Idiopathic pulmonary fibrosis associated with circulating autoantibodies: a Chinese cohort of a long-term follow-up study

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The term of interstitial pneumonia with autoimmune features (IPAF), based on a combination of clinical, serological, and morphological domains (specific chest imaging features, histopathological features, or multi-compartment involvement, including non-specific interstitial pneumonia [NSIP], organizing pneumonia, NSIP with organizing pneumonia overlap and lymphoid interstitial pneumonia), is proposed to describe patients with interstitial lung disease (ILD) and clinical features indicative of connective tissue disease (CTD) but not meeting established CTD classification criteria.[1] However, the usual interstitial pneumonia (UIP) pattern in chest high-resolution computed tomography (HRCT) is not included in IPAF morphological domain, thereby patients with UIP and positive autoantibodies without one of the seven symptoms in the IPAF clinical domain were excluded from IPAF and presumably are considered to have “idiopathic pulmonary fibrosis (IPF).”[2] Long-term follow-up studies are lacking now, particularly, few studies had described clinical characteristics and radiologic appearances of IPF patients with positive antibodies with or without extrapulmonary syndromes. As autoantibodies are present in about 22% of patients with IPF,[2] do the positive autoantibodies have clinical significance? Or do IPF patients with positive or negative autoantibodies have similar disease behaviors or survival outcomes? It is necessary to conduct a long-term follow-up study in patients with IPF with or without antibodies. We conducted this 9-year retrospective study in an ILD center of China to compare clinical characteristics, radiological findings, and long-term transplant-free survival between IPF patients with or without autoantibodies.

The diagnosis of IPF was established in accordance with the 2018 guideline by a multidisciplinary team consisting of an experienced respiratory physician, a radiologist, a rheumatologist, and if necessary, a pathologist.[3] Briefly, the diagnostic criteria were composed of the following items: (1) exclusion of other known causes of ILD, and either (2) or (3); (2) the presence of UIP pattern in HRCT not subjected to surgical lung biopsy; (3) specific combinations of HRCT and histopathology patterns in patients subjected to lung tissue sampling. UIP pattern on HRCT was characterized by the presence of subpleural, basal predominance, honeycombing, and reticular opacities with or without traction bronchiectasis.[3]

Electronic medical records of patients diagnosed with IPF were retrospectively reviewed at the Department of Pulmonary and Critical Care Medicine, Nanjing University Medical School Affiliated Drum Tower Hospital, from October 2010 to October 2019. This study was approved by the Ethics Committee of Nanjing Drum Tower Hospital (No. 31/93, 84/93, 29/01). Clinical information was collected at admission, including demographics, smoking history, clinical symptoms, lab parameters, and serological autoantibodies. Chest HRCT scans and pulmonary function tests were performed at admission. Treatment information was recorded. Patients were classified based on the presence or absence of circulating antibodies. All patients were informed to re-visit regularly every 3–6 months. Transplant-free survival was defined as the interval from the date of diagnosis to lung transplantation, or death of all causes, or the last day of follow-up. Survival status was obtained from telephone interviews and medical records. The follow-up time was censored on December 31, 2019.

The comparisons of baseline characteristics and treatments were made by independent t test or Mann-Whitney U test for continuous variables and χ² or Fisher exact test for categorical data presented as n (%). All P values were two-tailed, with statistical significance set at $P<0.05$. Linear mixed models were used to analyze pulmonary function...
change. Kaplan-Meier curves with log-rank tests were conducted to assess the correlations between transplant-free survival and autoantibodies. Statistical analyses were performed using IBM SPSS, version 22.0 (IBM Corp., Armonk, NY, USA).

There were 222 patients with a diagnosis of IPF enrolled in the study, including 203 (91.44%) males and 19 (8.56%) females with the mean age of 67.85 ± 8.44 years (range: 37–88 years old), and 126 (56.76%) of them had a smoking history [Supplementary Table 1, http://links.lww.com/CM9/A805]. Sixty-six (29.73%) patients were with positive autoantibodies and 156 (70.27%) patients were with negative autoantibodies. The most common antibody was the positivity of antinuclear antibodies (ANAs) (n = 35, 53.03%), followed by rheumatoid factors (n = 21, 31.82%) and anti-neutrophil cytoplasmic antibodies (ANCAs) (n = 10, 15.15%).

The serum level of immunoglobulin G (IgG) (15.55 ± 5.01 g/L vs. 13.32 ± 3.89 g/L, P = 0.025) and erythrocyte sedimentation rate (ESR) (24.50 [12.75, 50.50] mm/h vs. 19.00 [9.00, 38.50] mm/h, P = 0.049) in patients with positive antibody was significantly higher [Supplementary Table 1, http://links.lww.com/CM9/A805] and the presence of traction bronchiectasis was more frequent (21.15% vs. 9.09%, P = 0.034) in patients with negative antibody compared with patients with positive antibody. The baseline pulmonary function data or the decline rate had no significant differences between the two groups and the treatment information also had no significant differences (all P > 0.05) [Supplementary Table 2, http://links.lww.com/CM9/A805]. The median follow-up time was 44.57 months. There were three patients receiving lung transplantation (two patients with antibodies and one without antibodies). Ninety-five (95/222, 42.79%) patients died during the follow-up. In patients with positive antibodies, 27 (40.91%) died and the median transplant-free survival time was 18.50 (6.00, 44.25) months. In patients without antibodies, 68 (43.59%) died and the median transplant-free survival time was 17.00 (8.00, 49.75) months. The transplant-free survival had no significant differences between the two groups (P = 0.238) [Figure 1].

The clinical significances of circulating autoantibodies in IPF have been discussed for many years. In our study, the frequency of circulating autoantibodies in IPF was 29.73%. Similarly, the frequency of circulating autoantibodies in IPF was reported at 22% and ANA was the most common autoantibody. The study from Collins et al[4] showed that some patients with ILD with positive autoantibodies did have symptoms with an autoimmune flavor, such as esophageal dysmotility, muscle aches, pain, and some weaknesses that were not included in the proposed clinical domain of IPAF. Although future long-term clinical observations are still needed, the limited clinical domain in IPAF should be considered being broadened.

IgG autoantibodies were reported as key contributors to the pathology in some immune-induced diseases. IgG constant fragments had important pro-inflammatory activities and were associated with adaptive and innate immune responses. IgG could promote innate humoral immune responses through complement component C1q-dependent activation of the classical complement pathway and activate innate immune cells by binding to Fcγ receptors.[5] Our study showed that patients with positive antibodies had increased levels of IgG and ESR. Further study should investigate the exact immune processes participating in the pathogenesis of IPF.

Several studies showed that the most common HRCT pattern in patients with IPAF was NSIP. The study from Collins et al[4] showed that UIP was observed in all IPF patients with negative CTD serologies and most ILD patients with positive CTD serologies (75%). To be considered as having IPAF, patients with UIP pattern need to have at least one feature from the other two domains. It is difficult to use IPAF morphological domain to explain why the majority of patients with ILD with positive autoantibodies had the pattern of UIP whereas IPAF was defined as “interstitial pneumonia with autoimmune features.” When we compared HRCT findings between IPF patients with or without antibodies, traction bronchiectasis was more frequent in IPF patients without antibodies. More detailed pathological analysis should be performed to compare differences between IPF patients with or without antibodies.

Consistent with a previous study from Collins et al,[4] we did not find significant differences in pulmonary function decline between IPF patients with or without antibodies. A majority of UIP patterns may explain that no significant differences were observed among the four groups (IPAF, CTD-ILD, IPF, and autoimmune ILD) in the study from Raghu et al.[3] Similarly, a study comprising 61 patients with IPF reported that the decline rates of either absolute or percentage of predicted forced vital capacity (FVC) or
diffusion capacity of the lung for carbon monoxide (DLCO) were not associated with autoantibody status.\[^{6}\] The study showed that patients with non-UIP had improvement in FVC over 1 year compared with worsening or no change among patients with UIP or IPF,\[^{6}\] indicating a pattern of ILD had a larger effect on the clinical course than a specific diagnosis.

Several studies reported that IPF had significantly shorter survival compared with CTD-UIP. A study by Ahmad et al\[^{7}\] did not show a significant difference in 1-year and 2-year survival among patients with IPAF and IPF regardless of patterns of the disease. The validated study from Oldham et al\[^{8}\] also failed to find an association between UIP and increased mortality among patients with IPAF, implicating that outcome of patients depended on how ILD with autoimmune characteristics was defined. Ghang et al\[^{9}\] showed that ANCA or autoantibodies in IPF patients were associated with better outcomes. Longer follow-up studies are still needed to investigate the correlations of circulating antibodies with prognosis in IPF.

There were several limitations to this study. Firstly, most of the patients were confirmed the diagnosis by a combination of clinical characteristics and typical HRCT presentations, whereas few patients were performed a biopsy, which limited our abilities to compare the pathological differences in patients with or without antibodies. Further, due to the retrospective nature, the pulmonary functions of patients were not followed up at a uniform time. Therefore, we adopted linear mixed-effects model that could be a way to take such a data processing.

### Funding

This study was supported by the National Natural Science Foundation of China (No. 82170076) and the Jiangsu Provincial Medical Talent (No. ZDRCA2016058).

### Conflicts of interest

None.

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How to cite this article: Wang H, Chen H, Liu Y, Yan X, Gao Y, Cai H, Dai J. Idiopathic pulmonary fibrosis associated with circulating autoantibodies: a Chinese cohort of a long-term follow-up study. Chin Med J 2022;135:216–218. doi: 10.1097/CM9.000000000001834