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Progress in Quantitative Imaging Assessment of Dermatomyositis-Associated Interstitial Lung Disease

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Abstract

Interstitial lung disease (ILD) is the primary pulmonary complication leading to disability and mortality in patients with systemic autoimmune rheumatic diseases (SARDs), particularly idiopathic inflammatory myopathies (IIMs). Among these, rapidly progressive ILD (RP-ILD) associated with anti-melanocyte differentiation-associated gene 5 antibody-positive dermatomyositis (anti-MDA5+ DM) carries an extremely poor prognosis, necessitating a precise risk stratification system in clinical practice. This paper systematically reviews recent advances in IIM-ILD, particularly MDA5+ DM-ILD. Regarding pathogenesis and prognosis, anti-MDA5 antibodies have been confirmed as independent risk factors for RP-ILD and high mortality. Biochemical markers including ferritin, LDH, hypouricemia, and sCD40L have been incorporated into multiparametric prediction models such as FLAIR, FLATCAN, and SMAD. Regarding diagnostic and monitoring technologies, high-resolution CT (HRCT) remains the gold standard, while quantitative image analysis (QIA), radiomics, and deep learning (DL) models now enable objective quantification of pulmonary parenchymal lesions and dynamic prognostic prediction. Additionally, novel biomarkers such as HE4 and pulmonary vascular-related structural parameters (PVRS) have been demonstrated to correlate significantly with ILD severity and progression rate, offering new entry points for imaging-biology cross-validation.

Keywords

Idiopathic Inflammatory Myopathies (IIM), Interstitial Lung Disease (ILD), Anti-MDA5 Antibody, Rapidly Progressive ILD (RP-ILD), Quantitative Imaging Analysis (QIA), Radiomics, Risk Stratification

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1. Introduction

Interstitial lung disease (ILD) is a common pulmonary complication of connective tissue diseases (CTDs), posing a serious threat to patient survival and quality of life [1]. Among systemic autoimmune rheumatic diseases (SARDs), idiopathic inflammatory myopathies (IIMs)—particularly dermatomyositis (DM) and antisynthetase syndrome (ASS)—carry a high risk of ILD [2] [3]. The clinical phenotype of IIM-ILD is heterogeneous, ranging from indolent disease course to fatal rapidly progressive ILD (RP-ILD) [4].

Among IIM subtypes, anti-MDA5-positive dermatomyositis (anti-MDA5+ DM) carries the most severe prognosis, with its high mortality primarily attributable to RP-ILD [4] [5]. RP-ILD is characterized by rapid disease progression, often leading to acute respiratory failure within months of diagnosis [6]. Therefore, early identification of high-risk patients and precise assessment of disease activity are current clinical and research priorities. This review aims to summarize key advances in IIM-ILD, particularly MDA5+ DM-ILD, regarding risk factor identification and diagnostic monitoring tools (especially emerging quantitative imaging and biomarkers).

2. Clinical Spectrum and Key Autoantibodies in IIM-ILD

IIM-ILD primarily encompasses dermatomyositis (DM)/polymyositis (PM)-associated ILD and anti-synthetase syndrome (ASS)-associated ILD.

2.1. The Determinant Role of Autoantibodies in Phenotype and Prognosis

Autoantibodies play a central role in defining the clinical phenotype and prognosis of IIM-ILD:

Anti-MDA5 Antibody: This antibody marks RP-ILD, with particularly high reporting rates in East Asia [4]. Anti-MDA5-positive patients often present with characteristic skin lesions and non-myopathic or low-myopathic muscle involvement [4]. Its presence is recognized as a strong predictor of mortality risk (OR 6.20) [6]. Furthermore, it has been identified as a major risk factor for the development of ILD in juvenile dermatomyositis (JDM) [7].

Anti-Synthetase Antibodies (Anti-ARS): Anti-ARS antibodies, such as anti-EJ antibodies, are highly associated with ILD and arthritis [8]. The ILD pattern in these patients often manifests as non-specific interstitial pneumonia (NSIP) on imaging [9]. Although ASS patients frequently develop ILD, the presence of anti-tRNA synthetase antibodies has been found to be a protective factor against mortality (OR 0.24), contrasting sharply with MDA5 antibodies [6]. Specific ARS antibodies, such as anti-KS antibodies, are typically associated with chronic onset and long-term stable pulmonary function [10].

Anti-Ro52 Antibodies: Anti-Ro52 antibodies exhibit a high positivity rate (52.9%) in adult DM patients [11]. This antibody is considered an independent risk factor for the development of ILD across a wide spectrum of rheumatological

diagnoses [12]. In the specific context of anti-MDA5+ DM, the presence of anti-Ro52 antibodies is an independent risk factor for severe ILD [13].

2.2. Clinical and Imaging Phenotypes

The most common HRCT pattern in IIM-ILD patients is non-specific interstitial pneumonia (NSIP) (50%), followed by usual interstitial pneumonia (UIP) (28%) and organizing pneumonia (OP) (22%) [14]. However, the UIP pattern is significantly associated with radiographic ILD progression (QILD > 2%) [15]. In MDA5+ DM-ILD, HRCT features typically include ground-glass opacities (GGO), consolidation, and spontaneous pneumomediastinum (SP) [4]. Notably, pleural effusion has also been identified as an independent predictor of RP-ILD and mortality in IIM patients [16]. Beyond endogenous factors, environmental triggers such as COVID-19 infection have been reported to precipitate new-onset dermatomyositis [17].

3. Prognosis Factors and RP-ILD Risk Stratification Model

Given the high lethality of RP-ILD, accurate risk stratification is crucial for guiding early intervention.

3.1. Clinical and Biochemical Prognostic Indicators

RP-ILD and mortality risk correlate with multiple systemic inflammatory and organ dysfunction markers [5].

Inflammatory and Immune Markers: Elevated serum ferritin, LDH, CRP, and neutrophil-to-lymphocyte ratio (NLR) are common predictors of mortality risk [18].

Pulmonary Function and Clinical Symptoms: Baseline forced vital capacity percentage (FVC%) serves as a simplified risk stratification system [4]. Dyspnea, hypoxemia, and acute/subacute onset correlate with high mortality [6].

3.2. Novel Biomarkers

Hypouricemia: Serum uric acid (SUA) < 154 μmol/L has been identified as an independent predictor of mortality in MDA5+ DM-ILD patients [19]. The hypothesized mechanism linking low uric acid to poor prognosis involves the excessive consumption of uric acid—a key endogenous antioxidant—in response to the massive oxidative stress and hyperinflammation during the rapid progression of the disease.

Soluble CD40L (sCD40L): Levels of sCD40L correlate with IIMs-RP-ILD, suggesting potential involvement of coagulopathy in RP-ILD pathogenesis [20].

Human Epididymis Protein 4 (HE4): HE4 levels are significantly elevated in IIMs-ILD patients and negatively correlate with ILD presence and pulmonary function (DLCO, TLC) [21].

3.3. Multivariate Risk Scoring Model

To enhance predictive accuracy, scoring systems incorporating multiple risk fac-

tors have been established:

FLAIR Model: This model integrates ferritin, LDH, anti-MDA5 antibody titer, HRCT imaging score, and RPILD status. Patients can be effectively stratified into low-, intermediate-, and high-risk groups based on FLAIR scores [18].

FLATCAN Model: Integrates ferritin, LDH, age, $CD8^+$ T-cell count, CRP, albumin, and the CT pattern of NSIP + OP. This model demonstrates robust predictive power for mortality at 3, 6, and 12 months [5].

SMAD Model: Integrates serum sCD40L levels, MDA5 positivity, hypoalbuminemia, and elevated D-dimer to effectively predict RP-ILD risk and short-term survival [20].

4. Application of Imaging and Biomarkers in Diagnosis and Monitoring

4.1. HRCT and Quantitative Imaging Analysis (QIA)

HRCT serves as the core tool for diagnosing and evaluating CTD-ILD [1].

Traditional Scoring and Prognosis: Traditional semi-quantitative scoring systems (e.g., Warrick score) have been shown to correlate positively with ILD severity markers such as serum KL-6 levels [22]. In the specific population of juvenile dermatomyositis (JDM), a designated CT scoring system also demonstrated a positive linear correlation with KL-6 [23]. In MDA5+ ILD, semi-quantitative HRCT lesion assessment is relevant to the clinical outcome [4].

Quantitative CT Analysis (QCT): With advances in computer-aided systems, QCT provides objective quantification of lung injury, including quantitative ILD (QILD) and quantitative lung fibrosis (QLF) [15].

Clinical Significance of QCT: QILD scores show significant negative correlations with FVC and DLCO [24]. Higher baseline QILD scores (>28.1%) in IIM-ILD patients are associated with an increased risk of lung transplantation or mortality [15]. In MDA5+ ILD, short-term follow-up lung severity scores (LSS > 6.5) represent the strongest predictor of mortality, outperforming baseline assessments [25].

Longitudinal Monitoring: QIA demonstrates strong potential in monitoring disease, with longitudinal QIA scores in ASS-ILD correlating with pulmonary physiology and quality of life over time [24]. Similarly, quantitative chest CT has proven effective in monitoring the progression of ILD in patients with antisynthetase syndrome [26]. Furthermore, growth rate modeling analysis revealed that rapid progression patterns in QLF significantly correlate with mortality risk [27].

4.2. Radiomics, Deep Learning, and Multimodal Imaging

Artificial intelligence (AI) is playing an increasingly vital role in risk prediction and diagnosis for IIM-ILD:

Radiomics for RP-ILD Prediction: Radiomics-based risk scores derived from HRCT outperformed clinical-radiologic models alone in predicting RP-ILD and mortality in MDA5+ DM-ILD [28].

Deep Learning (DL) Diagnostics: Models constructed using DL-based quantitative CT parameters demonstrated high diagnostic efficiency (AUC 0.843) in identifying PM/DM-ILD [29]. DL models can also effectively classify multiple specific imaging patterns of IIM-ILD [30]. Moreover, deep learning analysis of chest CT has been applied to assess the efficacy of therapeutic interventions such as tofacitinib in anti-MDA5+ DM patients [31].

Multimodal Assessment:

PET/CT: Combining 18F-FDG PET/CT scores with HRCT scores and anti-MDA5 antibodies significantly enhances the ability to differentiate RP-ILD patients and predict poor prognosis [32].

Pulmonary Vascular-Related Structures (PVRS): AI-quantified PVRS parameters (e.g., mean pulmonary vascular diameter) have been identified as independent imaging biomarkers for rapid progression and poor prognosis in IIM-ILD [33].

4.3. Non-Imaging Monitoring Methods

Beyond conventional pulmonary function testing [1], physiological and biochemical metrics serve as essential tools to validate imaging findings. Lung ultrasound B-line scores show significant correlation with HRCT scores and KL-6 levels [22]. Small airway function, assessed via multiple breath nitrogen washout, provides a functional basis for evaluating early parenchymal changes [34]. Furthermore, changes in the 6-minute walk distance (6MWD) over time correlate with alterations in FVC and patient-reported dyspnea, confirming that longitudinal shifts in quantitative parameters reflect meaningful changes in the patient's functional status [35].

5. Conclusion

Interstitial lung disease associated with idiopathic inflammatory myopathies (IIM-ILD), particularly the phenotype linked to anti-MDA5 positive dermatomyositis (anti-MDA5+ DM-ILD), continues to represent a formidable challenge in the landscape of autoimmune diseases due to its clinical heterogeneity and high mortality. The current research paradigm has profoundly shifted from simple diagnostic identification to precision risk stratification driven by a synthesis of molecular and imaging characteristics. Clinical management increasingly relies on a panel of robust prognostic indicators, including anti-MDA5 antibody positivity, markers of hyperinflammation (such as elevated ferritin, LDH, and sCD40L), and metabolic factors like hypouricemia. Crucially, in the domain of disease monitoring, the integration of standard high-resolution computed tomography (HRCT) with cutting-edge computational technologies—specifically Quantitative Imaging Analysis (QIA), radiomics, and Deep Learning (DL) models—provides unprecedented, objective tools for assessing disease activity and severity. These advanced techniques overcome the subjectivity of traditional visual scoring systems. Furthermore, QIA offers dynamic insights beyond static evaluation; it not only pre-

cisely quantifies the volume of lung injury at baseline but also captures the trajectory of disease evolution. Longitudinal metrics, such as the growth rate of Quantitative Lung Fibrosis (QLF), have emerged as key prognostic indicators for predicting survival and treatment response. Future research should focus on longitudinal validation of these multimodal models in prospective cohorts, and explore the integration of liquid biopsy with imaging biomarkers for real-time monitoring.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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