Title: **Observational Study of Clinical Features and Outcome of Interstitial Lung Disease with Anti-neutrophil Cytoplasmic Antibody in Chinese Patients**

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Background and Objectives

Anti-neutrophil cytoplasmic antibody (ANCA) is occasionally positive in patients with interstitial lung disease (ILD), including patients with a diagnosis of ANCA-associated vasculitis (AAV) and patients with isolated ANCA-positive idiopathic interstitial pneumonia (IIP). Their clinical and prognostic differences are not well known. The purpose of this study is to investigate the clinical features and long-term outcome of ANCA-positive ILD and assess the difference between microscopic polyangiitis (MPA) associated ILD and isolated ANCA-positive IIP.

Methods

Study Population

Interstitial lung disease patients with anti-neutrophil cytoplasmic antibody.

Criteria

Inclusion Criteria:

- Males and females
- Aged from 18 to 85 years with informed consent
- Have a diagnosis of ILD based on clinical symptoms and radiologic features, with or without histopathologic results
- Have available ANCA testing results during the first visit and follow-up period

Exclusion Criteria:

- Connective tissue disease associated ILD
- ILD induced by drug, environment, or occupational exposure
- Hypersensitivity pneumonitis and sarcoidosis

Group Information

In all the patients with ANCA-positive ILD, those who were diagnosed with MPA according to 2012 Chapel Hill consensus criteria are defined as **MPA-ILD group**,

and patients with isolated ANCA-positivity who did not fulfill the MPA criteria are classified as **ANCA-IIP group**

Data collection

Baseline information at the time of initial diagnosis was obtained and the following items were analyzed:

- demographics information (age, gender)
- clinical course
- clinical symptoms and signs
- laboratory findings (blood and urine routine, liver and renal function tests, erythrocyte sedimentation rate [ESR], C reactive protein [CRP])
- rheumatoid factor
- serologic autoantibodies [ANA, anti-ENA, ANCA, anti-CCP])
- pulmonary function tests (PFTs) (ventilation and diffusion capacity test)
- chest high-resolution computed tomography (HRCT)

ANCA was assessed by indirect immunofluorescence while MPO-ANCA and PR3-ANCA titers were measured by ELISA.

Chest HRCT images were evaluated together by more than two pulmonologists and radiologists blinded to clinical and histopathological information. The HRCT scans were analyzed for the following characteristics: ground-glass opacity, consolidation, reticular pattern, honeycombing, traction bronchiectasis, interlobular septal thickening, curved linear opacity, pleural thickening, etc.

The patients were followed up at least once a year and basic laboratory tests, serologic autoantibodies, PFT and chest HRCT were evaluated routinely. The follow-up period ended in April 2019 and the outcomes were defined as death from all causes and lung transplantation.

Statistical Analysis Plan

All data are analyzed using statistical analysis software (version 24.0, SPSS, IBM

Corporation). Normally distributed variables are presented as means ± SD, and Student t test is used for comparisons. Continuous, non-normally distributed data are presented as median with interquartile ranges (IQR), and the Mann-Whitney U test is used for comparisons. Categorical variables are expressed as number (%), and $\chi 2$ test or Fisher's exact test is used for comparisons. Survival analysis is performed by Kaplan-Meier analysis using log-rank test. Cox models are used to examine the association between baseline characteristics and mortality. *P* values are two-sided, and $P < 0.05$ is considered statistically significant.