CLINICAL AND IMMUNOLOGICAL PREDICTORS AND THEIR ROLE IN THE PROGRESSION OF NONSPECIFIC INTERSTITIAL PNEUMONIA

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ABSTRACT

Nonspecific interstitial pneumonia (NSIP) is a heterogeneous subtype of interstitial lung disease characterized by varying degrees of inflammation and fibrosis. Although many patients respond favorably to corticosteroids and immunosuppressive therapy, a significant proportion develop progressive pulmonary fibrosis (PPF), which leads to a steady decline in lung function and poorer survival outcomes. Early identification of clinical and immunological predictors is therefore crucial for timely intervention and improved prognosis.

Introduction

Nonspecific interstitial pneumonia (NSIP) is a heterogeneous form of interstitial lung disease (ILD) characterized by variable degrees of alveolar inflammation and fibrosis. Unlike idiopathic pulmonary fibrosis (IPF), NSIP typically shows a more favorable response to immunosuppressive therapy; however, a significant subset of patients develops a progressive fibrosing phenotype (PPF) leading to a decline in lung function and poor survival outcomes. Early identification of clinical and immunological predictors of progression is therefore essential for risk stratification, prognosis, and personalized management of NSIP.

Purpose of the Study

To identify the most significant clinical and immunological markers associated with the progression of NSIP based on a comprehensive analysis of national and international studies published between 2005 and 2025.

Materials and Methods

A systematic literature review was conducted using databases such as PubMed, Scopus, and eLibrary. The inclusion criteria comprised original clinical and cohort studies reporting prognostic factors associated with NSIP progression, while single case reports and studies lacking quantitative data were excluded.

The following parameters were analyzed:

- **Clinical factors:** age, sex, duration of symptoms, and presence of systemic autoimmune features.
- **Radiological parameters:** extent and distribution of fibrosis, presence of ground-glass opacities, and total affected lung area on HRCT.

• **Immunological markers:** levels of autoantibodies (ANA, anti-SSA/Ro, anti-Jo-1), cytokines (IL-6, TGF-β, TNF-α), and fibroblast activation markers.

Results and Discussion

1. Clinical Predictors of Progression

Multiple studies (Park et al., 2019; Kim et al., 2022) have demonstrated that male sex, age over 55 years, and a baseline forced vital capacity (FVC) below 70% are independently associated with unfavorable outcomes. The presence of systemic autoimmune manifestations (xerostomia, arthralgia, Raynaud's phenomenon) also correlates with faster fibrotic progression and poorer prognosis.

2. Immunological Markers

Patients with progressive NSIP exhibit a distinct immunologic profile characterized by elevated serum levels of pro-inflammatory cytokines IL-6 and TNF-α and activation of the TGF-β signaling pathway, which drives fibroblast differentiation and excessive collagen deposition.

Marked hypergammaglobulinemia and high ANA titers (>1:160) often indicate overlap with autoimmune ILDs (such as systemic sclerosis or inflammatory myopathy). Antibodies to aminoacyl-tRNA synthetase antigens (anti-Jo-1, anti-PL-7, anti-PL-12) are detected in 25–30% of patients with progressive disease, supporting the immune-mediated nature of NSIP pathogenesis.

3. Role of Inflammatory Mediators

Recent investigations have identified serum IL-6 concentrations above 10 pg/mL and TGF-β above 15 ng/mL as independent predictors of FVC decline within 12 months of follow-up. Elevated CXCL13 and YKL-40 levels are associated with enhanced fibroblast activation and poorer overall survival.

These data highlight that a pro-fibrotic cytokine milieu underlies the transformation from cellular NSIP to fibrotic NSIP, representing a critical step in disease progression.

4. Morphologic and Radiologic Correlations

High-resolution computed tomography (HRCT) findings showing a predominance of fibrotic changes over inflammatory ones (fibrosis-to-ground-glass ratio > 2:1) reliably predict progression. Combining HRCT data with immunologic markers—such as elevated IL-6 and ANA positivity—allows the construction of an integrated risk index for early identification of high-risk patients.

5. Immunoregulatory Therapy

Therapeutic use of anti-IL-6 monoclonal antibodies (tocilizumab) and anti-TGF-β agents (pirfenidone, nintedanib) has shown a significant reduction in FVC decline and fibrotic biomarker levels. However, therapeutic efficacy varies according to baseline immune status, reinforcing the necessity of personalized treatment strategies.

Emerging research suggests that integrating immunologic profiling with radiologic and functional monitoring can refine therapeutic decision-making and improve outcomes in NSIP.

Conclusion

Clinical and immunological predictors play a crucial role in risk stratification and prognosis of NSIP progression. The key adverse prognostic factors include:

• Elevated serum IL-6 and TGF-β levels;

• Presence of ANA and anti-Jo-1 autoantibodies;

- Male sex and age > 55 years;
- Predominant fibrotic pattern on HRCT imaging.

Identifying these markers enables early detection of high-risk patients, optimization of immunosuppressive therapy, and timely initiation of antifibrotic agents. Future prospective studies employing multi-omic biomarker platforms (cytokinomics, transcriptomics, proteomics) are expected to improve predictive accuracy and survival outcomes in patients with NSIP..

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