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Title: Prevalence and clinical outcomes of fibrotic interstitial lung disease in ANCA associated vasculitis: a single-centre, retrospective, cohort study.

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Abstract

Background: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) may affect multiple organs and interstitial lung disease (ILD) might be the first manifestation.

Limited and discordant data are available on the prevalence of ILD in patients with AAV. Little is known about prognostic outcomes of these patients.

The primary aim of the study was to determine the prevalence of fibrotic ILD in a cohort of AAV patients followed-up in a University Hospital in Italy. Clinical and prognostic outcomes of AAV-ILD were also assessed.

Methods: Data from 71 AAV patients (mean age 60.3 ± 16 years; female 58.9%) were retrospectively collected and analyzed.

Results: Overall ILD prevalence was 50.7%. Fibrotic ILDs represented 32.4% with a variable distribution according to diagnosis: microscopic polyangiitis (MPA) 66.7%, eosinophilic granulomatosis with polyangiitis (EGPA) 41.1%, granulomatosis with polyangiitis (GPA) 31.8%.

The presence of ILD was significantly different across AAV subgroups. Fibrotic ILD was more prevalent in MPA (60%) than EGPA (11.8%) and GPA (9.1%) and most frequently associated with usual interstitial pneumonia (UIP) pattern. The presence of ANCA was significantly associated with fibrotic ILDs (p=0.01). In univariate analysis only MPA increased the risk of having ILD (OR 2 (CI 95%: 0.96-4.67). Mortality was significantly higher in patients with ILD (p=0.01), with fibrotic forms influencing this finding and MPA showing the highest mortality.

Conclusions: Fibrotic ILDs are common in patients with AAV and influence clinical and prognostic outcomes. MPA is the most frequent AAV associated to fibrotic ILD. ILD should be investigated at diagnosis in all patients with AAV, since early diagnosis might impact the prognosis of these patients.

Keywords: ANCA; vasculitis; ILD; fibrosis; MPA; GPA; EGPA; UIP; HRCT; mortality

Text

Background

Antineutrophil cytoplasmic antibody (ANCA)–associated vasculitis (AAV) represent a group of systemic autoimmune inflammatory disorders characterized by necrotizing vasculitis predominantly affecting small and medium-sized vessels, including arterioles, capillaries, and venules (1). These conditions are frequently associated with the presence of antineutrophil cytoplasmic antibodies (ANCA), particularly those directed against proteinase 3 (PR3) and myeloperoxidase (MPO), which play a central role in the pathogenesis of vascular inflammation (2).

The term ANCA-associated vasculitis, introduced following the revision of the Chapel Hill Consensus Conference (3), includes three distinct clinical entities: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA) (1).

The clinical course of AAV is highly variable, ranging from indolent to rapidly progressive phenotypes with multi-organ involvement, and requires timely diagnosis and treatment to prevent irreversible damage. Among the affected organs, the lung is involved in approximately 10–30% of patients with MPA, 70–95% of those with GPA, and over 95% of those with EGPA (4).

However, a few studies have specifically assessed the prevalence of interstitial lung disease (ILD) in AAV patients and data available are still limited and discordant.

Pulmonary involvement in AAV can present with a wide spectrum of manifestations, ranging from pauci-symptomatic conditions such as asthma, pulmonary nodules, or interstitial lung disease (ILD), to severe, life-threatening conditions such as diffuse alveolar haemorrhage (DAH) (5). More recently, growing evidence has shown that AAV may also manifest with chronic and progressive pulmonary disease due to interstitial lung involvement, which may accompany or, even precede, the diagnosis of AAV (6–9,10). In this scenario, interstitial lung involvement may anticipate or precede AAV diagnosis, with ILD appearing 1–5 years before onset or concurrently in nearly 80% of cases (11).

The pathogenesis of ILD in AAV remains poorly understood, but it is thought to involve a complex interplay of ANCA-mediated autoimmunity, environmental exposures (e.g., silica dust, air pollution,

cigarette smoke), chronic airway inflammation, persistent neutrophil activation, and alveolar injury (12). The role of the vasculature in fibrosis is a matter of interest and pulmonary fibrosis may precede the overt diagnosis of vasculitis by several years, suggesting that ILD could represent an early manifestation of the vasculitic process (11,12). While ILD is uncommon in PR3-ANCA–positive AAV, it is more frequently observed in patients with MPO-ANCA positivity, implicating anti-myeloperoxidase antibodies are directly involved in the development of pulmonary fibrosis (11,13,14). At high resolution computed tomography (HRCT), both fibrotic and non-fibrotic interstitial patterns can be observed. Several radiologic patterns have been reported in patients with AAV, usual interstitial pneumonia (UIP) or probable UIP being the most prevalent, with rates varying across studies and reaching up to 50–70%, particularly among patients with p-ANCA positivity (15,16).

Current literature suggests an increased mortality in individuals with AAV-ILD, especially in those presenting with a UIP pattern. This may account for the poorer prognosis observed in patients with microscopic polyangiitis (MPA) compared with other forms of vasculitis, as MPA more commonly exhibits interstitial lung involvement with a UIP pattern (17,18).

To date, real-life data on the prevalence and the main clinical-radiological characteristics of ILDs, in patients with AAV are scant and heterogeneous. Limited data are present on the prognostic outcomes of these patients.

The aim of the study was to determine the prevalence of AAV-ILD and its fibrotic form in a cohort of patients diagnosed with AAV and followed-up in a University Hospital in Northern Italy. Furthermore, clinical and prognostic outcomes of AAV-ILD were also analyzed.

Methods

Aims and study design

A single centre, retrospective, observational cohort study was carried out in Italy.

The primary aim was to determine the overall prevalence of ILD and the prevalence of fibrotic ILD in a cohort of patients affected by AAV. Clinical, functional, serological and radiological characteristics of the AAV patients were also analyzed to find a relationship with the presence of fibrotic ILD. Finally, mortality rates of patients with AAV-ILD were estimated.

Study population

Patients diagnosed with AAV (GPA, EGPA or MPA) from January 2018 to October 2024 were enrolled in the Pulmonology, Rheumatology and Nephrology Departments of the ASST Santi Paolo e Carlo University Hospitals in Milan – Italy, referring hospitals for vasculitis. The study was approved by the Local Institutional Review Board (IRB) with the number CET 349-2024. All the patients signed an informed consent form approved by the Local IRB, compliant with the Italian legislation (Codex on Privacy, D.Lgs 30 giugno 2003, n.196) and in accordance with the Declaration of Helsinki. The data were stored in a dedicated Institutional database. Patients with a follow up period less than 1 year or with age <18 years old were excluded from this study.

Variables collected

Demographic data, AAV biomarkers levels (including ANCA titers and specificity, serum creatinine levels), respiratory and extra-pulmonary involvements, comorbidities, chest HRCT patterns, lung function tests, and therapy (induction and maintenance) were collected through electronic medical records at baseline (diagnosis) and subsequently during follow up clinics. Clinical, laboratory and imaging tests were regularly repeated at time points according to standard practice of care and international guidelines. ANCA antibodies were determined through immunofluorescence (Euroimmun Anca Profile, Germany). When a c-ANCA or p-ANCA pattern (>1/20 dilution) was retrieved, then results were confirmed by ELISA (enzyme linked immunosorbent assay) determination of anti-PR3 and anti-MPO antibodies (Euroimmun Anca Profile, Germany). Values >3 UI/ml for anti-PR3 and anti-MPO antibodies were considered positive. Chest HRCT scans were either performed at

the time of AAV diagnosis or within 3 months in all the patients, according to the clinical context, with the hospital CT scanner (Somaton Definition As Plus 128, Siemens Healthineers, Erlangen, Germany), or in other radiology services outside the hospital. All CT examinations were recorded through the high resolution protocol (1 mm slices) and centrally reviewed by two blinded experts thoracic radiologists. Discordances were solved by a third senior thoracic radiologist. ILD patterns were reported as per the 2025 ERS/ATS Statement on Classification of the Interstitial Pneumonias (19). Baseline HRCT scans of the included patients were reviewed to screen for the presence of ILD. A radiologic ILD was defined in case at least one of the following patterns was detectable: Usual Interstitial Pneumonia (UIP) (definite and probable), UIP indeterminate, cellular Non Specific Interstitial Pneumonia (NSIP), fibrotic NSIP, other non-fibrotic ILD pattern (including Organizing Pneumonia (OP), Bronchiolocentric interstitial pneumonia (BIP), Lymphoid Interstitial Pneumonia (LIP), Alveolar Macrophage Pneumonia (AMP)). Moreover, the presence of Diffuse Alveolar Haemorrhage and other abnormalities (e.g. nodules) was also considered and reported.

Pulmonary function tests (PFT) including spirometry, body plethysmography and diffusion capacity of the lung for carbon monoxide (DLCO) were recorded with a dedicated spirometer and body cabin plethysmography (Quark PFT and Q-Box, Cosmed, Rome, Italy) in the Pulmonology Department. PFT included Forced Vital Capacity (FVC), Forced expiratory volume in 1 second (FEV1), the ratio FEV1/FVC, Residual Volume (RV), Total Lung Capacity (TLC). DLCO was registered by single-breath methodology. All the data were registered according to the manufacturer's instructions.

Statistical analysis

Quantitative and qualitative variables were collected. The normality of continuous variables was assessed using the Shapiro - Wilk test. Continuous variables were reported as mean and Standard Deviation (SD) or median and Interquartile Ranges (IQR) according to the presence or not of a normal distribution. Categorical variables were expressed as absolute and relative frequencies.

Standardized residuals, Fisher's exact test, Kruskal-Wallis and Mann-Whitney test were adequately applied. Univariate and multivariate logistic regression were performed. Mortality was assessed through Kaplan-Meier Analysis, and differences between groups were compared using the log-rank test. Statistical significance was considered for each test in case p-values <0.05. Data analysis was performed using the STATA 14 package (Stata Corp LP, College Station, TX, USA).

Results

Descriptive characteristics of the population

71 patients were enrolled during the study period, with a mean age at AAV diagnosis of 60.3 years. 43 patients were females (60.6%). The distribution of AAV diagnosis was the following: MPA was the most frequent diagnosis, accounting for 30 patients (42.3% of cases), followed by GPA (22 patients, 31%) and EGPA (17 patients, 23.9%,). 2 patients (2.8%) were considered not classifiable in any AAV diagnosis at baseline, although systemic signs of vasculitis were present. ILD could be recognized in near half of AAV cases (36 patients, 50.7%) at the baseline evaluation. The vast majority of those were fibrotic ILDs (63.9%, 23 patients). The median (IQR) follow up time of patients was 1063 days (2079). The main demographic, clinical, radiological, functional and serological characteristics of the population were included in Table 1.

When considering ANCA serology, p-ANCA were the most detected in the sample, with 35 patients showing positive levels (49.3%), while c-ANCA were detected in 15 patients (21.1%). 15.5% of patients were diagnosed with a seronegative vasculitis (double negative ANCA) and for 10 (14.1%) patients, no basal determination of ANCA could be retrieved from electronic medical records. ELISA test for the determination of the MPO and PR3 specificities were available for the majority of patients: 53.5% of the sample proved positive for MPO-ANCA, with a mean level of 96.1 (±70.9) U/ml, while 15.5% for PR3-ANCA, with a mean level of 83.1 (±72.3) U/ml.

Of notice, most patients showed signs of fibrosis at baseline, with the prevalent chest HRCT pattern being UIP (11 patients, 17.7%), followed by fibrotic NSIP (9 patients, 14.5%). Unfortunately, 4 patients

(6.4%) presented with diffuse alveolar haemorrhage and were then diagnosed with AAV. Lung nodules were present in 8 (12.9%) patients, and none of them developed lung cancer during the follow-up. In the analysed cohort, respiratory symptoms (i.e. dyspnoea, cough), though often subtle, were reported in all the patients.

Drugs prescribed in the induction phase were methylprednisolone in 50 (90.9%) patients, rituximab in 20 (36.4%), cyclophosphamide in 7 (2.7%), and azathioprine in 4 (7.3%). Avacopan, methotrexate or plasmapheresis were used in the remaining cases.

Prevalence of ILD and Fibrotic ILD

At diagnosis, ILD was detectable in 50.7% of patients (36). 23 of them (32.4% of all the cohort) were fibrotic ILD, while 13 patients (36.1%) presented with a non-fibrotic ILD. Overall, among the 36 AAV-ILD patients, 63.9% presented with a fibrotic ILD.

ILD was more present among MPA patients (66.7%), followed by EGPA (41.2%) and GPA (31.8%). When stratifying for the presence of fibrotic ILD, this condition could be detected in 60% of MPA cases, while far less in EGPA (11.7%) and GPA (9%) (Table 2).

Association between AAV diagnosis subgroups and ILD

When stratifying for AAV subgroups, ILD was significantly unequally distributed between them ($p=0.034$), with the MPA group showing the highest prevalence of ILD (66.7%). While there were no statistically relevant differences in the distribution of non-fibrotic ILD across the AAV groups, a highly significant difference in this distribution could be observed for the fibrotic ILD ($p<0.001$), with the MPA group showing the highest prevalence of fibrotic ILD.

The MPA group was significantly more associated with ILD, and especially with fibrotic ILD, compared to the GPA ($p<0.001$) and EGPA groups ($p=0.001$).

No pairwise comparison was significant for non-fibrotic ILD. These results are summarized in Table 2 and Figure 1.

A significant association between MPA diagnosis and the presence of Fibrotic ILD (standardized residual 2.73).

Prevalence of HRCT patterns among AAV diagnosis and their association

Fibrotic pattern at HRCT (UIP and fibrotic NSIP) was prevalent in MPA patients (respectively 100% of UIP and 66.7% of fibrotic NSIP), while inflammatory ground glass opacities related to cellular NSIP were more commonly detected in EGPA (44.4%) and GPA (33.3%). Nodules were detected in 12.9% of CT scans, 50% of them being diagnosed in patients with GPA. Diffuse alveolar haemorrhage, a recognised harmful manifestation of AAV, was described in 6.45% of patients, predominantly in GPA and MPA, while no cases were detected among EGPA patients in our cohort. A significant association was observed between the presence of a detectable ILD at HRCT scan and the diagnosis of AAV, independently from the specific subgroup (p=0.0022).

When stratifying for AAV subgroups, UIP pattern and fibrotic NSIP were significantly unequally distributed between groups (respectively with a p=0.004 and p=0.03). A significant difference in the overall distribution between groups was also present for the other non-fibrotic ILD pattern (p=0.04). No statistically significant differences in the distribution per AAV could be observed for other considered HRCT patterns (UIP indeterminate, and cellular NSIP). UIP pattern was almost exclusively present in MPA, with a significant difference at pairwise comparisons against GPA (p=0.003) and EGPA (p=0.01). Fibrotic NSIP was statistically more present in MPA than GPA (p=0.02) while non-fibrotic ILD patterns were far less common in MPA than GPA (p=0.03). These results are summarized in Table 3 and Figure 2. A significant association between MPA diagnosis and UIP pattern was observed (standardized residual 2.71).

Association between ANCA test result and ILD

Based on the prevalence of fibrotic and non-fibrotic ILD across the ANCA-test result groups, a statistically significant relationship between the presence of a positive ANCA-test result and the

presence of ILD (p=0.0118) was confirmed. Particularly, p-ANCA were seven-fold more detectable in fibrotic ILD than non-fibrotic ILD (OR 7.3) with a prevalence of 48.6% in fibrotic ILD vs 11.4% in non-fibrotic ILD (p= 0.0026).

Risk factors for the development of ILD

The effects of some variables as potential risk factors for ILD were evaluated using logistic regression (Table 4).

No statistical significance for the association between cigarette smoking and the development of ILD in the analyzed cohort (p-value of 0.5587).

The association between comorbidities and ILD was not statistically significant (p-value = 0.5414).

No significant effect was attributable to other relevant variables considered (age at AAV diagnosis; gender; ANCA-test result). EGPA diagnosis was not a significant risk factor for the development of ILD. However, it can be considered clinically relevant that univariate analysis showed that a diagnosis of MPA more than doubled the odds of developing ILD (odds ratio of 2.11), with an upper limit of the 95% confidence interval of 4.6. The association did not reach statistical significance (p=0.0648, confidence interval 0.96 – 4.67). The results of the analysis are graphically shown in the forest plot (Figure 3).

AAV-ILD Survival analysis

The prognosis of AAV-ILD was determined in the study cohort using the Kaplan-Meier method for survival analysis. Patients with missing mortality information (n=6) were excluded from the analysis. For each comparison, only patients with complete data were thus considered. The follow-up period was defined from the date of AAV diagnosis to either the date of death or the last available follow-up for surviving patients. Number of patients at risk at each time interval was reported below the Kaplan-Meier survival curves. Albeit median survival time was not reached for both the ILD and the Non-ILD group, since the cumulative survival remained above 50% throughout the observation period, survival

analysis showed that the presence of ILD in AAV was associated with significantly reduced survival compared to the absence of ILD (p=0.0142), suggesting that ILD was associated with worse prognosis and increased mortality in AAV. This result highlighted how the presence of interstitial lung disease resulted in a worse prognosis in patients with AAV (Figure 4, panel a).

When stratified by ILD subtype, mortality trend was numerically worse in fibrotic ILD compared to non-fibrotic group, though not reaching statistical significance (Figure 4, panel b).

Furthermore, although median survival time was not reached across all subgroups of patients with ILD, a trend toward worse survival could be observed in MPA group. More in details, a statistically significant result was detected in the direct comparison between MPA and EGPA (p=0.05), while comparison between GPA vs EGPA (p=0.3776) and GPA vs MPA (p=0.2148) were not significant (Figure 4, panel c).

Discussion

Our study confirmed that ILD represents a frequent and clinically relevant manifestation in AAV patients, with remarkable diagnostic and prognostic implications.

Overall, 50.7% of AAV patients presented concomitant interstitial lung diseases. Notably, fibrotic ILDs were predominant, with a prevalence of 30% in the whole cohort, and 63.9% among ILD patients. The high prevalence of MPA patients in our study might explain these findings.

Heterogeneous data on the prevalence of ILD in AAV are present in the literature.

Some studies reported lower prevalence rates of ILD in AAV. An American cohort study involving 1862 patients estimated a prevalence of ILD of 7.7% (8), while the study by Doliner et al., involving 684 AAV patients, showed that 13% of AAV patients had ILD which was mostly associated with anti-MPO positivity (7). However, a prospective, Japanese cohort study which included 144 MPA patients, found that 51% showed HRCT signs of interstitial pneumonia (20). These results suggest that a careful search for any sign of ILD must be performed when diagnosing AAV, mostly when MPA is suspected.

Anti-MPO antibodies and p-ANCA were the most represented, particularly in the fibrotic forms, in our cohort. This highlights their potential correlation with the development of interstitial disease, and, in particular, with progressive fibrotic forms, as previously reported in several studies (7,8,20–22).

The subgroup diagnosed with MPA, representing 42% of the sample, was confirmed to be the most frequently associated with ILD in our cohort. Within this group, ILD prevalence reached 66%, with more than half of the patients showing a fibrotic pattern on chest HRCT, particularly the aggressive UIP pattern. The significant association between presence of a detectable ILD at HRCT scan and the diagnosis of AAV was further supported by the analysis of standardized residuals and radiological findings.

These results are consistent with the literature. A retrospective study showed that UIP pattern was observed in 63% of patients with MPA-associated ILD, more frequent than other radiological patterns; many of these patients also tested positive for anti-MPO (or p-ANCA) antibodies (23). Similarly, in the study by Doliner et al., patients with ILD showed a significantly higher prevalence of anti-MPO positivity (85 of 91 cases), with UIP being the most frequent pattern (approximately 42% of cases) (7). In our study, p-ANCA were the most represented antibodies, and ANCA positivity was significantly associated with the development of pulmonary fibrosis ($p=0.0118$). This reinforces the hypothesis of a pathophysiological link between MPO-mediated autoimmune activity and the progression toward fibrotic damage of the lung parenchyma, and confirmed results from the literature (23,24). In experimental animal models, MPO-ANCA have shown potential pro-fibrotic activity (14), stimulating fibroblasts in a chronic inflammatory environment and promoting abnormal repair processes of alveolar tissue (11).

Some studies in the literature suggested that ILD may be present at diagnosis or precede the clinical manifestation of vasculitis by several years. A previous study by Valero-Martínez et al. showed that 10 out of 23 recruited patients, where UIP was the predominant pattern, subsequently developed MPA vasculitis. In that study, AAV positivity, together with CT pattern and age, was significantly associated with an increased risk of premature death. Therefore, ANCA testing is advisable as part of the

screening of all patients with ILD (25). Of notice, as in other ILD secondary to connective tissue diseases (26), in our AAV-ILD cohort lung nodules showed benign behaviour and no cases of cancer were retrieved during the follow-up.

From a functional perspective, patients with ILD showed a significantly higher prevalence of restrictive abnormalities on pulmonary function tests, consistent with the typical clinical picture of fibrotic disease. This aligns with previous studies, in which AAV-ILD patients presented significant reductions in FEV_1, FVC, and DLCO (7).

No significant differences were found in creatinine levels between patients with and without ILD, suggesting that renal impairment, although clinically relevant in AAV, does not directly correlate with the presence of interstitial lung involvement.

A recent systematic review and meta-analysis of 25 studies identified male gender, age, smoking history, honeycombing or interlobular septal thickening and the presence of MPO-ANCA as risk factors for the development of AAV-ILD (27). In our study no significant risk factors were found to be associated with the development of ILD, but the presence of MPA showed a clinically relevant trend toward it. This discrepancy might be interpreted with the limited sample size of our cohort.

Our analysis showed a significantly higher mortality in patients with ILD ($p=0.0142$), particularly in those with fibrosis. Moreover, in the direct comparison of the three diagnostic groups, MPA showed the worse prognosis. In line with these findings, Doliner et al. documented that AAV-ILD patients had an almost 40% higher risk of death compared with those without interstitial involvement, although in that study the association did not reach statistical significance (7). Similarly, Tzelepis et al. demonstrated that pulmonary fibrosis was associated with a higher risk of mortality compared with non-fibrotic forms (28) while Hirayama et al. that mortality was worse in MPA patients with ILD than in those without ILD (29). On the opposite, a retrospective cohort study found that typical UIP pattern in AAV-ILD was associated with better survival, particularly in MPO-ANCA patients (8).

The evidence of increased mortality in patients with fibrotic patterns raises the question of whether antifibrotic agents may be beneficial in this population, especially considering that UIP, known for its

worse clinical trajectory, was the most frequent pattern observed. Although no clinical trials have yet evaluated the combined efficacy of immunosuppressants and antifibrotic therapies in AAV, this therapeutic strategy may represent a promising opportunity to slow functional decline and improve prognosis in patients with progressive disease (30,31,32).

Moreover, like in other rare diseases with ILD pulmonary involvement, exploring the role of epigenetics and genetics might open new scenarios, mostly in familial cases (33,34).

The role of the vascular system in fibrosis is emerging as a central driver, and pulmonary fibrosis can precede the clinical diagnosis of vasculitis by several years, as ILD might represent an early manifestation of the vasculitic process (11,12). Several studies over the years have investigated capillary vascular alterations in patients with vasculitis. A recent study by Screm et al. in patients with EGPA showed that nailfold videocapillaroscopy in this population could reveal multiple abnormalities, including the presence of neoangiogenesis, pericapillary stippling, capillary rolling, and inverted capillary apex.

Neoangiogenesis thus represents an important marker of vascular inflammatory activity and has been correlated to pulmonary fibrosis (35).

Our study has some limitations: its retrospective design and the relatively small sample size may have affected the statistical power of some analyses, which, despite showing clear trends, did not reach statistical significance. A larger cohort could allow for more robust confirmation of the observed associations, exploration of additional predictive factors, and a more accurate assessment of the prognostic impact of interstitial involvement. Therefore, prospective multicenter studies with larger sample sizes are desirable to validate these results, elucidate the pathophysiological mechanisms underlying the association between AAV and ILD, and contribute to the development of more targeted therapeutic strategies, potentially including antifibrotic agents in selected cases.

Conclusions

Our study confirms that ILD is a common and significant clinical manifestation in patients with AAV, particularly in the MPA subgroup. The presence of pulmonary fibrosis, especially with UIP pattern, is associated with a worse prognosis and increased risk of mortality. These data support the need to systematically include radiological assessment of the lung parenchyma in the initial diagnostic workup of each patient with AAV, for an early detection of cases at increased risk of progression.

List of abbreviations

ANCA: Antineutrophil cytoplasmic antibody

AAV: ANCA-associated vasculitis

GPA: granulomatosis with polyangiitis

EGPA: eosinophilic granulomatosis with polyangiitis

MPA: microscopic polyangiitis

ILD: interstitial lung disease

PR3: proteinase 3

MPO: myeloperoxidase

ELISA: enzyme linked immunosorbent assay

UIP: Usual interstitial pneumonia

NSIP: Non-specific interstitial pneumonia

OP: Organizing Pneumonia

BIP: Bronchiolocentric interstitial pneumonia

LIP: Lymphoid Interstitial Pneumonia

AMP: Alveolar Macrophage Pneumonia

PFT: Pulmonary function tests

DLCO: diffusion capacity of the lung for carbon monoxide

FVC: Forced Vital Capacity

FEV1: Forced expiratory volume in 1 second

RV: Residual Volume

TLC: Total Lung Capacity

SD: Standard Deviation

IQR: Interquartile Range

Ethics approval and consent to participate: The study was approved by the Local Institutional Review Board (IRB) Comitato Etico Territoriale Lombardia 1 with the number CET 349-2024. All the patients signed an informed consent form approved by the Local IRB, compliant with the Italian legislation (Codex on Privacy, D.Lgs 30 giugno 2003, n.196).

Consent for publication: Not applicable

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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Authors' contributions:

CT: conception, design of the work, acquisition and analysis, interpretation of the data, drafted the work; SM: conception, design of the work, acquisition and analysis, interpretation of the data, drafted the work; TS: conception, design of the work, interpretation of the data;

SarMir: acquisition and analysis;

MI: acquisition and analysis;

FP: statistical analysis, interpretation of the data;

SF: acquisition and analysis;

CA: acquisition and analysis;

FA: acquisition and analysis;

LS: statistical analysis, interpretation of the data, substantively revised the work;

GMP: interpretation of data, substantively revised the work;

MGC: interpretation of data, substantively revised the work;

MM: conception, design of the work, interpretation of the data, substantively revised the work.

All authors read and approved the final manuscript.

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Tables

Table 1: Clinical and demographic characteristics of the AAV population at baseline. § images available for 62 patients at baseline.

Enrolled patients, n		71
Mean (SD) Age at diagnosis, years		60.3 (16.4)
Sex	* Females, n (%)	43 (60.6)
	* Males, n (%)	28 (39.4)
Ethnicity	* Caucasian, n (%)	65 (91.6)
	* Afroamerican, n (%)	2 (2.8)
	* Hispanic, n (%)	3 (4.2)
	* Other, n (%)	1 (1.4)
Smoking history, n (%)	* Never Smoker, n (%)	19 (26.7)
	* Former Smoker, n (%)	19 (26.7)
	* Current Smoker, n (%)	13 (18.3)
	* Not declared, n (%)	20 (28.3)
	Median (IQR) pack-years	20 (22.5)
AAV diagnosis	* GPA, n (%)	22 (31.0)
	* EGPA, n (%)	17 (23.9)

	* MPA, n (%)	30 (42.3)
	* Not classifiable, n (%)	2 (2.8)
Interstitial Lung Disease	ILD, n (%)	36 (50.7)
	Fibrotic ILD, n (%)	23 (32.4)
HRCT ILD pattern §	* Definite and Probable UIP, n (%)	11 (17.7)
	* Indeterminate UIP, n (%)	2 (3.2)
	* Cellular NSIP, n (%)	9 (14.5)
	* Fibrotic NSIP, n (%)	9 (14.5)
	* Diffuse Alveolar Hemorrhage, n (%)	4 (6.4)
	Nodules, n (%)	8 (12.9)
ANCA	* p-ANCA positive, n (%)	35 (49.3)
	* c-ANCA positive, n (%)	15 (21.1)
	* ANCA negative, n (%)	11 (15.5)
	* ANCA not available at baseline, n (%)	10 (14.1)
	* MPO positive, n (%)	38 (53.5)
	* PR3 positive, n (%)	11 (15.5)
	* MPO/PR3 negative, n (%)	10 (14.1)
	* MPO/PR3 not available at baseline, n (%)	12 (16.9)
	* Mean (SD) MPO, U/ml	96.1 (70.9)
	* Mean (SD) PR3, U/ml	83.1 (72.3)
Other autoantibodies	* ANA, n (%)	29 (40.8)
	* Anti-ENA, n (%)	11 (15.5)
	* CCP, n (%)	14 (19.7)
	* RF, n (%)	13 (18.3)
PFT	Mean (SD) FVC (% pred)	74.0 (20.2)
	Mean (SD) FEV1 (% pred)	57.0 (19.1)
	Mean (SD) DLCO (% pred)	60.1 (16)
Induction Therapy	*Methylprednisolone, n (%)	50 (90.9)
	*Rituximab, n (%)	20 (36.4)
	*Cyclophosphamide, n (%)	7 (12.7)
	*Azathioprine, n (%)	4 (7.3)
	*Avacopan, n (%)	1 (1.4)
	*Plasmapheresis, n (%)	1 (1.4)
	*Methotrexate, n (%)	1 (1.4)

Table 2: Prevalence of ILD and distribution of Fibrotic and non-fibrotic ILD across the AAV subgroups

	AAV diagnosis			**p-value**			
Presence of ILD	**GPA (n=22)**	**EGPA (n=17)**	**MPA (n=30)**	**p-value (global)**	**GPA vs EGPA**	**GPA vs MPA**	**EGPA vs MPA**
ILD, n (%)	7 (31.8%)	7 (41.2%)	20 (66.7%)	**0.034**	0.74	**0.020**	0.083
Fibrotic ILD, n (%)	2 (9.1%)	2 (11.8%)	18 (60.0%)	**<0.001**	0.77	**<0.001**	**0.001**
Non-fibrotic ILD, n (%)	5 (22.7%)	5 (29.4%)	2 (6.7%)	0.10	0.73	0.20	0.12

Table 3: Prevalence of HRCT patterns across the AAV subgroups.

	AAV diagnosis	**p-value**

HRCT Pattern	GPA (n=22)	EGPA (n=17)	MPA (n=30)	p-value (global)	GPA vs EGPA	GPA vs MPA	EGPA vs MPA
UIP	0 (0%)	0 (0%)	9 (30%)	**0.004**	1.0	**0.003**	**0.01**
UIP indeterminate	1 (4.5%)	0 (0%)	2 (6.6%)	0.78	1.0	1.0	1.0
NSIP cellular	0 (0%)	0 (0%)	1 (3.3%)	0.45	1.0	1.0	1.0
NSIP fibrotic	1 (4.5%)	2 (11.8%)	7 (23.3%)	**0.03**	0.56	**0.02**	0.12
Other Non Fibrotic ILD patterns	5 (22.7%)	5 (29.4%)	1 (3.3%)	**0.04**	0.71	**0.03**	0.06
Diffuse Alveolar Hemorrhage	3 (13.6%)	0 (0%)	1 (3.3%)	0.18	0.22	0.58	1.0
Nodules	4 (18.2%)	3 (17.6%)	1 (3.3%)	0.20	1.0	0.20	0.36
Negative HRCT	7 (31.9%)	6 (35.3%)	6 (20%)	0.40	1.0	0.39	0.36

Table 4: Risk Factors for ILD in patients with AAV (Univariate Logistic Regression Analysis). NS: not significant.

Risk Factor	Type	Patients Included (n)	Odds Ratio (OR)	95% CI OR	p-value	Notes
AAV Subgroup	Categorical	69				Reference: GPA
EGPA Diagnosis		69	0.70	0.27 – 1.84	0.469	NS
MPA Diagnosis		69	2.11	0.96 – 4.67	0.064	Trend toward higher risk
Age at AAV diagnosis	Continuous	69	1.00	0.99 – 1.01	0.907	NS
Gender (Male vs Female)	Binary	69	1.14	0.56 – 2.34	0.715	NS
ANCA-test result (positive vs negative)	Binary	59	1.18	0.67 – 2.09	0.564	NS

Figures

Figure 1: Distribution of ILD patterns among AAV subtypes.

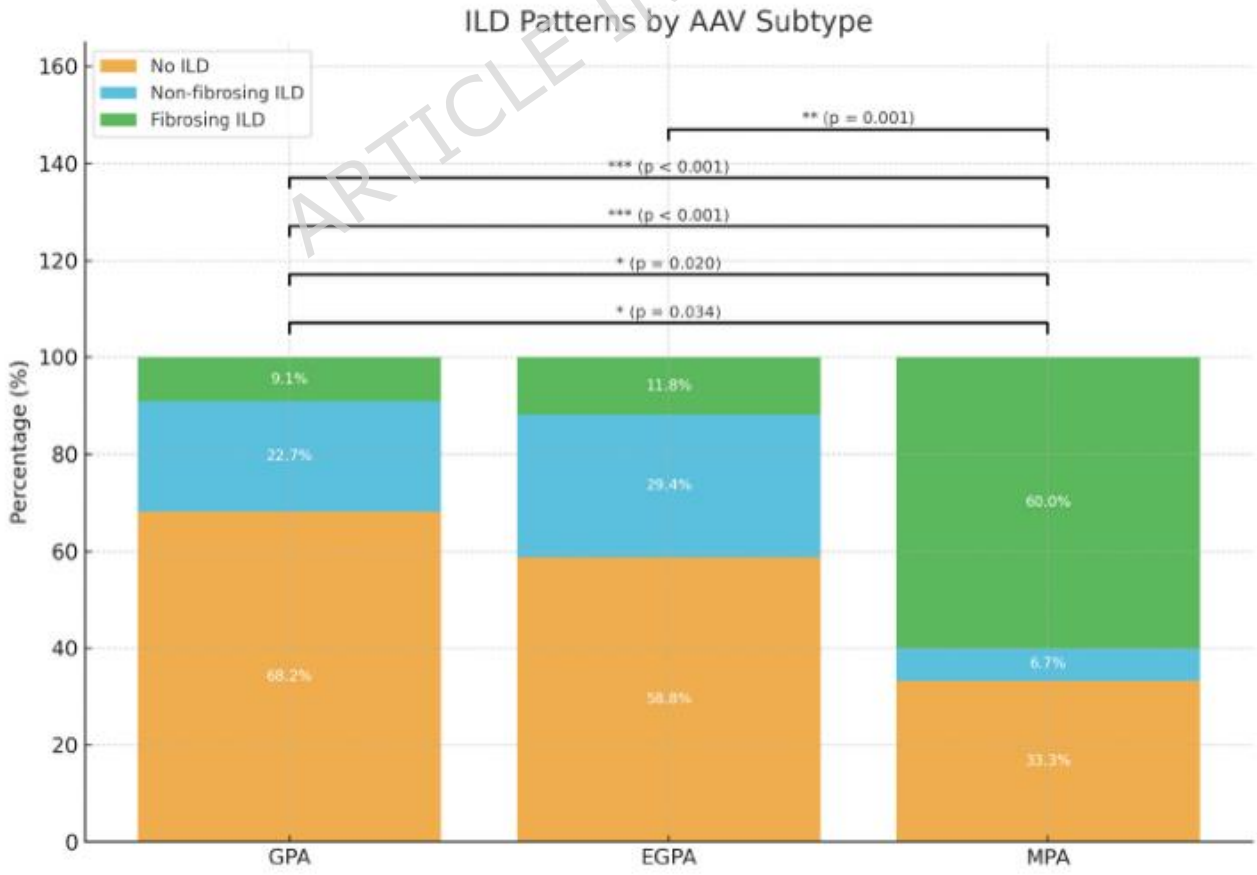

Figure 2: Distribution of HRCT patterns across AAV subtypes and comparative statistical analysis.

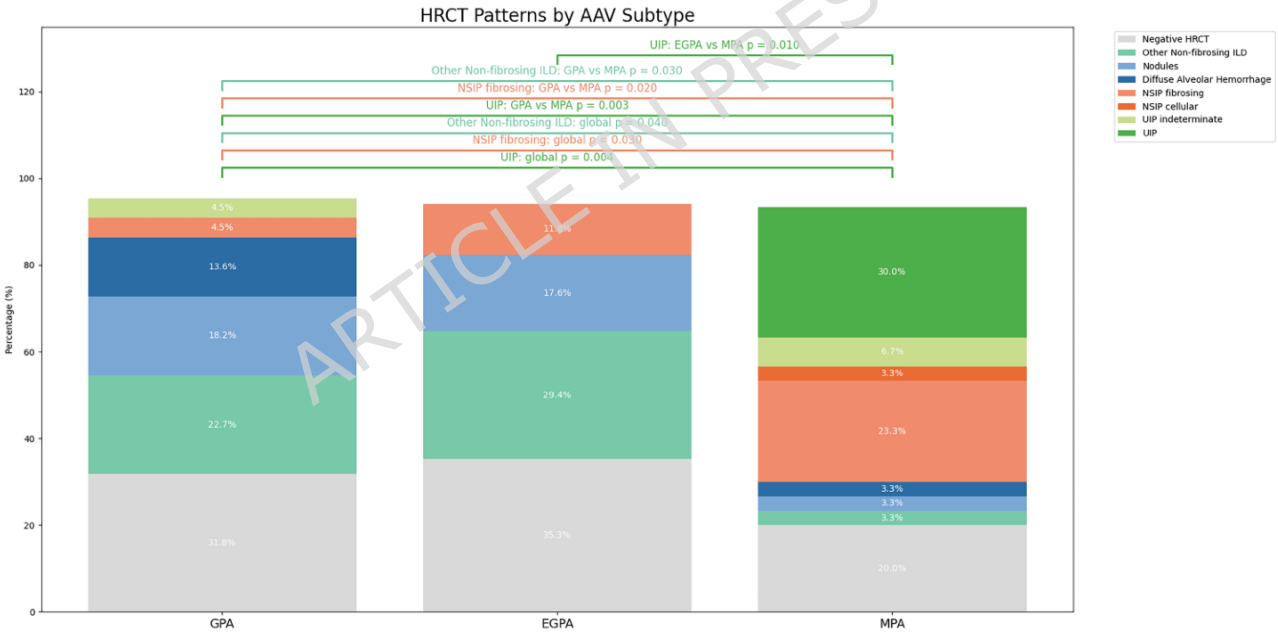

Figure 3: Forest plot of the possible risk factors for the development of ILD in AAV patients.

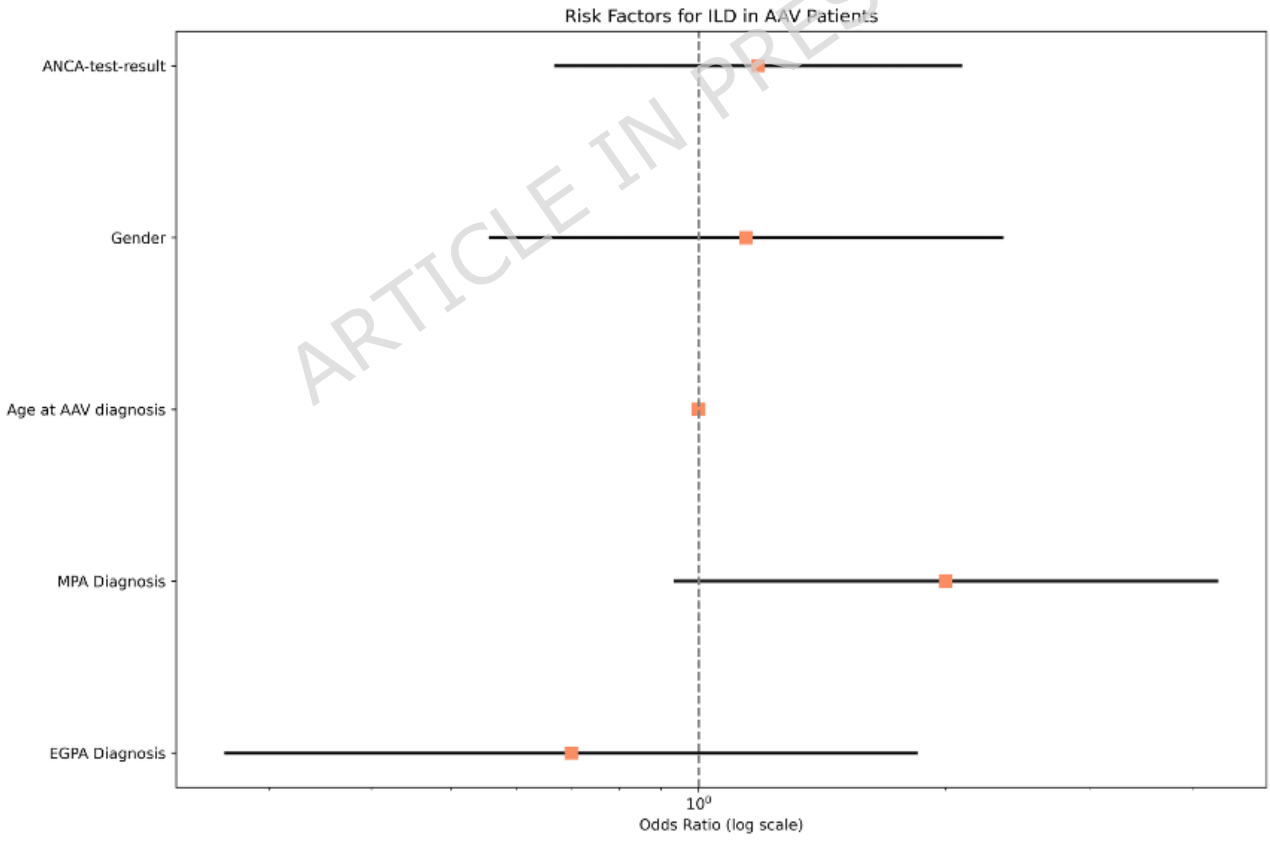

Figure 4: Kaplan-Meier survival analysis. Panel a): survival analysis for ILD (blue) vs non-ILD (red) AAV patients. Panel b): survival analysis for the group AAV non-fibrotic ILD (blue) vs fibrotic ILD (red). Panel c): survival analysis for the MPA (green) vs GPA (blue) vs EGPA (red) patients with ILD.