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Clinical significance of anti-neutrophil cytoplasmic antibody in idiopathic interstitial pneumonia: a retrospective observational study

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Abstract

Background Patients with anti-neutrophil cytoplasmic antibody (ANCA)-positive interstitial lung disease (ILD) but without evidence of systemic vasculitis have been reported in studies and are classified as isolated ANCA-positive idiopathic interstitial pneumonia (IIP). However, the clinical significance of ANCA, particularly myeloperoxidase (MPO) -ANCA in IIP remains poorly understood. This study aims to investigate the differences between ANCA-positive and ANCA-negative IIP patients and further explore the impact of MPO-ANCA on clinical manifestations and prognostic outcomes.

Methods We reviewed 408 ILD patients with available ANCA results from January 2012 to September 2021. 61 patients diagnosed with microscopic polyangiitis-associated ILD were not included in the analysis. A comparative analysis was performed between 61 isolated ANCA-positive IIP patients (ANCA-IIP group) and 286 ANCA-negative IIP patients (IIP group). We further conducted subgroup analyses based on the status of MPO-ANCA.

Results Baseline clinical characteristics, pulmonary function tests, radiological features and all-cause mortality were similar between ANCA-IIP and IIP groups. When comparing the MPO-ANCA-IIP group with the IIP group and the non-MPO-ANCA-IIP group separately, a higher proportion of fibrotic features was observed on imaging ($P=0.004$ vs IIP group; $P=0.031$ vs non-MPO-ANCA-IIP group). After one year of treatment, the MPO-ANCA-IIP group showed a significantly greater decline in pulmonary function parameters compared to both the IIP group and the non-MPO-ANCA-IIP group. The frequency of pulmonary function decline was significantly higher in the MPO-ANCA-IIP group compared to the non-MPO-ANCA-IIP group ($P=0.026$). Additionally, MPO-ANCA was not found to be statistically associated with mortality among patients with IIP.

Conclusion ANCA-IIP patients had similar clinical characteristics and prognoses with IIP patients. MPO-ANCA-IIP patients had more prominent fibrosis on imaging and a greater decline in pulmonary function following treatment. Special attention should be paid to MPO-ANCA positivity during the diagnosis and treatment of IIP patients.

Trial registration ClinicalTrials.gov: NCT04413149, May 2020.

Keywords Idiopathic interstitial pneumonia, ANCA, MPO-ANCA, Pulmonary function progression

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Background

Anti-neutrophil cytoplasmic antibodies (ANCAs) are a family of autoantibodies that target antigens within the cytoplasmic granules of neutrophils and the lysosomes of monocytes [1]. ANCA-associated vasculitis (AAV) refers to a category of systemic, necrotising vasculitides that predominantly affect small vessels [2]. Since at least 1990, interstitial lung disease (ILD) has been increasingly recognised as a significant pulmonary manifestation of AAV, particularly in microscopic polyangiitis (MPA) [3–6]. Over the past two decades, cases have been reported about patients with ILD and ANCA positivity without extrapulmonary manifestations or histopathological evidence of vasculitis. Anti-myeloperoxidase (MPO)-ANCA is the most prevalent subtype in these cases [7–16].

Several hypotheses have been proposed to explain the association between ANCA, particularly MPO-ANCA, and ILD. For instance, MPO-ANCA may directly contribute to the pathogenesis of lung fibrosis. Specifically, oxidative products generated by MPO activation, as well as proteolytic enzymes and neutrophil extracellular traps (NETs) released from ANCA-activated neutrophils, can promote fibroblast proliferation, differentiation and extracellular matrix deposition [17–19]. Conversely, ANCA might be induced by various pathological stimuli such as tobacco smoke exposure, infections, and other chronic inflammation processes [20–22]. This could explain the emergence of ANCA following the onset of ILD in predisposed individuals, where localized production of MPO-ANCA could lead to the development of AAV.

Most studies about isolated ANCA-positive ILD patients focused on idiopathic pulmonary fibrosis (IPF) patients. Previous large cohort studies have shown that the prevalence of ANCA positivity in patients initially diagnosed with IPF ranges between 4–36% for MPO-ANCA and 2–4% for proteinase 3 (PR3)-ANCA [7–13]. During follow-up, 13.8 to 25% of ANCA-positive IPF patients subsequently developed clinical manifestations of systemic vasculitis [7, 8, 12, 13]. ANCA-positive IPF without evidence of systemic involvement is predominantly observed in patients older than 65 years and is frequently accompanied by nonspecific symptoms such as cough, dyspnea, and fever. Studies by Nozu et al. [10] and Liu et al. [11] reported no significant difference in survival between ANCA-positive IPF and ANCA-negative IPF, whereas Kagiyama et al. [12] observed a higher mortality rate among patients with ANCA-positive IPF compared to those with ANCA-negative IPF. Additional evidence also supports that p-ANCA/MPO-ANCA positivity may serve as an important predictor for the progression of usual interstitial pneumonia towards systemic vasculitis in IPF patients [23, 24].

Previous studies have also identified isolated ANCA-positive patients in non-IPF types of idiopathic interstitial pneumonia (IIP) [14–16, 25, 26]. Our prior data [15] demonstrated that patients with isolated ANCA-positive IIP exhibit lower erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels, as well as a more favourable prognosis compared to patients with MPA-associated ILD. ANCA-positive IIP patients differ from those with interstitial pneumonia with autoimmune features (IPAF), as our findings indicated a more pronounced decline in lung function and a higher mortality rate among ANCA-positive IIP patients [27, 28]. However, ANCA-positive IIP patients are still classified as IIP based on the current criteria [29], and no studies have directly compared the clinical and prognostic differences between ANCA-positive IIP and ANCA-negative IIP. Additionally, due to limitations in sample size, studies comparing MPO-ANCA positivity with other types of ANCA positivity in IIP patients are scarce. To address these gaps, our study aimed to investigate the distinctions between ANCA-positive IIP and ANCA-negative IIP patients and further assess the impact of MPO-ANCA on clinical and prognostic characteristics.

Methods

Study population

We retrospectively reviewed consecutive patients who had been diagnosed with ILD at Peking Union Medical College Hospital (PUMCH) between January 2012 and September 2021. To be included in this study, patients were required to 1. have a diagnosis of ILD based on clinical symptoms and radiologic features, with or without histopathologic results [30]. Radiological features in chest high-resolution computed tomography (HRCT) include diffuse ground-glass opacities, reticular opacities or consolidation, with or without honeycombing and traction bronchiectasis. 2. have available ANCA testing results during the first visit and follow-up period. Patients with ILD secondary to connective tissue disease (CTD), IPAF, drug, environment, or occupational exposure, hypersensitivity pneumonitis, and sarcoidosis were excluded from the study. ANCA tests were performed at the central laboratory of PUMCH and ANCA was assessed by indirect immunofluorescence (IIF), while MPO-ANCA and PR3-ANCA titers were measured by ELISA [31]. According to the laboratory testing standards of our hospital, pANCA and cANCA were defined as positive if their titers were equal to or greater than 1:10. MPO-ANCA or PR3-ANCA titers greater than 20RU/ml were defined as positive. Patients were classified into different groups based on their diagnoses: (1) Patients who were ANCA-positive (either by IIP or ELISA) and diagnosed with MPA according to 2022 ACR/EULAR classification

criteria were defined as the MPA-ILD group [32], which were not included in this analysis according to our study objectives. (2) ILD patients with isolated ANCA positivity (either by IIP or ELISA) were classified into the ANCA-IIP group. (3) Patients who did not meet any of these criteria were classified into the IIP group. In the ANCA-IIP group, patients were further divided into the MPO-ANCA-IIP and the non-MPO-ANCA-IIP groups based on whether they were positive for MPO-ANCA. Figure 1 presents the flowchart of patient screening and classification for this study.

Data collection

Baseline information at the time of initial diagnosis was obtained, and the following items were analysed: demographic information (age, gender), clinical course, clinical symptoms and signs, laboratory findings (routine blood and urine, liver and renal function tests, ESR, CRP, rheumatoid factor and serologic anti-cyclic citrullinated peptides [anti-CCP]), pulmonary function tests (PFTs), and chest HRCT scans.

Chest HRCT images were evaluated by at least two pulmonologists and radiologists. The HRCT scans were analysed for the following characteristics: ground-glass opacities, reticular patterns, honeycombing and traction bronchiectasis. Fibrosis was described as the presence of honeycombing and traction bronchiectasis; honeycombing and reticular patterns; or traction bronchiectasis and reticular patterns [33].

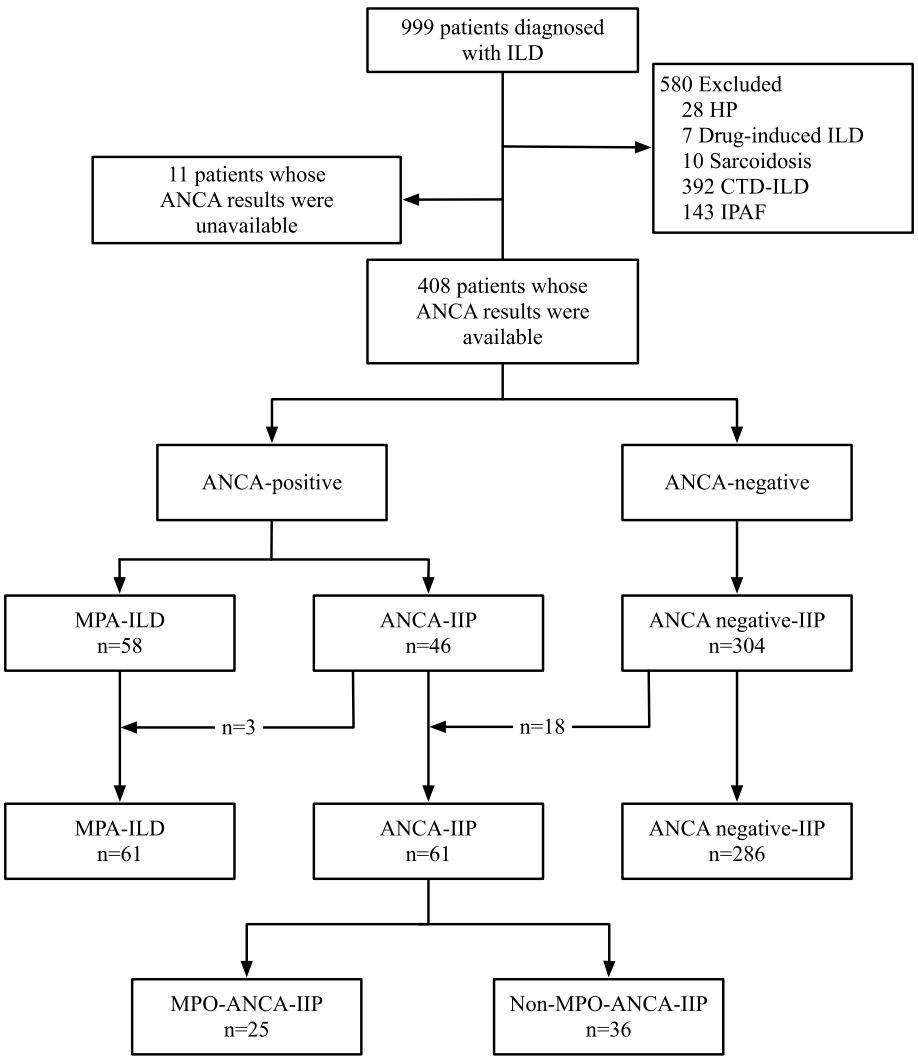

Fig. 1 Flowchart of the study. Flowchart illustrating the selection of patients with ANCA-IIP and IIP. ILD, interstitial lung disease; HP, Hypersensitivity pneumonitis; CTD, connective tissue disease; ANCA, anti-neutrophil cytoplasmic antibody; IIP, idiopathic interstitial pneumonia; IPAF, interstitial pneumonia with autoimmune features; MPA, microscopic polyangiitis

PFTs were performed according to standardised guidelines. Results of the PFTs were expressed as percentages of the predicted values and were adjusted for age, gender, and body weight. The baseline PFT was performed at the time of diagnosis and a follow-up PFT was performed within 12 ±3 months post-treatment. Patients were therefore divided into three groups based on absolute changes in forced vital capacity (FVC)% predicted and diffusing capacity of lung for carbon monoxide (DLco)% predicted (corrected for haemoglobin): pulmonary function progression (either FVC decline ≧5% predicted or DLco decline ≧10% predicted) [30]; pulmonary function improvement (FVC improvement ≧5% predicted and DLco improvement ≧10% predicted); pulmonary function stable (FVC decline or improvement < 5% predicted or DLco decline or improvement < 10% predicted).

Treatment regimens were recorded. Corticosteroids were graded according to the dose administered at the time of diagnosis. The medium dose was defined as ≥ 0.5 mg/kg prednisone equivalent per day but < 1 mg/kg prednisone equivalent per day; the high dose was defined as ≥ 1 mg/kg prednisone equivalent a day, and if it exceeded ≥ 250 mg prednisone equivalent a day for one or a few days, it was considered pulse therapy [34–36].

Patients were scheduled for outpatient follow-up visits at Month 3, Month 6, and Month 12 post-diagnosis according to the follow-up protocol established in PUMCH. During these follow-up visits, routine laboratory tests, ANCA tests, assessment of extrapulmonary involvement, PFTs and chest HRCT were performed. For patients who achieve disease stability, follow-up intervals were gradually extended to once per year. The follow-up period ended in September 2022, and the outcomes were defined as death from any cause.

The informed consent for the utilisation of medical records was obtained from each patient and/or their legal guardian upon admission to the hospital. This study was approved by the Peking Union Medical College Hospital Institutional Review Board (Reference number: S-634).

Statistical analysis

All data were analysed using SPSS software version 26.0 and GraphPad Prism software version 8. Normally distributed variables are presented as the means ± SDs, and Student's t-test was used for comparisons. Continuous, non-normally distributed data are presented as medians with interquartile ranges (IQRs), and the Mann–Whitney U test was used for comparisons. Categorical variables are expressed as numbers (%), and the $\chi 2$ test or Fisher's exact test was used for comparisons. Survival analysis was performed by Kaplan–Meier analysis using the log-rank test. P values are two-sided, and $P < 0.05$ was considered statistically significant.

Results

A total of 999 patients were diagnosed with ILD, among whom 408 had available ANCA testing results. At first diagnosis, 104 patients were ANCA-positive, composed of 58 patients in MPA-ILD group and 46 patients in ANCA-IIP group. 304 patients with ANCA-negative IIP were included in the IIP group. During follow-up, 18/304 (5.9%) patients with IIP converted to ANCA positive. 3 patients in the ANCA-IIP group developed MPA and were reclassified into the MPA-ILD group. By September 2022, 61 patients with ANCA-IIP and 286 patients with IIP were analysed. Among the 61 ANCA-IIP patients, 25 were MPO-ANCA positive, which were classified as the MPO-ANCA-IIP group. The other 36 patients were classified as the non-MPO-ANCA-IIP group (Fig. 1).

Comparison between ANCA-IIP and IIP patients

Baseline characteristics were compared between the ANCA-IIP and IIP groups (Table 1 and Table 2). There were no significant differences in age or gender between the two groups. ANCA-IIP group had a significantly lower frequency of smoke (16.4% vs 35.0%, $P = 0.005$), but a higher frequency of arthralgia compared with the IIP group (19.7% vs 7.7%, $P = 0.004$). There were no differences in other symptoms, signs, and laboratory tests. The major HRCT features of ANCA-IIP patients included ground-glass opacities (90.2%), reticular patterns (59.0%) and traction bronchiectasis (34.4%). The frequencies of ground-glass opacities (90.2% vs 73.1%, $P = 0.005$) and traction bronchiectasis (34.4% vs 21.7%, $P = 0.034$) tended to be higher in the ANCA-IIP group. Non-usual interstitial pneumonia (UIP) was the most common radiologic pattern in ANCA-IIP group. There were no significant differences in baseline PFTs or PFT changes during follow-up between the groups (Table 2, Fig. 2a).

Patients in ANCA-IIP group received individual-based treatment involving rheumatologists and respirologists. Compared with IIP group, the proportions of glucocorticoids (85.2% vs 71.7%, $P = 0.028$) and cyclophosphamide (23.0% vs 10.8%, $P = 0.011$) administration were significantly higher in ANCA-IIP group. Only 9.8% of the patients in ANCA-IIP group received anti-fibrotic therapy. During the follow-up period, all-cause mortality was 18.0% in the ANCA-IIP group and 21.0% in the IIP group, with no statistically significant difference (Table 2).

Comparison between MPO-ANCA-IIP and IIP patients

Patients in ANCA-IIP group were further divided into the MPO-ANCA-IIP group and the non-MPO-ANCA-IIP group based on the presence of MPO-ANCA positivity. Comparisons between the MPO-ANCA-IIP and IIP groups are summarised in sTable 1 and

Table 1 Demographic, Clinical, and Serologic Characteristics of ANCA-IIP and IIP

Characteristic	ANCA-IIP ($n = 61$)	IIP($n = 286$)	*P* -value
Age, y	60.00 (50.00,68.00)	58.50 (50.00,66.00)	0.328
Sex, male	29 (47.5)	156 (54.5)	0.319
Former or current smoker	10 (16.4)	100 (35.0)	0.005
Follow-up time, months	64.00 (43.00,83.50)	62.50 (37.75,87.00)	0.923
Symptoms			
Fever	14 (23.0)	78 (27.3)	0.488
Cough	46 (75.4)	215 (75.2)	0.969
Fatigue	8 (13.1)	44 (15.4)	0.652
Arthralgia	12 (19.7)	22 (7.7)	0.004
Signs			
Rash	7 (11.5)	19 (6.6)	0.188
Mechanics hand	5 (8.2)	9 (3.1)	0.079
Gottron's sign	3 (4.9)	12 (4.2)	0.734
Laboratory findings			
WBC,10^9/L	6.68 (5.90,9.04)	7.33 (6.01,9.21)	0.516
NE,10^9/L	4.54 (3.40,6.43)	4.61 (3.55,6.18)	0.780
PLT,10^9/L	237.00 (175.50,287.00)	225.00 (185.50,295.25)	0.976
ESR, mm/h	19.00 (8.00,44.00)	16.00 (8.00,37.25)	0.397
Hs-CRP, mg/dL	2.22 (0.85,7.87)	3.85 (1.23,11.91)	0.085
ANCA			
c-ANCA	9 (14.8)	-	-
p-ANCA	47 (77.0)	-	-
MPO-ANCA	25 (41.0)	-	-
PR3-ANCA	8 (13.1)	-	-
anti-CCP positive	1 (1.6)	4 (1.4)	1.000
RF positive	10 (16.4)	27 (9.4)	0.080

Data are presented as the medians (IQRs), means ± SDs or No. (%)

ANCA anti-neutrophil cytoplasmic antibody, *IIP* idiopathic interstitial pneumonia, *WBC* white blood cell, *PLT* platelet, *ESR* erythrocyte sedimentation rate, *Hs-CRP* hypersensitivity-C reactive protein, *MPO* myeloperoxidase, *PR3* proteinase 3, *anti-CCP* anti-cyclic citrullinated peptide antibody, *RF* rheumatoid factor

sTable 2, Additional file 1. No significant differences were observed in clinical symptoms, signs, and laboratory tests. Traction bronchiectasis (44.0% vs 21.7%, $P = 0.012$) and fibrotic features (52.0% vs 25.2%, $P = 0.004$) were more frequently seen in patients in MPO-ANCA-IIP group. As for PFTs, MPO-ANCA-IIP patients had significantly higher levels of baseline %FEV1 (87.40% vs 78.00%, $P = 0.017$) and %FVC (87.40% vs 77.10%, $P = 0.031$) than IIP patients. 48.0% (12/25) of MPO-ANCA-IIP patients and 38.1% (109/286) of IIP patients had follow-up PFTs. The follow-up PFTs showed that the pulmonary functions in the IIP group were improved after one year of treatment, while the pulmonary functions in the MPO-ANCA-IIP groups continually deteriorated compared to the baseline data. Accordingly, we found a significant decline of ΔFEV1% (−5.43 vs 1.81, $P = 0.027$), ΔFVC% (−6.71 vs 3.87, $P = 0.006$), ΔTLC% (−6.13 vs 1.32, $P = 0.047$) and ΔDL_{CO}% (−8.77 vs 1.33, $P = 0.015$) in the MPO-ANCA-IIP group (sTable 2, Fig. 2a).

Comparison between MPO-ANCA-IIP and Non-MPO-ANCA-IIP patients

To further assess the impact of MPO-ANCA in IIP patients, we compared the MPO-ANCA-IIP group with the non-MPO-ANCA-IIP group (Table 3 and Table 4). Median age (64.00 vs 60.00, $P = 0.533$) and the proportion of males (52.0% vs 44.4%, $P = 0.561$) were not significantly different between the two groups. The frequency of cough was higher in the non-MPO-ANCA-IIP group (86.1% vs 60.0%, $P = 0.020$).

On imaging, 52.0% of the patients in MPO-ANCA-IIP group had fibrosis characteristics on HRCT, which was higher than that of non-MPO-ANCA-IIP group. Comparative analysis of PFTs revealed significantly higher levels of %FEV1 (87.40% vs 75.75%, $P = 0.034$) in the MPO-ANCA-IIP group. Treatment regimens were comparable between groups. Again, after 1-year of follow-up, we found significantly lower levels of ΔFEV1% (−5.43 vs 2.02, $P = 0.016$), ΔFVC% (−6.71 vs 4.09, $P = 0.004$), ΔTLC% (−6.13 vs 3.57, $P = 0.020$)

Table 2 Radiologic features and Pulmonary function test of ANCA-IIP and IIP

Characteristic	ANCA-IIP ($n = 61$)	IIP($n = 286$)	*P* -value
HRCT Abnormalities			
Ground-glass opacity	55 (90.2)	209 (73.1)	0.005
Traction bronchiectasis	21 (34.4)	62 (21.7)	0.034
Honeycombing	10 (16.4)	48 (16.8)	0.941
Reticular pattern	36 (59.0)	169 (59.1)	0.991
Fibrosis[a]	22 (36.1)	72 (25.2)	0.082
HRCT patterns			
UIP	9 (14.8)	41 (14.3)	0.933
Non-UIP			
NSIP	36 (59.0)	112 (39.2)	0.004
OP	1 (1.6)	31 (10.8)	0.024
NSIP with OP overlap	0 (0)	3 (1.0)	1.000
Unclassifiable	15 (24.6)	99 (34.6)	0.130
Pulmonary function tests			
Baseline FEV1, % predicted	80.60 (6.10,94.00)	78.00 (64.40,90.90)	0.209
Baseline FVC, % predicted	82.50 (68.30,93.80)	77.10 (62.30,91.10)	0.129
Baseline TLC, % predicted	73.80 (65.80,85.25)	73.30 (59.20,83.50)	0.293
Baseline DL_{CO}, % predicted	60.00 (47.20,69.40)	56.30 (43.00,70.25)	0.317
ΔFEV1, % predicted [b]	−0.61 ± 8.82	1.81 ± 10.92	0.243
ΔFVC, % predicted [b]	0.28 ± 11.01	3.87 ± 12.74	0.143
ΔTLC, % predicted [b]	0.33 ± 10.9	1.32 ± 11.34	0.675
ΔDL_{CO}, % predicted [b]	−0.89 ± 11.89	1.33 ± 12.99	0.390
pulmonary function progression [b]	11 (32.3)	32 (29.3)	0.740
Pulmonary function stable [b]	19 (55.9)	56 (51.4)	0.646
Pulmonary function improvement [b]	4 (11.8)	21 (19.3)	0.315
Treatment			
Corticosteroids	52 (85.2)	205 (71.7)	0.028
Medium dose	17 (27.9)	59 (20.6)	0.191
High dose	34 (55.7)	144 (50.3)	0.445
Cyclophosphamide	14 (23.0)	31 (10.8)	0.011
Other immunosuppressants [c]	3 (4.9)	22 (7.7)	0.591
Anti-fibrosis [d]	6 (9.8)	36 (12.6)	0.550
None [e]	10 (16.4)	25 (8.7)	0.068
Death of all cause	11 (18.0)	60 (21.0)	0.605

Data are presented as the medians (IQRs), means ± SDs or No. (%)

ANCA anti-neutrophil cytoplasmic antibody, *IIP* idiopathic interstitial pneumonia, *HRCT* high resolution computed tomography, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *TLC* total lung capacity, DL_{CO} diffusing capacity of lung for carbon monoxide

[a] Fibrosis was radiologically defined as the presence of honeycombing and traction bronchiectasis; honeycombing and reticular patterns; or traction bronchiectasis and reticular patterns

[b] ANCA-IIP: $n = 34$; IIP: $n = 109$

[c] Other immunosuppressants include tacrolimus, azathioprine, mycophenolate mofetil, methotrexate, hydroxychloroquine, and tripterygium wilfordii

[d] Anti-fibrosis include nintedanib and pirfenidone

[e] None represents not receiving anti-inflammatory and anti-fibrotic therapy

and ΔDL_{CO}% (−8.77 vs 3.24, $P = 0.005$) in the MPO-ANCA-IIP group compared with that in the non-MPO-ANCA-IIP group (Table 4, Fig. 2a). Additionally, the incidence of pulmonary function progression was significantly higher in the MPO-ANCA-IIP group than in the non-MPO-ANCA-IIP group (58.3% vs 18.2%, $P = 0.026$), whereas the proportion of pulmonary function improvement was lower than that in the non-MPO-ANCA-IIP group (0% vs 18.2%, $P = 0.273$) (Table 4, Fig. 2b).

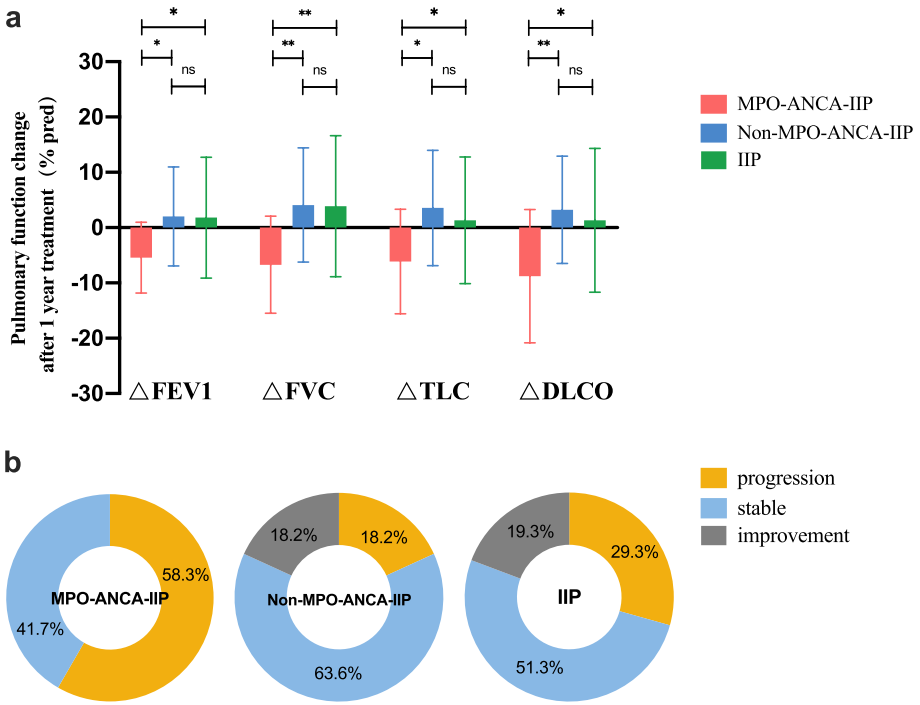

Fig. 2 Changes in pulmonary function and incident of pulmonary function decline after 1 year of treatment. **a** A greater decline in %FEV1, %FVC, %TLC and %DL_{CO} was observed in MPO-ANCA-IIP group than non-MPO-ANCA-IIP group and IIP group. No statistical differences were observed between non-MPO-ANCA-IIP group and IIP groups. **b** The proportion of pulmonary function progression at 1-year follow-up in MPO-ANCA-IIP group was higher than non-MPO-ANCA-IIP group and IIP group. The proportion of pulmonary function improvement was lower in the MPO-ANCA-IIP group. ANCA, anti-neutrophil cytoplasmic antibody; IIP, idiopathic interstitial pneumonia; MPO, myeloperoxidase; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; TLC, total lung capacity; DL_{CO}, diffusing capacity of lung for carbon monoxide. $^{*}P < 0.05$ $^{**}P < 0.01$ ns, not significant

Outcomes

The survival time during the follow-up period was analysed using the Kaplan–Meier curve. We observed no statistical difference in the overall survival rate in the comparison between ANCA-IIP and IIP groups ($p = 0.592$ by log-rank test) (Fig. 3a). Patients in the non-MPO-ANCA-IIP group tended to have better survival rates than those in the MPO-ANCA-IIP group, with no statistical difference in log-rank test (Fig. 3b).

Discussion

This study analysed the differences in clinical and prognostic characteristics between ANCA-IIP and IIP patients and focused on the significance of MPO-ANCA positivity in IIP by comparing MPO-ANCA-IIP with non-MPO-ANCA-IIP. Key findings include: (1) Most baseline characteristics, including demographic, radiologic and pulmonary function features, were similar between the ANCA-IIP and IIP groups. However, a higher proportion of patients in ANCA-IIP received immunosuppressive therapy. In terms of outcomes, we found no statistically significant differences in the incidence of pulmonary function progression or all-cause mortality between the two groups. (2) When comparing the MPO-ANCA-IIP group with both IIP and non-MPO-ANCA-IIP groups, more pronounced fibrotic HRCT features and a greater decline in pulmonary function following treatment were observed in MPO-ANCA-IIP patients.

Based on the classification of IIP published by the American Thoracic Society (ATS) and the European Respiratory Society (ERS) in 2013 [29], ANCA-IIP is categorised within the IIP population. A limited number of studies have described and compared the characteristics of ANCA-IIP patients [14–16, 27]. Consistent with prior studies, our data indicated that ANCA-IIP predominantly affects elderly patients presenting with nonspecific symptoms such as cough, fever, and fatigue, along with restrictive ventilatory dysfunction. Non-UIP was the predominant pattern on HRCT. Our current study further investigated the differences between ANCA-positive IIP and ANCA-negative IIP, revealing that demographic and clinical features were mostly similar between the two groups.

The prognostic implications of ANCA positivity on ILD, particularly IPF, have yielded conflicting results.

Table 3 Comparision of Clinical Characteristics MPO-ANCA-IIP and non-MPO-ANCA-IIP

Characteristic	MPO-ANCA-IIP($n = 25$)	Non-MPO-ANCA-IIP($n = 36$)	*P* -value
Age, y	64.00 (46.00,70.50)	60.00 (53.25,64.00)	0.533
Sex, male	13 (52.0)	16 (44.4)	0.561
Former or current smoker	5 (20.0)	5 (13.9)	0.526
Follow-up time, months	62.00 (29.00,83.00)	65.50 (49.00,85.75)	0.486
Symptoms			
Fever	6 (24.0)	8 (22.2)	0.871
Cough	15 (60.0)	31 (86.1)	0.020
Fatigue	3 (12.0)	5 (13.9)	1.000
Arthralgia	5 (20.0)	7 (19.4)	1.000
Signs			
Rash	3 (12.0)	4 (11.1)	1.000
Mechanics hand	0	5 (13.9)	0.072
Gottron's sign	0	3 (8.3)	0.262
Laboratory findings			
WBC,10^9/L	7.20 (5.65,9.01)	6.65 (5.94,9.09)	1.000
NE,10^9/L	4.71 (3.22,6.10)	4.51 (3.42,6.93)	0.747
PLT,10^9/L	226.00 (173.50,277.50)	252.50 (178.25,290.50)	0.472
ESR, mm/h	16.50 (8.00,58.50)	20.50 (8.00,42.25)	0.780
Hs-CRP, mg/dL	3.79 (0.64,13.09)	1.98 (0.99,4.14)	0.342
ANCA			
c-ANCA	0	9 (22.0)	-
p-ANCA	23 (92.0)	24 (66.7)	-
MPO-ANCA	25 (100)	0	-
PR3-ANCA	3 (12.0)	5 (13.9)	-
anti-CCP positive	1 (4.0)	0	0.400
RF positive	3 (12.0)	7 (19.4)	0.727

Data are presented as the medians (IQRs), means ± SDs or No. (%)

ANCA anti-neutrophil cytoplasmic antibody, *IIP* idiopathic interstitial pneumonia, *WBC* white blood cell, *PLT* platelet, *ESR* erythrocyte sedimentation rate, *Hs-CRP* hypersensitivity-C reactive protein, *MPO* myeloperoxidase, *PR3* proteinase 3, *anti-CCP* anti-cyclic citrullinated peptide antibody, *RF* rheumatoid factor

Previous studies predominantly focused on IPF, with the majority of studies reporting similar outcomes between ANCA-positive and ANCA-negative groups [8, 10, 11]. However, some studies have reported a higher mortality rate among ANCA-positive IPF patients [12]. The impact of ANCA positivity on the prognosis of IIP patients has been less extensively examined. In our study, we found no significant differences in all-cause mortality, which is consistent with previously reported findings in IPF.

Pulmonary function progression is a critical indicator of disease progression and poor prognosis in patients with IPF and can also be observed in various forms of ILDs beyond IPF [37–39]. In our study, 11 out of 34 (32.4%) ANCA-IIP patients exhibited pulmonary function deterioration following one year of treatment. This finding is consistent with a recent retrospective study from Japan, which reported that 35.3% of ANCA-IIP patients experienced pulmonary function decline [40]. No statistically significant differences were noted in PFT changes between the ANCA-IIP and IIP groups. However, among patients with MPO-ANCA positivity, a more pronounced deterioration of pulmonary function was observed compared to the IIP group despite a higher proportion of patients receiving immunosuppressive therapy.

Accumulating evidence from animal models and in vitro studies has demonstrated the direct involvement of MPO-ANCA in the pathogenesis of pulmonary fibrosis. Several hypotheses have been proposed to elucidate the mechanisms [41, 42]. For example, Guilpain et al. [17] introduced the oxidative stress hypothesis, positing that MPO interacts with anti-MPO antibody in vitro to generate oxidation products such as hypochlorous acid. These products subsequently promote fibroblast proliferation and extracellular matrix deposition. Furthermore, neutrophils activated by MPO-ANCA can locally release elastase or form neutrophil extracellular traps, which play a crucial role in the activation and differentiation of lung fibroblasts into myofibroblasts, ultimately leading to lung tissue damage and fibrosis [42–45]. To further

Table 4 Comparision of Radiologic and Pulmonary function features between MPO-ANCA-IIP and non-MPO-ANCA-IIP

Characteristic	MPO-ANCA-IIP($n = 25$)	Non-MPO-ANCA-IIP($n = 36$)	*P* -value
HRCT Abnormalities			
Ground-glass opacity	22 (88.0)	33 (91.7)	0.682
Traction bronchiectasis	11 (44.0)	10 (27.8)	0.190
Honeycombing	5 (20.0)	5 (13.9)	0.526
Reticular pattern	16 (64.0)	20 (55.6)	0.510
Fibrosis[a]	13 (52.0)	9 (22.0)	0.031
HRCT patterns			
UIP	5 (20.0)	4 (11.1)	0.336
Non-UIP			
NSIP	13 (52.0)	23 (63.9)	0.353
OP	0 (0.0)	1 (2.8)	1.000
NSIP with OP overlap	0 (0.0)	0 (0.0)	1.000
Unclassifiable	7 (28.0)	8 (22.2)	0.606
Pulmonary function tests			
Baseline FEV1, % predicted	87.40 (77.80,95.00)	75.75 (66.23,89.15)	0.034
Baseline FVC, % predicted	84.40 (71.80,92.60)	77.10 (61.83,96.30)	0.276
Baseline TLC, % predicted	80.10 (66.25,87.20)	73.10 (64.30,82.03)	0.267
Baseline DL_{CO}, % predicted	62.10 (57.30,76.65)	55.55 (44.33,67.75)	0.098
ΔFEV1, % predicted [b]	−5.43 ± 6.41	2.02 ± 8.96	0.016
ΔFVC, % predicted [b]	−6.71 ± 8.79	4.09 ± 10.33	0.004
ΔTLC, % predicted [b]	−6.13 ± 9.44	3.57 ± 10.42	0.020
ΔDL_{CO}, % predicted [b]	−8.77 ± 12.07	3.24 ± 9.70	0.005
Pulmonary function progression [b]	7 (58.3)	4 (18.2)	0.026
Pulmonary function stable [b]	5 (41.7)	14 (63.6)	0.218
Pulmonary function improvement [b]	0 (0)	4 (18.2)	0.273
Treatment			
Corticosteroids	22 (88.0)	30 (83.3)	0.725
Medium dose	8 (32.0)	9 (25.0)	0.549
High dose	13 (52.0)	21 (58.3)	0.624
Cyclophosphamide	6 (24.0)	8 (22.2)	0.871
Other immunosuppressants [c]	2 (8.0)	1 (2.8)	0.562
Anti-fibrosis [d]	3 (12.0)	3 (8.3)	0.682
None [e]	3 (12.1)	7 (19.4)	0.727
Death of all cause	6 (24.0)	5 (13.9)	0.747

Data are presented as the medians (IQRs), means ± SDs or No. (%)

MPO myeloperoxidase, *ANCA* anti-neutrophil cytoplasmic antibody, *IIP* idiopathic interstitial pneumonia, *HRCT* high resolution computed tomography, *UIP* usual interstitial pneumonia, *NSIP* nonspecific interstitial pneumonia, *OP* organizing pneumonia, *FEV1* forced expiratory volume in 1 s, *FVC* forced vital capacity, *TLC* total lung capacity, DL_{CO} diffusing capacity of lung for carbon monoxide

[a] Fibrosis was radiologically defined as the presence of honeycombing and traction bronchiectasis; honeycombing and reticular patterns; or traction bronchiectasis and reticular patterns

[b] MPO-ANCA-IIP: $n = 12$; Non-MPO-ANCA-IIP: $n = 22$

[c] Other immunosuppressants include tacrolimus, azathioprine, mycophenolate mofetil, methotrexate, hydroxychloroquine, and tripterygium wilfordii

[d] Anti-fibrosis include nintedanib and pirfenidone

[e] None represents not receiving anti-inflammatory and anti-fibrotic therapy

elucidate the differences between MPO-ANCA and non-MPO-ANCA, our study conducted subgroup analyses among 25 MPO-ANCA-IIP patients and 36 non-MPO-ANCA-IIP patients. Our analyses revealed comparable baseline characteristics between the two groups in terms of demographic, symptoms, and laboratory tests results. However, fibrosis features and the proportion of UIP patterns were more prominent in MPO-ANCA-IIP patients. Notably, despite receiving similar treatment, a more significant decline in pulmonary functions was observed

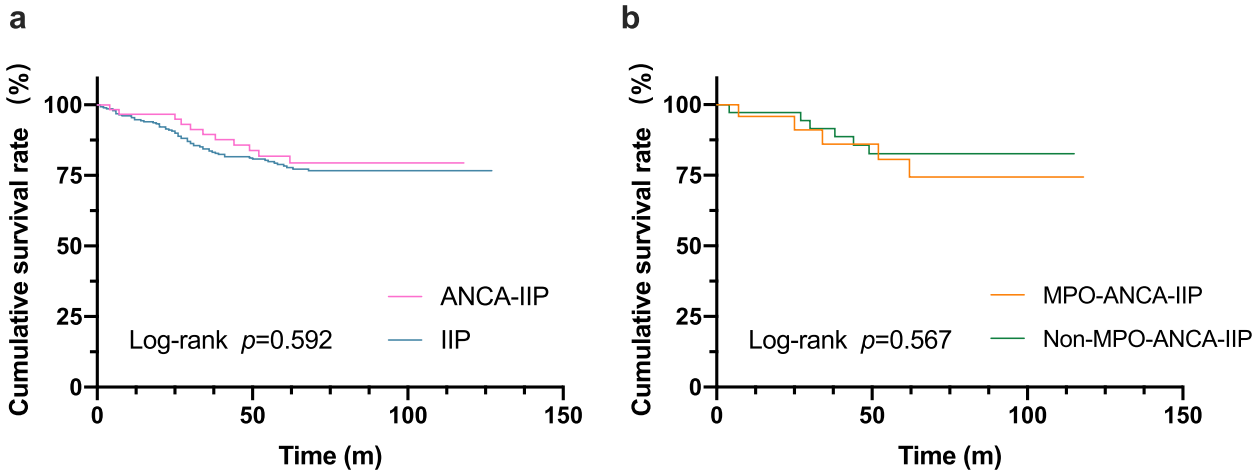

Fig. 3 Kaplan–Meier survival curves. **a** Kaplan–Meier curves comparing survival time in patients with ANCA-IIP versus patients with IIP. $P = 0.592$ by log-rank test. **b** The prognosis of Non-MPO-ANCA-IIP was better than MPO-ANCA-IIP. $P = 0.567$ by log-rank test. ANCA, anti-neutrophil cytoplasmic antibody; IIP, idiopathic interstitial pneumonia; MPO, myeloperoxidase

in the MPO-ANCA-IIP group. Pulmonary function progression was noted in over 50% of MPO-ANCA-IIP patients, while no patients showed improvement, which is lower than in the non-MPO-ANCA-IIP group. Our results are consistent with previous findings and indicate that MPO-ANCA may play a pathogenic role in the progression of pulmonary fibrosis, which could potentially result in a more rapid decline in pulmonary function.

Currently, there is no international consensus on the management of isolated ANCA-positive IIP patients [46], and reported therapeutic regimens vary across studies, ranging from the use of glucocorticoids alone to combination regimens with immunosuppressants such as cyclophosphamide or azathioprine [7, 13, 40]. Several studies have indicated that immunosuppressive therapy may reduce the risk of MPA progression in MPO-ANCA-positive patients initially diagnosed with IPF [8, 12, 13]. Anti-fibrotic agents have been administered to some ANCA-IIP patients with UIP patterns. However, their efficacy remains uncertain. In our study, approximately 85.2% of ANCA-IIP patients received glucocorticoids and cyclophosphamide, while only 9.8% were treated with anti-fibrotic therapy. Nintedanib and pirfenidone, two FDA-approved drugs, have demonstrated the ability to slow the decline in lung function in IPF patients [47], as well as in patients with other progressing fibrosing ILD [30, 48–50]. The INBUILD trial confirmed that nintedanib could slow the rate of FVC decline in patients with progressive fibrosing autoimmune disease related ILDs [48]; however, most of the patients enrolled were diagnosed with rheumatoid arthritis and scleroderma. Our study found that patients with MPO-ANCA-IIP had more prominent fibrotic features on imaging and experienced a significantly greater decline in pulmonary function parameters compared to patients with IIP and Non-MPO-ANCA-IIP. This suggests importance of implementing more proactive therapeutic strategies to mitigate disease progression. Based on the treatment recommendations for ANCA-IIP patients proposed by Thompson et al. and Yamakawa et al. [51, 52], monotherapy with antifibrotic agents (without immunosuppression) may be appropriate for ANCA-IIP patients with UIP pattern, while combination therapy with both immunosuppressants and antifibrotic agents could be potentially beneficial for ANCA-IIP patients with NSIP pattern. In the future, a multidisciplinary approach will be pivotal in managing these patients effectively, and high-quality randomized controlled clinical trials will play an essential role in validating the efficacy of these treatments.

Our study had several limitations. Firstly, this was a single-centre retrospective study. Although our cohort size was relatively large compared to the published literature, it remains limited for drawing a definitive conclusion. Larger, multi-centre studies are necessary to validate our findings. Secondly, variations in treatment regimens may have influenced the survival analyses between groups. Finally, our study did not include histological data to fully assess the extent of lung fibrosis. However, given the ANCA positivity and clinal features indicative of ILD, a lung biopsy may not be essential for histopathological diagnosis.

Conclusions

In conclusion, patients with ANCA-IIP exhibited comparable baseline characteristics and prognosis to those with IIP. However, compared to ANCA-negative IIP patients and non-MPO-ANCA IIP patients, MPO-ANCA-IIP patients had more prominent fibrotic features on imaging and were more likely to experience a decline in pulmonary function following treatment. Therefore, particular attention should be given to MPO-ANCA positivity during the diagnosis and management of IIP patients.

Abbreviations

AAV	Anti-neutrophil cytoplasmic antibody-associated vasculitis
ANCA	Anti-neutrophil cytoplasmic antibody
CCP	Cyclic citrullinated peptide antibody
CRP	C-reactive protein
CTD	Connective tissue disease
DLCO	Diffusing capacity of lung for carbon monoxide
ESR	Erythrocyte sedimentation rate
FEV1	Forced expiratory volume in 1 s
FVC	Forced vital capacity
HRCT	High-resolution computed tomography
IIP	Idiopathic interstitial pneumonia
ILD	Interstitial lung disease
IPAF	Interstitial pneumonia with autoimmune features
IPF	Idiopathic pulmonary fibrosis
MPA	Microscopic polyangiitis
MPO	Myeloperoxidase
NSIP	Nonspecific interstitial pneumonia
OP	Organizing pneumonia
PFT	Pulmonary function test
PR3	Proteinase 3
TLC	Total lung capacity
UIP	Usual interstitial pneumonia

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12890-025-03736-4.

Additional file 1

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Clinical trial registration

This retrospective observational study was first registered in ClinicalTrials.gov in May 2020 and the trial registration number was NCT04413149.

Authors' contributions

Conceptualization, J. Shi, M. Peng; Data curation, X. Sun, W. Zhu, Z. Li, W. Zhang; Formal analysis, X. Sun, W. Zhu, C. Zhou; Funding acquisition, J. Shi; Investigation, X. Sun, W. Zhu, C. Zhou, P. Xue; Methodology, X. Sun, C. Zhou; Project administration, J. Shi; Resources, J. Shi; Software, X. Sun, C. Zhou; Supervision, J. Shi, M. Peng, T. Zhang; Validation, J. Shi; Visualization, X. Sun, C. Zhou, W. Zhu, J. Shi; Writing—original draft, X. Sun, W. Zhu;—Writing—review & editing, C. Zhou, J. Zhao, J. Shi, T. Zhang, M. Peng, C. Wang.

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Data availability

This retrospective observational study was first registered in ClinicalTrials.gov in May 2020 and the trial registration number was NCT04413149. The datasets generated and analysed during the current study are available in the ClinicalTrials repository [https://clinicaltrials.gov/ct2/show/NCT04413149?term=NCT04413149&draw=2&rank=1].

Declarations

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Peking Union Medical College Hospital Institutional Review Board (Reference number: S-634). Written informed consent from study subjects was waived because of the retrospective design.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Falk RJ, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. N Engl J Med. 1988;318:1651–7.
2. Jennette JC, Falk RJ, Bacon PA, Basu N, Cid MC, Ferrario F, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum. 2013;65:1–11.
3. Nada AK, Torres VE, Ryu JH, Lie JT, Holley KE. Pulmonary Fibrosis as an Unusual Clinical Manifestation of a Pulmonary-Renal Vasculitis in Elderly Patients. Mayo Clin Proc. 1990;65:847–56.
4. Sada KE, Yamamura M, Harigai M, Fujii T, Dobashi H, Takasaki Y, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. Arthritis Res Ther. 2014;16:R101–201.
5. Comarmond C, Crestani B, Tazi A, Hervier B, Adam-Marchand S, Nunes H, et al. Pulmonary Fibrosis in Antineutrophil Cytoplasmic Antibodies (ANCA)-Associated Vasculitis: A Series of 49 Patients and Review of the Literature. Medicine. 2014;93:340–9.
6. Hozumi H, Kono M, Hasegawa H, Yasui H, Suzuki Y, Karayama M, et al. Clinical Significance of Interstitial Lung Disease and Its Acute Exacerbation in Microscopic Polyangiitis. Chest. 2021;159:2334–45.
7. Foulon G, Delaval P, Valeyre D, Wallaert B, Debray MP, Brauner M, et al. ANCA-associated lung fibrosis: analysis of 17 patients. Respir Med. 2008;102:1392–8.

8. Hosoda C, Baba T, Hagiwara E, Ito H, Matsuo N, Kitamura H, et al. Clinical features of usual interstitial pneumonia with anti-neutrophil cytoplasmic antibody in comparison with idiopathic pulmonary fibrosis. Respirology. 2016;21:920–6.
9. Tanaka T, Otani K, Egashira R, Kashima Y, Taniguchi H, Kondoh Y, et al. Interstitial pneumonia associated with MPO-ANCA: clinicopathological features of nine patients. Respir Med. 2012;106:1765–70.
10. Nozu T, Kondo M, Suzuki K, Tamaoki J, Nagai A. A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. Respiration. 2009;77:407–15.
11. Liu GY, Ventura IB, Achtar-Zadeh N, Elicker BM, Jones KD, Wolters PJ, et al. Prevalence and Clinical Significance of Antineutrophil Cytoplasmic Antibodies in North American Patients With Idiopathic Pulmonary Fibrosis. Chest. 2019;156:715-23.
12. Kagiyama N, Takayanagi N, Kanauchi T, Ishiguro T, Yanagisawa T, Sugita Y. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Respir Res. 2015;2:e000058.
13. Ando M, Miyazaki E, Ishii T, Mukai Y, Yamasue M, Fujisaki H, et al. Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. Respir Med. 2013;107:608–15.
14. Wu T, Zhang Y, Cen Z, Ying Y, Sun C, Lv C, et al. Clinical significance of acute exacerbation in interstitial lung disease with antineutrophil cytoplasmic antibody: an indicator of poor prognosis. Ther Adv Respir Dis. 2022;16:17534666221140974.
15. Sun X, Peng M, Zhang T, Li Z, Song L, Li M, et al. Clinical features and long-term outcomes of interstitial lung disease with anti-neutrophil cytoplasmic antibody. BMC Pulm Med. 2021;21:88.
16. Hozumi H, Oyama Y, Yasui H, Suzuki Y, Kono M, Karayama M, et al. Clinical significance of myeloperoxidase-anti-neutrophil cytoplasmic antibody in idiopathic interstitial pneumonias. Plos One. 2018;13:e0199659.
17. Guilpain P, Chéreau C, Goulvestre C, Servettaz A, Montani D, Tamas N, et al. The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis. Eur Respir J. 2011;37:1503.
18. Chrysanthopoulou A, Mitroulis I, Apostolidou E, Arelaki S, Mikroulis D, Konstantinidis T, et al. Neutrophil extracellular traps promote differentiation and function of fibroblasts. J Pathol. 2014;233:294–307.
19. Frangou E, Vassilopoulos D, Boletis J, Boumpas DT. An emerging role of neutrophils and NETosis in chronic inflammation and fibrosis in systemic lupus erythematosus (SLE) and ANCA-associated vasculitides (AAV): Implications for the pathogenesis and treatment. Autoimmun Rev. 2019;18:751–60.
20. Borie R, Crestani B. Antineutrophil Cytoplasmic Antibody-Associated Lung Fibrosis. Seminars in Respiratory and Critical Care Medicine. 2018;39:465–70.
21. Tzelepis GE, Kokosi M, Tzioufas A, Toya SP, Boki KA, Zormpala A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. Eur Respir J. 2009;36:116–21.
22. Churg A, Zay K, Shay S, Xie C, Shapiro SD, Hendricks R, et al. Acute cigarette smoke-induced connective tissue breakdown requires both neutrophils and macrophage metalloelastase in mice. Am J Respir Cell Mol Biol. 2002;27:368–74.
23. Suarez-Cuartin G, Molina-Molina M. Clinical implications of ANCA positivity in idiopathic pulmonary fibrosis patients. Breathe (Sheff). 2020;16:190321.
24. Libra A, Muscato G, Ielo G, Spicuzza L, Palmucci S, Fagone E, et al. Clinical and Prognostic Significance of p-ANCA Positivity in Idiopathic Pulmonary Fibrosis: A Retrospective Observational Study. Diagnostics (Basel). 2023;13:1882.
25. Hozumi H, Enomoto N, Oyama Y, Kono M, Fujisawa T, Inui N, et al. Clinical Implication of Proteinase-3-antineutrophil Cytoplasmic Antibody in Patients with Idiopathic Interstitial Pneumonias. Lung. 2016;194:235–42.
26. Kang BH, Park JK, Roh JH, Song JW, Lee CK, Kim M, et al. Clinical significance of serum autoantibodies in idiopathic interstitial pneumonia. J Korean Med Sci. 2013;28:731–7.
27. Zhu W, Zhou C, Sun X, Xue P, Li Z, Zhang W, et al. Interstitial lung diseases associated with ANCA positivity: A different disease spectrum from interstitial pneumonia with autoimmune features. Respir Med Res. 2024;86:101111.
28. Fischer A, Antoniou KM, Brown KK, Cadranel J, Corte TJ, du Bois RM, et al. An official European Respiratory Society/American Thoracic Society research statement: interstitial pneumonia with autoimmune features. Eur Respir J. 2015;46:976–87.
29. Travis WD, Costabel U, Hansell DM, King TE Jr, Lynch DA, Nicholson AG, et al. An official American Thoracic Society/European Respiratory Society statement: Update of the international multidisciplinary classification of the idiopathic interstitial pneumonias. Am J Respir Crit Care Med. 2013;188:733–48.
30. Raghu G, Remy-Jardin M, Richeldi L, Thomson CC, Inoue Y, Johkoh T, et al. Idiopathic Pulmonary Fibrosis (an Update) and Progressive Pulmonary Fibrosis in Adults: An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline. Am J Respir Crit Care Med. 2022;205:e18–47.
31. Bossuyt X, Cohen Tervaert JW, Arimura Y, Blockmans D, Flores-Suárez LF, Guillevin L, et al. Position paper: Revised 2017 international consensus on testing of ANCAs in granulomatosis with polyangiitis and microscopic polyangiitis. Nat Rev Rheumatol. 2017;13:683–92.
32. Suppiah R, Robson JC, Grayson PC, Ponte C, Craven A, Khalid S, et al. 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology classification criteria for microscopic polyangiitis. Ann Rheum Dis. 2022;81:321–6.
33. Rodriguez K, Ashby CL, Varela VR, Sharma A. High-Resolution Computed Tomography of Fibrotic Interstitial Lung Disease. Semin Respir Crit Care Med. 2022;43:764–79.
34. Buttgereit F, da Silva JA, Boers M, Burmester GR, Cutolo M, Jacobs J, et al. Standardised nomenclature for glucocorticoid dosages and glucocorticoid treatment regimens: current questions and tentative answers in rheumatology. Ann Rheum Dis. 2002;61:718–22.
35. Furuta S, Nakagomi D, Kobayashi Y, Hiraguri M, Sugiyama T, Amano K, et al. Effect of Reduced-Dose vs High-Dose Glucocorticoids Added to Rituximab on Remission Induction in ANCA-Associated Vasculitis: A Randomized Clinical Trial. JAMA. 2021;325:2178–87.
36. Hellmich B, Sanchez-Alamo B, Schirmer JH, Berti A, Blockmans D, Cid MC, et al. EULAR recommendations for the management of ANCA-associated vasculitis: 2022 update. Ann Rheum Dis. 2024;83:30–47.
37. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2003;168:538–42.
38. Paterniti MO, Bi Y, Rekić D, Wang Y, Karimi-Shah BA, Chowdhury BA. Acute Exacerbation and Decline in Forced Vital Capacity Are Associated with Increased Mortality in Idiopathic Pulmonary Fibrosis. Ann Am Thorac Soc. 2017;14:1395–402.
39. Chan C, Ryerson CJ, Dunne JV, Wilcox PG. Demographic and clinical predictors of progression and mortality in connective tissue disease-associated interstitial lung disease: a retrospective cohort study. BMC Pulm Med. 2019;19:192.
40. Sakamoto S, Suzuki A, Homma S, Usui Y, Shimizu H, Sekiya M, et al. Outcomes and prognosis of progressive pulmonary fibrosis in patients with antineutrophil cytoplasmic antibody-positive interstitial lung disease. Sci Rep. 2023;13:17616.
41. Foucher P, Heeringa P, Petersen AH, Huitema MG, Brouwer E, Tervaert JW, et al. Antimyeloperoxidase-associated lung disease. An experimental model. Am J Respir Crit Care Med. 1999;160:987–94.
42. Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci U S A. 1990;87:4115–9.
43. Negreros M, Flores-Suárez LF. A proposed role of neutrophil extracellular traps and their interplay with fibroblasts in ANCA-associated vasculitis lung fibrosis. Autoimmun Rev. 2021;20:102781.
44. Poli G, Parola M. Oxidative damage and fibrogenesis. Free Radic Biol Med. 1997;22:287–305.
45. Yoshida M, Yamada M, Sudo Y, Kojima T, Tomiyasu T, Yoshikawa N, et al. Myeloperoxidase anti-neutrophil cytoplasmic antibody affinity is associated with the formation of neutrophil extracellular traps in the kidney and vasculitis activity in myeloperoxidase anti-neutrophil cytoplasmic antibody-associated microscopic polyangiitis. Nephrology (Carlton). 2016;21:624–9.
46. Kadura S, Raghu G. Antineutrophil cytoplasmic antibody-associated interstitial lung disease: a review. Eur Respir Rev. 2021;30:210123.
47 Raghu G, Rochwerg B, Zhang Y, Garcia CA, Azuma A, Behr J, et al. An Official ATS/ERS/JRS/ALAT Clinical Practice Guideline: Treatment of Idiopathic

Pulmonary Fibrosis. An Update of the 2011 Clinical Practice Guideline. Am J Respir Crit Care Med. 2015;192:e3-19.
48. Matteson EL, Kelly C, Distler JHW, Hoffmann-Vold AM, Seibold JR, Mittoo S, et al. Nintedanib in Patients With Autoimmune Disease-Related Progressive Fibrosing Interstitial Lung Diseases: Subgroup Analysis of the INBUILD Trial. Arthritis Rheumatol. 2022;74:1039–47.
49. Maher TM, Corte TJ, Fischer A, Kreuter M, Lederer DJ, Molina-Molina M, et al. Pirfenidone in patients with unclassifiable progressive fibrosing interstitial lung disease: a double-blind, randomised, placebo-controlled, phase 2 trial. Lancet Respir Med. 2020;8:147–57.
50. Torrisi SE, Kahn N, Wälscher J, Sarmand N, Polke M, Lars K, et al. Possible value of antifibrotic drugs in patients with progressive fibrosing non-IPF interstitial lung diseases. BMC Pulm Med. 2019;19:213.
51. Thompson GE, Specks U. Update on the Management of Respiratory Manifestations of the Antineutrophil Cytoplasmic Antibodies-Associated Vasculitides. Clin Chest Med. 2019;40:573–82.
52. Yamakawa H, Toyoda Y, Baba T, Kishaba T, Fukuda T, Takemura T, et al. Anti-Inflammatory and/or Anti-Fibrotic Treatment of MPO-ANCA-Positive Interstitial Lung Disease: A Short Review. J Clin Med. 2022;11:3835.

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