0.336*
UIP	3 (8.11%)	37 (100%)	6 (6.74%)	89 (100%)	*0.524*
AIP	2 (5.41%)	37 (100%)	0 (0%)	89 (100%)	*0.085*

Results are presented as mean ± standard deviation, median (interquartile range), and frequency (percentage). T-test or Mann-Whitney U-test for continuous data, and the χ^2 test or Fisher's exact test for categorical data.

ILD: interstitial lung; disease BMI: body mass index; CMV: cytomegalovirus; EB: Epstein-Barr virus; PJP: pneumocystis Jiroveci pneumonia; PM: polymyositis; DM: dermatomyositis; CADM: clinically amyopathic dermatomyositis; CRP: C-reactive protein; PCT: procalcitonin; IL-6: interleukin-6; ESR: erythrocyte sedimentation rate; KL-6: Krebs von den Lungen-6; RF: rheumatoid factor; CK: creatine kinase; AST: aspartate aminotransferase; ALT: alanine aminotransferase; TG: triglyceride; CEA: carcinoembryonic antigen; CCP: cyclic citrullinated peptide; PET-CT: positron emission tomography-computed Ttmography; TLC: total lung capacity; FVC: forced vital capacity; DLCO: diffusing lung capacity; FEV1: forced expiratory volume in one second; MSA: myositis-specific antibody; MAA: myositis-associated autoantibody; TLV: total lung volume; NLD: normal lung density; NLI: normal lung index; HAA: high attenuation areas; MLA: mean lung attenuation; NSIP: non-specific interstitial pneumonia; OP: organising pneumonia; UIP: usual interstitial pneumonia; AIP: acute interstitial pneumonia.

(anti-TIF1γ) were more significant for non-ILD progressors.

Quantitative lung densitometry findings

Except for TLV, all quantitative lung densitometry variables significantly differed between the groups, especially HAA and MLA. The HAA was significantly higher in progressors (645.9cm^3±177.3cm^3) than in non-progressors (513.4cm^3±173.00cm^3), (p<0.001). Similarly, the MLA was higher in progressors [-699.0HU IQR: (-742.5HU – -647.6HU)] than in non-progressors [-759.9HU IQR: (-805.2HU – -696.6)], (p<0.001). Moreover, progressors had a higher HAA% [25.4% IQR: (20.1%–34.6%)] than non-progressors [17.5% IQR: (11.1%–28.6%)], (p=0.002). The NLD [1489.0cm^3 IQR: (1074.7cm^3–2185.6cm^3)] and NLI 59.4% (8.8%) of progressors were lower than those of non-progressors [1929.1cm^3 IQR: (1397.6cm^3 – 2513.7cm^3)] (p=0.018) and 65.9% (10.3%) (p=0.001), respectively.

Predictors of ILD progression in IIM patients

As potential risk factors of ILD progression in individuals with IIM, we selected 15 factors for analysis, including ILD, CRP, CEA, PO_2, A-aDO_2, FVC, FEV1/FVC, NLD, NLI, HAA, HAA%, MLA, Anti-Jo-1, Anti-EJ, Anti-MDA5, Anti-Ro52, and CMV/EB infection. Patients were divided into two groups using optimal cut-off values for NLD, NLI, HAA, HAA%, and MLA, respectively. Each index underwent COX univariate analysis, which identified several significant factors, including ILD, CEA, PO_2, HAA (>465.745 cm^3), HAA% (>20.835%), MLA (>-744.29 HU), anti-EJ, Anti-MDA5, and Anti-Ro52.Among these factors, HAA (>465.745 cm^3), HAA% (>20.835%), and MLA (>-744.29 HU) are all quantitative lung densitometry analysis indices. A correlation analysis revealed significant associations among these three indices. Consequently, they were subjected to multivariate analysis along with other relevant single-factor analysis indices. The multivariate analysis results revealed that HAA (>465.745 cm^3) and positive Anti-MDA5 status emerged as independent risk factors associated with ILD progression in IIM individuals (Table II). Intriguingly, the risk of ILD progression was prominently amplified, showing a remarkable 7.874-fold increase in patients who exhibited positive anti-MDA5 results compared to their negative counterparts. HAA (>465.745cm^3) were positively correlated with ILD progression. The combination of HAA (>465.745 cm^3) and anti-MDA5 positivity was employed for diagnosing ILD progression in IIM patients, and the ROC curve analysis yielded an AUC of 0.745. This AUC value was higher than that of either HAA (>465.745 cm^3) or Anti-MDA5 positivity alone (Fig. 3).

Table II. Prediction of ILD progression in IIM patients.

Variables	Univariate analysis		Multivariate analysis	
	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value
ILD	0.032 (0.001~0.819)	*0.037*		
CRP, mg/dL	1.005 (0.998~1.012)	*0.173*		
CEA, ng/ml	1.036 (1.004~1.069)	*0.027*		
PO_2	0.980 (0.962~0.997)	*0.025*		
A-aDO_2	1.005 (0.997~1.013)	*0.236*		
FVC	0.551 (0.320~0.946)	*0.031*		
FEV1/FVC	1.050 (0.997~1.105)	*0.064*		
Anti-Jo-1	2.559 (0.994~6.588)	*0.052*		
Anti-EJ	0.399 (0.175~0.912)	*0.029*		
Anti-MDA5	0.239 (0.122~0.468)	*<0.001*	0.127 (0.041~0.396)	*<0.001*
Anti-Ro52	0.437 (0.199~0.960)	*0.039*		
CMV	0.776 (0.106~5.696)	*0.803*		
EB	0.631 (0.259v1.541)	*0.312*		
HAA (>465.745cm^3)	5.007 (1.773~14.144)	*0.002*	4.758 (1.009~22.440)	*0.049*

Univariate and multivariate Cox regression were used to identify predictors of disease outcomes.

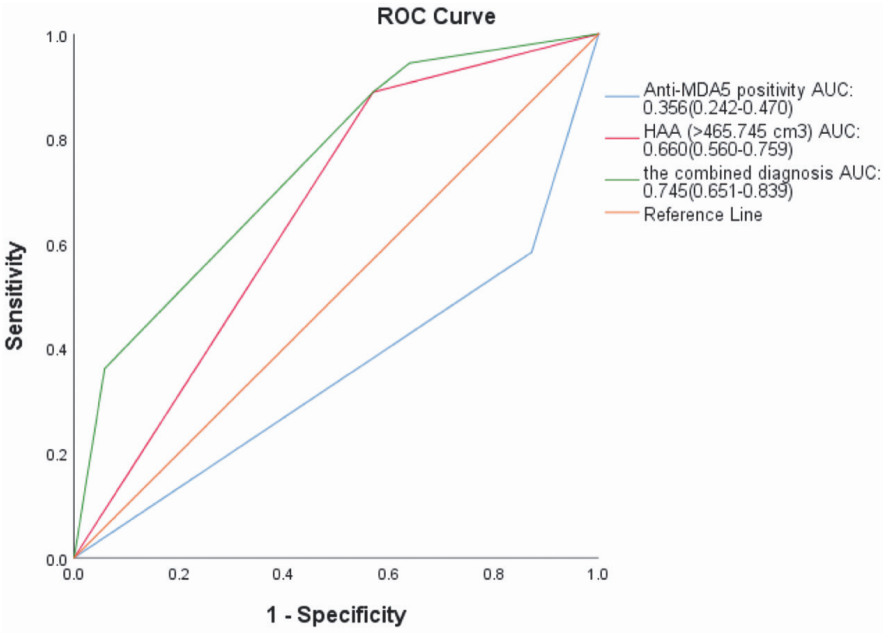

Fig. 3. The AUC for HAA (>465.745 cm^3), anti-MDA5 positivity, and the combined diagnosis using both.

Discussion

In recent years, the utilisation of MSAs as autoantibodies exclusively found in IIM individuals has garnered significant attention due to their association with specific clinical symptoms, disease progression, and treatment response (16, 17). These antibodies have become pivotal in the clinical diagnosis and prognostic assessment of IIM, particularly with regard to anti-ARS and anti-MDA5, which have been

identified as playing a critical role in IIM-ILD.

Remarkably, MDA5 has emerged as a pivotal prognostic marker, particularly concerning the onset of RP-ILD in individuals grappling with DM-ILD (18-20). In our study, we reaffirmed the predictive efficacy of anti-MDA5 positivity. The outcomes of the multivariate Cox regression analysis clearly revealed that patients with a positive anti-MDA5 status were significantly more inclined to experience the progression of ILD ($p<0.001$). However, it is essential to acknowledge that despite the robust predictive potential of anti-MDA5 positivity, a significant portion of patients with this marker may still undergo a stable trajectory of ILD over an extended duration. To avoid excessive clinical intervention due to overemphasis on anti-MDA5, this study integrated a comprehensive analysis of multiple baseline clinical data to enhance diagnostic efficiency and maximise clinical benefits by enabling joint prediction.

After conducting a retrospective analysis of initial features of 126 individuals with IIM and their relationship to ILD progression, the study identified HAA (>465.745cm^3) and anti-MDA5 positivity as independent prognostic risk factors for ILD progression in IIM patients ($p=0.049$, $p=0.001$, respectively). The combination of HAA (>465.745 cm^3) and anti-MDA5 positivity significantly enhances the diagnostic efficiency for ILD progression in individuals with IIM.

This study represents a pioneering investigation into the use of quantitative lung densitometry and clinical data for predicting ILD progression in patients with IIM. The advantage of quantitative lung densitometry over CT evaluation conducted by radiologists lies in its quantitative nature and operator-independence, making it easily applicable to standard clinical CT scans. The study incorporated six quantitative CT indexes (QIs), and in the final multiple-factor COX regression analysis, HAA (>465.745cm^3) emerged as an independent prognostic risk factor of ILD progression. The study revealed that IIM patients with a HAA (>465.745 cm^3) had a 4.758 times higher risk of ILD progression compared to those with a HAA (≤465.745 cm^3) ($p=0.049$). HAA, a crucial parameter in quantitative lung densitometry, serves as a quantitative measure of abnormal lung density distribution, aiding in the diagnosis and monitoring of pulmonary conditions. In this study, HAA encompasses lung regions with attenuation densities exceeding -700HU, which, in the chest CT scans of our study cohort, primarily correspond to ground glass opacities, linear high-density opacities, and thickening of interlobular septa. From a histopathological perspective, HAA is regarded as a consequence of subclinical alveolar epithelial injury, pulmonary inflammation, extracellular matrix remodelling, and interstitial fibrosis, making it a potential surrogate density marker for subclinical interstitial lung disease (12).

Elevated HAA levels have shown significant associations with increased serum levels of MMP-7 and IL-6, alongside diminished FVC, reduced exercise capacity, and heightened ILD-related mortality (21). These research findings underscore a robust correlation between elevated inflammatory markers, clinical events linked to ILD progression, and higher HAA levels. Prior investigations have indicated that HAA could serve as a valuable marker for detecting interstitial lung abnormalities (ILA), carrying substantial implications for the timely identification and effective management of RA-ILD (22). Furthermore, some studies have suggested that even modest elevations in HAA are linked to a heightened risk of clinical ILD events, further emphasising the clinical relevance of HAA (23).

This study breaks new ground by introducing quantitative lung densitometry analysis as an indicator for forecasting ILD advancement in individuals with IIM. Importantly, it conclusively establishes that HAA (>465.745cm^3) stands as an independent predictor of ILD progression. HAA is considered indicative of latent lung injury, subclinical pulmonary inflammation, and possible initial extracellular matrix remodelling (21). Given that HAA may reflect early pathological changes in ILD, potentially representing structural alveolar alterations preceding clinically relevant ILD, the observation of elevated HAA levels in this study may effectively signal the likelihood of ILD progression in IIM patients. Consequently, it is believed that HAA can serve as an indicator of disease progression in ILA or ILD, holding significant clinical implications.

The utilisation of quantitative lung densitometry analysis allows radiologists to automatically obtain HAA values based on CT scans, facilitating the evaluation of lesions that may not be easily quantifiable by visual examination and aiding in the prediction of disease progression. Combining these research findings, it was observed that IIM patients with HAA (>465.745cm^3) are more susceptible to experiencing ILD progression.

In addition to the findings related to quantitative lung densitometry, our analysis of clinical data also revealed important associations with ILD progression in patients with IIM. Notably, our observations highlighted a significant association between advanced age and an increased likelihood of ILD progression in individuals with IIM ($p=0.007$). Moreover, individuals with CMV or EB virus infections demonstrated a heightened risk of ILD progression as well ($p=0.009$, $p=0.007$, respectively).

IIM-ILD can be classified into different types based on CT presentations, including non-specific interstitial pneumonia (NSIP), organising pneumonia (OP), NSIP/OP overlap, usual interstitial pneumonia (UIP), and acute interstitial pneumonia (AIP). It is generally acknowledged that the first three ILD patterns are relatively more common in IIM-ILD patients, which aligns with the distribution observed in our cases. The majority of our cases indeed conform to the NSIP pattern.

Prior research has suggested a potential association between disease progression and the OP pattern (24), while other studies have not found a significant correlation between ILD patterns and disease progression (25). In our study, we conducted a comparative analysis of different ILD patterns and disease progression and did not identify any significant correlations.

Furthermore, a comparison between patient groups, in line with the outcomes of the univariate Cox regression analysis, highlighted that those with pre-existing ILD at the time of initial diagnosis showed an elevated susceptibility to undergo ILD progression over the course of the follow-up (p=0.037).

These comparisons of clinical data offer valuable insights into potential risk factors linked to ILD progression in IIM patients, further underscoring the significance of a comprehensive assessment in forecasting disease outcomes.

Our study encompassed a range of laboratory examination parameters, including routine biochemical markers, inflammatory factors, and autoantibody indicators. These indicators have consistently demonstrated diverse degrees of relevance with the diagnosis, treatment, and prognosis of IIM or ILD in both earlier studies and clinical practice (25-29). Consequently, we included these factors in our investigation to explore their potential correlation with ILD progression in individuals with IIM.

Prior investigations have highlighted that heightened CEA levels are frequently detected in individuals with CADM and could potentially serve as an indicator of RP-ILD, a condition associated with an adverse prognosis (30). Similarly, research has shown that elevated CEA levels are autonomously associated with an increased risk of RP-ILD in patients diagnosed with anti-synthetase syndrome (ASS) (31). Therefore, we included CEA as a predictive parameter in our study. The outcome of the Cox univariate regression analysis indicated that CEA (HR=1.036, 95% CI 1.004-1.069) emerged as a notable contributor to the progression of ILD (p=0.027) in individuals with IIM. These findings indicate that elevated CEA levels suggest an elevated risk of ILD progression in individuals with IIM, underscoring the importance of early detection and intervention.

Regarding arterial blood gas analysis for ILD patients, we focused on whether the main manifestation was hypoxemia with a decrease in arterial partial pressure of carbon dioxide and an increased alveolar-arterial oxygen pressure difference. Thus, we included these three indicators to explore their predictive ability in ILD progression in individuals with IIM. The findings from the Cox univariate analysis indicated that an increase in PO_2 was a protective factor for ILD progression (p=0.025), which is consistent with our clinical practice.

Furthermore, pulmonary function tests (PFTs) play a vital role in examining potential IIM-ILD patients, primarily used to detect the presence of restrictive ventilation impairment and decreased diffusion function, aiding in disease screening and progression evaluation. Our study's COX univariate analysis findings suggested that FVC serves as a safeguard against ILD progression (p=0.031). These results provide valuable insights into the potential factors influencing ILD progression in IIM patients and underscore the significance of monitoring these indicators in clinical practice.

Among patients with IIM-ILD, anti-ARS antibodies were the most frequently identified. Numerous independent studies have consistently shown that anti-ARS-positive patients are markedly more susceptible to developing ILD than their negative counterparts. Moreover, this ILD is known to typically follow a chronic clinical course (32-34).

Regarding anti-EJ, although it belongs to the anti-ARS category, it is relatively uncommon, and there is limited research on its link to ILD progression. Li *et al*. conducted a study in 2019 and found that ILD was more frequent among patients with anti-EJ antibodies (OR 14.202, 95% CI 1.696-118.902), and the OR value was higher than that for other anti-ARS antibodies. However, that study did not specifically investigate the prediction of ILD progression (28). Our study aimed to investigate the link between different anti-ARS antibodies and predicting ILD progression. The outcomes of the univariate Cox regression analysis in our investigation unveiled that anti-EJ stood out as a noteworthy risk factor for ILD progression (p=0.029).

MAAs can be detected in various connective tissue diseases, although their specificity for IIM is relatively low (35). Among these, Anti-Ro52 is the most prevalent MAA and is frequently coexistent with MSAs (36). In our study, the findings from the univariate Cox regression analysis highlighted Anti-Ro52 as a notable risk factor for ILD progression (p=0.039). Additionally, prior studies have shown that patients positive for anti-MDA5 or anti-Jo1 antibodies often have concurrent positivity for anti-Ro52 antibodies. In anti-Ro52-positive patients, particularly when also positive for anti-MDA5 antibodies, the risk of RP-ILD development increases, leading to poorer prognostic outcomes (37, 38).

This study aimed to differentiate baseline clinical and imaging characteristics between IIM patients with and without ILD progression and predict ILD progression in IIM patients. However, several potential limitations should be acknowledged.

Firstly, we did not exclude the influence of drug treatments for the disease, which may have affected the accuracy of our predictions. Medications and their dosages could potentially impact disease progression and outcomes, and not accounting for these factors might have introduced some confounding effects.

Secondly, our study did not stratify ILD progression into different risk levels for more in-depth prediction. Such stratification could offer more precise and tailored clinical guidance based on individual patient risk profiles.

Thirdly, the CT scans were conducted using different models of CT machines, which were not standardised. This variability may have resulted in differences in HU values and could have affected the accuracy of our predictions.

Finally, it has been suggested that there may be a correlation between COVID-19 and certain forms of IIMs. The widespread dissemination of the novel coronavirus in recent years may have implications for research on this condition (39).

Despite these limitations, our study has significant implications. Unlike previous observational studies that mainly focused on patients already diagnosed with IIM-ILD, which may have reflected late-stage disease and the impact of ILD rather than its underlying causes, our study included IIM patients with different ILD statuses, allowing for pre-

dictions of progression from non-existing to existing ILD, as well as from existing to worsened ILD. This approach provided a more objective and accurate prediction of ILD progression in the overall IIM population.

Moreover, our study utilised quantitative lung densitometry and clinical baseline data for prediction, making the process more objective and less reliant on subjective interpretations. This approach enhances the robustness of our findings and contributes to a more accurate assessment of ILD progression in individuals with IIM.

Conclusion

In conclusion, among IIM patients, those who are anti-MDA5-positive and exhibit HAA (>465.745cm^3) are more likely to experience ILD progression. Importantly, the combined predictive efficacy of these two factors is even higher, suggesting their potential utility as valuable indicators for identifying individuals at risk of ILD progression in this patient population.

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