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Authors

Liu, Gabrielle Y
Ventura, Iazsmin Bauer
Achtar-Zadeh, Natalia
et al.

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Title: Prevalence and Clinical Significance of Antineutrophil Cytoplasmic Antibodies in North American Patients with Idiopathic Pulmonary Fibrosis

Short Title: ANCA antibodies in North American IPF patients

Authors: Gabrielle Y. Liu, MD[1], Iazsmin Centura, MD[2], Natalia Achtar-Zadeh, BA[1]; Brett M. Elicker, MD[3]; Kirk D. Jones, MD[4]; Paul J. Wolters, MD[1]; Harold R. Collard, MD[1]; Ayodeji Adegunsoye, MD[5]; Mary E. Strek, MD[5]; Brett Ley, MD[1]

[1]Department of Internal Medicine, University of California San Francisco, [2]Section of Rheumatology, Department of Medicine, University of Chicago, [3]Department of Radiology, University of California San Francisco, [4]Department of Pathology, University of California San Francisco, [5]Section of Pulmonary and Critical Care, Department of Medicine, University of Chicago,

Corresponding Author: Gabrielle Y. Liu, MD., 505 Parnassus Ave. M-987, San Francisco, CA 94143, gabrielle.liu@ucsf.edu

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Abbreviation List

ANCA: Antineutrophil cytoplasmic antibodies

CLIA: Clinical Laboratory Improvement Amendments

CT: Computed tomography

CTD: Connective tissue disease

DLCO: Diffusing capacity of the lung for carbon monoxide

FEV1: Forced expiratory volume in one second

FVC: Forced vital capacity

HR: Hazard ratio

ILD: Interstitial lung disease

IPF: Idiopathic pulmonary fibrosis

MPA: microscopic polyangiitis

MPO: Myeloperoxidase

PR3: Proteinase 3

TLC: Total lung capacity

UC: University of Chicago

UCSF: University of California San Francisco

UIP: Usual interstitial pneumonia

ABSTRACT

Background:

Antineutrophil cytoplasmic antibodies (ANCA) have been reported to occur in 7-10% of patients with idiopathic pulmonary fibrosis (IPF), but their clinical relevance remains unclear. The aim of this study was to estimate the prevalence of ANCA antibodies in a North American population with IPF and evaluate their clinical significance.

Methods:

This was a retrospective study of two independent cohorts of patients diagnosed with idiopathic pulmonary fibrosis (IPF) at the University of California San Francisco (discovery cohort) and the University of Chicago (replication cohort). Myeloperoxidase (MPO) and proteinase 3 (PR3)-ANCA antibodies were measured in all patients. Prevalence and associations of ANCA antibodies with clinical characteristics and transplant-free survival were evaluated.

Results:

A total of 14/353 (4.0%, 95% CI 2.2-6.5) and 20/392 (5.1%, 95% CI 3.1-7.8) of patients with IPF were positive for ANCA-antibodies at the time of diagnosis in the discovery and replication cohorts, respectively. Among those positive for MPO-antibodies, 2/6 (33%) in the discovery cohort and 3/12 (25%) in the replication cohort developed vasculitis. None of the PR3-positive patients developed vasculitis. ANCA-positive patients were more likely to be female compared to ANCA-negative patients, and were more likely to have ground glass opacities on CT. In the combined cohort of 745 patients, median transplant-free survival was not significantly different in ANCA-positive versus ANCA-negative patients ($p = 0.57$).

Conclusions:

ANCA-antibody positivity is uncommon in North American patients with IPF and not associated with baseline disease severity or transplant-free survival; however, a significant proportion of MPO-positive IPF patients develop clinical vasculitis.

INTRODUCTION

As more is understood about the differences in treatment response and outcomes between idiopathic pulmonary fibrosis (IPF), interstitial pneumonia with autoimmune features, and connective tissue disease-associated interstitial lung disease (CTD-ILD), there is an increasing need to understand the significance of various autoantibodies in patients with ILD. While antineutrophil cytoplasmic antibodies (ANCAs) are most often associated with systemic vasculidities rather than CTD, ILD is reported to be a manifestation of ANCA-associated vasculidities, particularly microscopic polyangiitis (MPA).[1] Despite this finding, testing for ANCA antibodies, specifically myeloperoxidase (MPO) and proteinase 3 (PR3) antibodies, is not part of the current major society recommendations for serologic evaluation in patients with suspected IPF, CTD-ILD or interstitial pneumonia with autoimmune features.[2–5]

Autoantibodies are found in up to 22% of patients with IPF.[6] ANCA antibodies are estimated to be present in 7-10% of patients with IPF without other symptoms of systemic vasculitis at the time of IPF diagnosis and are estimated to develop in another 10% of patients during follow-up.[7–9] This is significantly higher than the prevalence found in a study of an unselected Greek population of over 10,000 persons with a mean age of 60 years, which found the total prevalence of either MPO or PR3 antibodies to be 1.35%.[10] After exclusion of persons diagnosed with small-vessel vasculitis, the prevalence was only 0.37%, suggesting that false-positives for MPO and PR3 antibodies are uncommon.[10]

Several small single-center studies have examined the clinical significance of MPO and PR3 antibodies with inconsistent findings in how these patients may differ from ANCA-negative IPF patients with respect to clinical, radiographic, or pathologic findings. [7–9,11,12] Differences in survival between ANCA-positive and ANCA-negative IPF patients have also been inconsistent across studies to date.[7–9,12]

Almost all of the studies exploring the prevalence and significance of ANCA-antibodies in IPF have occurred in Japanese populations, where MPO antibodies and MPA are more common in the general population.[1] This is notable because MPA is the vasculitis mostly commonly associated with ILD. The clinical significance of ANCA antibodies in North American patients with IPF remains unclear. Therefore, we aimed to estimate the prevalence of ANCA antibodies in two North American populations diagnosed with IPF and explore any associated differences in survival as well as clinical, radiographic, and pathologic features between ANCA-positive and ANCA-negative IPF patients.

METHODS

Study Population

This was a retrospective cohort study of consecutive patients diagnosed with IPF prospectively enrolled in longitudinal registries and biorepositories at the University of California San Francisco (UCSF, discovery cohort) and the University of Chicago (UC, replication cohort). All new patients evaluated at the UCSF ILD clinic from 2002 to 2017 and UC ILD clinic from 2006 to 2017 were invited to enroll in these ongoing registries. To be included in this study, patients were required to have a diagnosis of IPF, based on in-person multidisciplinary discussion and supported by clinical guidelines.[3,4] Included patients at UCSF were also required to have at least 50 µl of stored serum (stored at -80^{o}C), obtained at diagnosis. All included patients from UC had ANCA-antibody results as part of their ILD clinic evaluation. This study was conducted in accordance with the amended Declaration of Helsinki and was approved by the UCSF Committee on Human Research (IRB# 10-01592) and UC Institutional Review Board (IRB #14163-A). All patients provided written informed consent at the time of enrollment.

Data collection

Baseline clinical information including demographics, pulmonary function tests, radiologic and histopathologic studies and blood samples were collected at the time of enrollment. The date of death was recorded clinically and confirmed using the United States Social Security Death Index at 6-month intervals. Lung transplants and date of lung transplants were also recorded clinically and cross-referenced with transplant records. For patients found to have ANCA antibodies, a more in-depth, retrospective chart review was performed using a standardized data collection form for the following information: any diagnosis of vasculitis, presence of other autoantibodies, descriptions of lung pathology, and treatments.

ANCA antibodies are not routinely measured at the UCSF ILD practice in the diagnostic evaluation of patients with suspected IPF, and therefore MPO and PR3 ANCA antibodies were systematically measured from stored serum samples on all included UCSF patients using a clinical-grade ELISA performed by a CLIA-certified laboratory (Exsera BioLabs, Aurora, CO, USA). At UC, ANCA-antibodies are included in the ILD autoimmunity serology panel, and therefore nearly all patients seen in the ILD clinic have ANCA-antibodies tested at the time of their initial evaluation.

For the patients in the discovery cohort, computed tomography (CT) chest scans obtained at the time closest to enrollment were scored by a chest radiologist (B.E.) using a standardized data collection form for specific features relevant to ILD and classified as definitive, possible, or inconsistent with usual interstitial pneumonia based on 2011 IPF guidelines.[4] For patients in the discovery cohort who had surgical lung biopsies, a lung pathologist (K.J.) scored the specimens for specific features and provided histopathologic classification using a standardized data collection form. The radiologist and pathologist were blinded to ANCA status. Standardized CT and pathology scores were not available for the replication cohort.

Statistical analysis

The proportion of patients with MPO, PR3, or either antibody was reported along with 95% binomial confidence intervals (95% CI). Given the low prevalence of either ANCA antibody, all subsequent associations were analyzed by categorizing patients as positive or negative for either MPO or PR3 antibodies (i.e. ANCA-positive versus ANCA-negative). Clinical and radiographic characteristics were compared between ANCA-positive and negative patients using the Fisher's exact test or t-test as appropriate. Transplant-free survival between the two groups was visualized using Kaplan-Meier survival plots and compared using the log-rank test and Cox proportional hazards models (stratified by cohort) both unadjusted and adjusted for other baseline variables commonly associated with survival in IPF; these included age, gender, FVC percent predicted, and DLCO percent predicted.

RESULTS

Clinical characteristics

Among 353 patients with IPF in the discovery cohort, 14 (4.0%, 95% CI 2.2-6.5) were found to have ANCA-antibodies present at the time of study enrollment. Of the patients with ANCA-antibodies, 8/14 (57%) had PR3 antibodies and 6/14 (43%) had MPO antibodies. The proportion of patients with positive ANCA-antibodies was similar in the replication cohort (20/392 [5.1%, 95% CI 3.1-7.8]). Of these, 2/20 (10%) had PR3 antibodies, 12/20 (60%) had MPO antibodies, and 6/20 (30%) had non-specific ANCA positivity (by immuno-fixation) but did not have specific PR3 or MPO testing done. The comparison of clinical characteristics between ANCA-positive and ANCA-negative IPF patients is summarized in **Table 1**. Compared to ANCA-negative IPF patients, ANCA-positive IPF patients were more likely to be female in both cohorts (discovery cohort: 47.1% vs 22.9%, p=0.09; replication cohort: 50.0% vs 25.0%, p = 0.01). There was also a trend in the combined cohort toward there being more non-white patients in the ANCA-positive group than the ANCA-negative group. There were no differences in severity of lung disease at enrollment, as measured by baseline pulmonary function tests. Six of the 14

ANCA-positive IPF patients in the discovery cohort, and all of the ANCA-positive patients in the replication cohort had positive titers of other antibodies (**Table 2**).

Radiologic Features

Radiographic usual interstitial pneumonia (UIP) classification and specific CT chest findings are compared between ANCA-positive and ANCA-negative IPF patients from the discovery cohort in **Table 3**. Compared to ANCA-negative IPF patients, ANCA-positive IPF patients were significantly more likely to have ground glass opacities (33.3% vs 9.3%, p=0.02) and moderate or severe (vs. mild or absent) honeycombing (33.3% vs 10.5%, p=0.04). There were no significant differences in 2011 UIP classification, distribution of fibrosis, or in the presence vs. absence of honeycombing, traction bronchiectasis, consolidation, nodules, or small airways disease. CT scans were not available for scoring using the same methods in the replication cohort.

Histopathologic Features

Eight ANCA-positive IPF patients in the discovery cohort had lung biopsies, five of which were formally scored using a standardized data collection form. Ten ANCA-positive IPF patients in the replication cohort had lung biopsies and results were obtained from chart review and were not formally scored. Given the limited number of patients with lung biopsies, there were no statistical comparisons made between ANCA-positive and ANCA-negative IPF patients. Summary of pathologic findings for ANCA-positive IPF patients are included in **Table 2**. None of these patients had evidence of capillaritis or vasculitis on pathology.

Treatment and outcomes

After a median follow-up time of 18.3 months by chart review, two of the six (33%) patients with MPO antibodies in the discovery cohort developed a clinical diagnosis of MPA, both at least one year after their diagnosis of IPF (**Table 2**). In the replication cohort, 3/12 (25%) patients with MPO antibodies subsequently developed clinical vasculitis (one developed MPA and two developed non-specific ANCA-associated vasculitis) after a median follow up of 10.5 months. Additionally, all of the patients who developed vasculitis in both the discovery and replication cohorts were female. None of the patients with PR3 antibodies in either cohort developed vasculitis during the follow-up period.

As outlined in **Table 2**, choice of pharmacologic treatment in discovery cohort appears to be based largely on time of study enrollment. The three ANCA-positive IPF patients enrolled before 2012, when the results of the PANTHER-IPF trial had been published, were all recommended azathioprine, and most patients enrolled after this time were recommended antifibrotic agents alone.[13] In the replication cohort, 12/20 (60%) ANCA-positive IPF patients received immunosuppressive medications alone, 4/20 (20%) received immunosuppressive and antifibrotic medications, 3/20 (15%) did not receive any disease-specific treatment, and 1/20 (5%) received antifibrotic medications alone.

Including combined data from both cohorts, median transplant-free survival was 5.0 years (95% CI 3.8-infinite) for ANCA-positive versus 4.9 years (95% CI 3.8-5.6) for ANCA-negative patients (log-rank p=0.57) (**Figure 1**). There was no significant difference in survival after controlling for age, gender, and baseline pulmonary function (HR = 0.84, 95% CI 0.39-1.80, p=0.65).

Discussion

This study demonstrates that a small percentage of North American IPF patients are positive for ANCA antibodies, but only a subset of patients with MPO antibodies appear to develop clinical vasculitis. It also provides further evidence that ANCA-antibody positivity is more common in IPF patients compared to the general population, but suggests that it may be less common in North American

populations than previously reported in Japanese IPF populations. This difference appears to be due largely to differences in prevalence of MPO-antibody positivity. In this study, 1.7-3.1% of IPF patients were MPO-positive, whereas prior studies performed in Japan found that MPO positivity was seen in about 4-10% of patients with IPF.[7,9,12,14] In contrast, the prevalence of PR3 positivity in the discovery cohort (2.3%) was similar to prior studies (2-5%). [8,9,14]

Clinically, ANCA-positive IPF patients appear to be similar to ANCA-negative patients except for a more even gender distribution in ANCA-positive patients compared to the ANCA-negative patients. This mirrors the gender distribution in the ANCA-associated vasculidities where the percentage of males to females is also often equal or just slightly male-predominant.[15,16] However, this finding contrasts prior studies of ANCA-positive IPF patients which found low proportions of female patients, similar to ANCA-negative patients.[1,2,11,12]

To date, there have been no consistent CT chest findings that distinguish ANCA-positive IPF patients from ANCA-negative IPF patients. Nozu et al. and Foulon et al. found no significant difference in chest CT features between ANCA-positive and ANCA-negative pulmonary fibrosis patients.[17] Ando et al. found low attenuation areas (i.e. mosaic perfusion) to be more common in MPO-positive IPF patients, although there were significantly more smokers in the MPO-positive IPF group.[1] In this study, the most significant difference seen on chest CT of ANCA-positive IPF patients was the increased prevalence of ground glass opacities. This is consistent with Hosoda et al's finding of increased attenuation around honeycombing and cysts in MPO-positive patients with UIP pattern on surgical lung biopsy.[12] The increased ground glass or areas of increased attenuation may reflect increased inflammation in the lungs of these ANCA-positive IPF patients, as Hosoda et al also found that MPO-positive patients had more prominent inflammatory cell infiltration and lymphoid follicles with germinal centers. We were unable to replicate these findings due to the low number of ANCA-positive patients with surgical lung biopsies.

Regarding outcomes of ANCA-positive patients with IPF, 25-33% of patients with MPO antibodies subsequently developed clinical manifestations of vasculitis. This is similar to prior studies of MPO-positive IPF patients which found 16-26% go on to develop MPA, although one study found a much higher percentage (83%).[1,3,11,12] Interestingly, all of the patients in this study who developed clinical vasculitis were MPO positive and female, while none of the PR3 or male patients developed vasculitis during follow up. The lack of development of vasculitis in PR3-positive pulmonary fibrosis patients is consistent with prior studies.[2,3] None of the lung biopsies from the ANCA-positive IPF patients showed any evidence of vasculitis at baseline. This finding is consistent with almost all prior studies, although one study did report evidence of vasculitis in the lung biopsies of 5 of 15 patients with MPO-positive IPF.[1,7,12,14,18]

ILD is now recognized as a relatively common manifestation of MPA, seen in 2.7-45% of MPA patients, with UIP pattern seen histologically in 45-100% of these patients.[1,19–21] Additionally, pulmonary fibrosis is a morbid manifestation of MPA. One study found four-fold higher mortality in MPA patients with ILD compared to those without ILD.[21] Another study of MPA patients with and without ILD found that respiratory failure was the cause of death in all the patients with MPA and ILD, while none of the MPA patients without ILD died during follow-up.[19] However, in the context of IPF, this study did not find a statistically significant difference in survival between ANCA-positive and ANCA-negative patients, which may be due to the high mortality of IPF.[1,2,11,12]

This study has several key strengths compared to prior studies of ANCA positivity in IPF. It is the first study to systematically estimate the prevalence of ANCA-antibody positivity in two independent North American populations of IPF patients. It is also the largest study to date examining the clinical associations of ANCA positivity in IPF patients. There are, however, notable limitations to this study. First, the radiographic associations found in the discovery cohort could not be replicated, and therefore these results are provisional. Second, the limited duration of clinical follow-up for ANCA positive

patients may have resulted in an under-estimation of the risk of developing vasculitis. Third, the incidence of ANCA sero-conversion during follow up could not be determined because only baseline serum samples were evaluated.

These findings have important clinical implications. Given the low prevalence of PR3-antibody positivity in North American IPF patients and the lack of any associated impact on survival or development of vasculitis, these results do not support the routine measurement of PR3-antibodies in patients with suspected IPF. In contrast, MPO-positivity, while uncommon in IPF patients, when present is associated with at least a 25-33% risk of developing clinical manifestations of vasculitis. Because development of vasculitis has therapeutic implications and may impact morbidity, measurement of MPO-antibodies may be indicated in patients with suspected IPF, especially female patients who have the highest risk of MPO-positivity and vasculitis.

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TABLES

Table 1. Clinical characteristics of idiopathic pulmonary fibrosis patients that are positive versus negative for anti-neutrophil cytoplasmic antibodies

	Combined			Discovery			Replication		
Characteristic	**ANCA-negative**	**ANCA-positive**	**p-value**	**ANCA-negative**	**ANCA-positive**	**p-value**	**ANCA-negative**	**ANCA-positive**	**p-value**
Total number of patients	711	34		339	14		372	20	
Age, mean (SD)	70.3 (8.3)	67.9 (8.9)	0.09	70.6 (8.6)	66.6 (7.8)	0.09	70.1 (8.0)	68.8 (9.6)	0.48
Female, n (%)	163 (22.9)	16 (47.1)	0.001	70 (20.6%)	6 (42.9%)	0.09	93 (25.0%)	10 (50.0%)	0.01
Race/Ethnicity, n (%)			0.06			0.21			0.05
White or Caucasian	590 (83.0%)	24 (70.6%)		272 (80.2%)	10 (71.4%)		318 (85.5%)	14 (70.0%)	
Asian or Pacific Islander	36 (5.1%)	1 (2.9%)		27 (8.0%)	0 (0.0%)		9 (2.4%)	1 (5.0%)	
Black or African American	23 (3.2%)	4 (11.8%)		3 (0.9%)	0 (0.0%)		20 (5.4%)	4 (20.0%)	
Hispanic or Latino	53 (7.5%)	4 (11.8%)		28 (8.3%)	3 (21.4%)		25 (6.7%)	1 (5.0%)	
Other or Unknown	9 (1.3%)	1 (2.9%)		9 (2.7%)	1 (7.1%)				
FVC%, mean (SD)	67.4 (18.1)	66.3 (20.7)	0.72	69.8 (18.1)	70.5 (17.9)	0.88	65.3 (17.9)	63.3 (22.4)	0.63
DLCO%, mean (SD)	48.4 (17.5)	50.4 (22.2)	0.54	47.4 (16.7)	53.0 (26.2)	0.25	49.4 (18.2)	48.6 (19.3)	0.86
*Ever smoker, n (%)	504 (70.9%)	26 (76.5%)	0.48	236 (69.6%)	12 (85.7%)	0.20	268 (72.0%)	14 (70.0%)	0.84

Unless otherwise specified, data presented as number of patients (% total)

*Ever smoker (current or former) vs never smoker

Abbreviations: n, number of patients; ANCA, anti-neutrophil cytoplasmic antibodies; SD, standard deviation; FVC%, forced vital capacity percent predicted; DLCO%, diffusing capacity of lung for carbon monoxide percent predicted;

Table 2. Clinical characteristics, treatment, and outcomes of idiopathic pulmonary fibrosis patients positive for anti-neutrophil cytoplasmic antibodies

ID/ Cohort	Age/ Sex	ANCA type	Vasculitis diagnosis	Other auto-antibodies, titers	Lung biopsy results	Outcome	Treatment	Months of database follow-up	Months of chart follow-up
1/D	72F	PR3	no	*	Emphysema, some areas of fibroblast foci, lung fibrosis with architectural distortion and subpleural accentuation. Nonclassifiable fibrosing interstitial pneumonitis.	Deceased	AZA	25	0
2/D	73F	MPO	no	*	UIP	Deceased	AZA	59	0
3/D	54F	MPO	MPA	ANA 1:160, RF 157	*	Deceased	Steroids, AZA, CYC, MMF, RTX	101	102
4/D	65M	PR3	no	none	Moderate to severe fibrosis with subpleural and bronchiolocentric accentuation, fibroblast foci and patchy airway-centered fibrosis. No well-developed microscopic honeycombing.	Transplant	Pirfenidone, Nintendanib	60	73
5/D	63F	MPO	MPA	ANA 1:160	*	Alive	Steroids, RTX, NAC	48	27
6/D	67M	MPO	no	ANA 1:40	*	Alive	*	42	0.0
7/D	65F	MPO	no	none	*	Alive	Nintendanib	36	46
8/D	67M	MPO	no	ANA 1:640, RF 351	*	Alive	Nintendanib	25	34
9/D	59M	PR3	no	ANA 1:160, anti-dsDNA, anti-CCP	UIP	Alive	*	16	0
10/D	55F	PR3	no	*	UIP	Alive	Pirfenidone	12	18
11/D	84M	PR3	no	ANA 1:40	*	Alive	Nintendanib	14	20
12/D	65M	PR3	no	none	Emphysema, insufficient material.	Alive	Pirfenidone, Nintendanib,	11	18
13/D	76M	PR3	no	none	UIP. Scattered lymphoid aggregates with occasional germinal centers noted in the fibrotic regions. Pulmonary arteries show mild to moderate thickening.	Alive	Pirfenidone, Nintendanib	11	7
14/D	67M	PR3	no	none	*	Alive	Nintendanib	5	11
15/R	84M	NS	no	SSA	*	Alive	None	4	7
16/R	53M	NS	no	ANA 1:160	Extensive OP, superimposed on UIP	Alive	Steroids, AZA	8	7
17/R	65M	PR3	no	ANA 1:160	UIP, emphysema, moderate to severe pulmonary hypertension	Alive	Nintedanib, Pirfenidone	26	32
18/R	75F	MPO	no	ANA 1:320, anti-CCP	*	Alive	Steroids, Nintendanib	14	16
19/R	72M	MPO	no	RF 166, Scl70	UIP, centrilobular emphysema, scattered regions of dendriform calcifications	Alive	Steroids, MMF, Pirfenidone	0	15

20/R	82F	MPO	no	RF 37, SSA, SSB, anti-Ku	*	Alive	Steroids, MMF, Pirfenidone	3	2
21/R	46F	MPO	no	ANA 1:160, RF 62	UIP with poorly formed granulomas consistent with chronic hypersensitivity pneumonitis; secondary pulmonary hypertension	Alive	Steroids, AZA, RTX, CYC	26	22
22/R	67F	MPO	MPA	ANA 1:160	UIP	Alive	Steroids, AZA, MMF, RTX	0	4
23/R	61F	MPO	AAV	ANA 1:320	UIP, NSIP in less involved areas, rare multinucleated giant cells	Alive	Steroids, AZA, MMF	60	66
24/R	71M	NS	no	ANA 1:40	*	Alive	Steroids	2	12
25/R	69M	MPO	no	ANA 1:280, RF 78	UIP, lymphoid follicles with germinal centers. Focal giant cells without granulomas	Transplant	Steroids	24	31
26/R	70M	NS	no	ANA 1:160	*	Alive	Steroids, Pirfenidone	1	2
27/R	74M	NS	no	ANA 1:2560	UIP, few non-necrotizing granulomas consistent with chronic hypersensitivity pneumonitis	Alive	Steroids, MMF	11	15
28/R	62F	MPO	no	ANA 1:640	UIP with extensive OP	Deceased	Steroids	3	2
29/R	76F	MPO	No	ANA 1:80, RF, SSA	*	Alive	Steroids, AZA	72	0
30/R	55F	NS	No	ANA 1:160	*	Alive	Steroids, AZA	29	48
31/R	77F	PR3	No	ANA 1:320	UIP	Alive	None	80	85
32/R	77M	MPO	No	RF 23	*	Deceased	None	8	0
33/R	71M	MPO	No	ANA 1:160	*	Deceased	Steroids	5	5
34/R	68F	MPO	AAV	RF 20	*	Deceased	Steroids, CYC	45	9

Treatment recommended or received reflects medication recommended by consulting pulmonologist or medication that patient was recorded as taking. Months of database follow-up reflects time since time from study enrollment to most recent vital status check. Months of chart follow-up reflects time from study enrollment to most recent clinical documentation for review in the patient's electronic medical record.

*No data available.

D, discovery cohort; R, replication cohort; NS, nonspecific ANCA; ANCA, antineutrophil cytoplasmic antibody; PR3, proteinase 3 antibody; MPO, myeloperoxidase; MPA, microscopic polyangiitis; AAV, ANCA-associated vasculitis; ANA, antinuclear antibody; RF, rheumatoid factor; anti-dsDNA, anti-double stranded DNA antibody; anti-CCP, anti-cyclic citrullinated peptide antibody; SSA, anti-Ro; SSB, anti-La; UIP, usual interstitial pneumonia; NSIP, nonspecific interstitial pneumonia; OP, organizing pneumonia; AZA, azathioprine; CYC, cyclophosphamide; MMF mycophenolate mofetil; RTX, rituximab; NAC, N-acetylcysteine

Table 3. Chest computed tomography findings of idiopathic pulmonary fibrosis patients in the discovery cohort that are positive versus negative for anti-neutrophil cytoplasmic antibodies

Feature	ANCA-negative	ANCA-positive	p-value
Total number with CT scored	313	12	
UIP, Definite or possible*, n (%)	249 (79.6%)	9 (75.0%)	0.72
Reticulation, moderate or severe+, n (%)	249 (79.6%)	8 (66.7%)	0.28
Traction bronchiectasis present, n (%)	307 (98.1%)	12 (100.0%)	1.0
moderate or severe+	195 (62.3%)	4 (33.3%)	0.07
Honeycombing present, n (%)	211 (67.4%)	9 (75.0%)	0.76
moderate or severe+	33 (10.5%)	4 (33.3%)	0.04
Fibrosis, cranial-caudal distribution, n (%)			0.64
Diffuse	14 (4.5%)	1 (8.3%)	
Lower	288 (92.0%)	11(91.7%)	
Middle or Upper	11 (3.5%)	0 (0.0%)	
Fibrosis, axial distribution, n (%)			1.0
Central	2 (0.6%)	0 (0.0%)	
Diffuse	23 (7.3%)	1 (8.3%)	
Peripheral	288 (92.0%)	11 (91.7%)	
Ground glass opacity present, n (%)	29 (9.3%)	4 (33.3%)	0.02
Consolidation present, n (%)	11 (3.5%)	0 (0.0%)	1.0
Nodules present, n (%)	2 (0.6%)	0 (0.0%)	1.0
Small airways disease present, n (%)	68 (97%)	4/4 (100%)	1.0

Computed tomography scans of the chest evaluated for UIP pattern as well as specific radiographic findings pertinent to interstitial lung disease.

*Definite or possible UIP pattern vs inconsistent with UIP pattern

+Moderate or severe vs mild or none

ANCA, anti-neutrophil cytoplasmic antibody; UIP, usual interstitial pneumonia; ns, non-significant

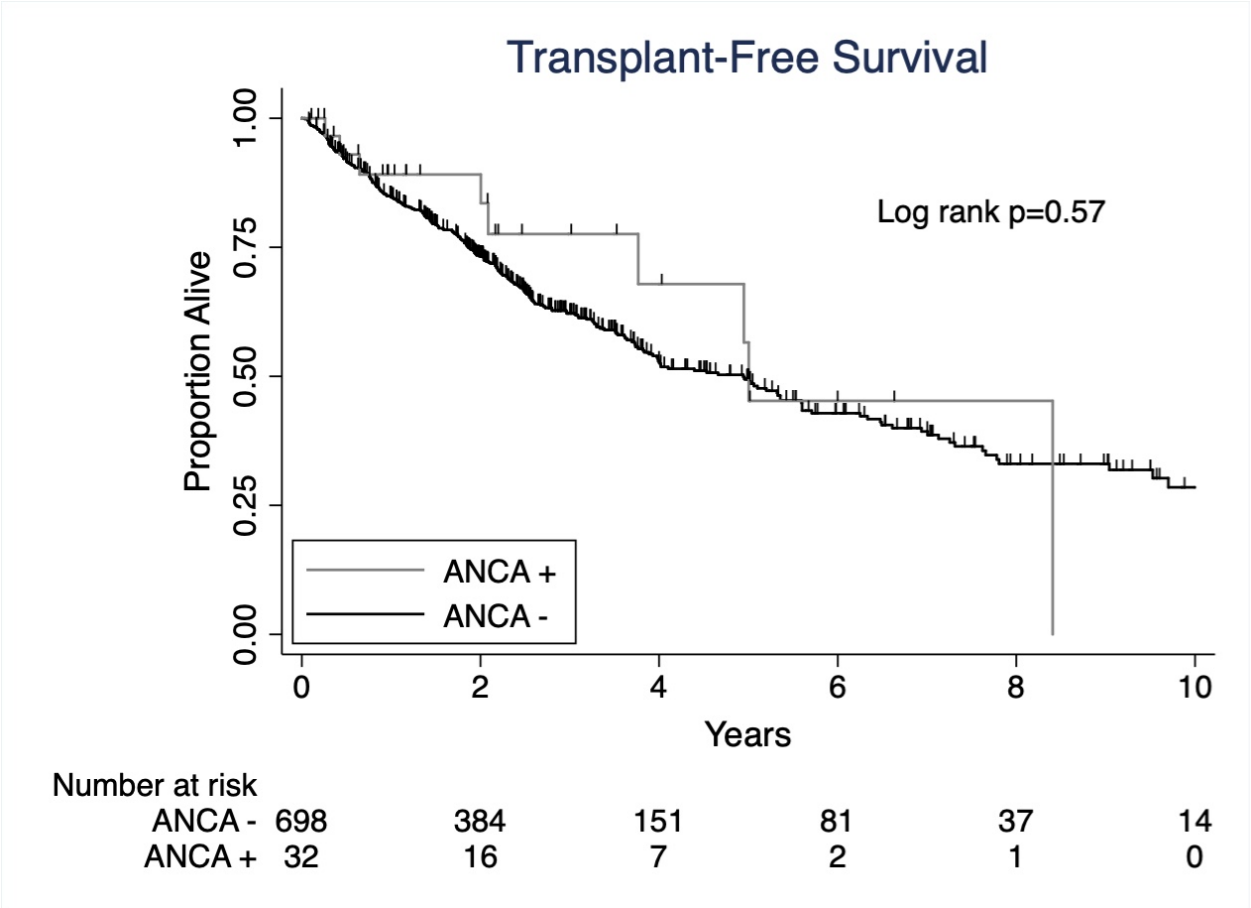

Figure 1. Kaplan-Meier curve comparing transplant-free survival in idiopathic pulmonary fibrosis patients that are positive versus negative for anti-neutrophil cytoplasmic antibodies.

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Guarantor statement:

Gabrielle Y. Liu is the guarantor of the content of the manuscript, including the data and analysis.

Author's contributions to the study:

- Conception and design: GYL, HRC, BL
- Acquisition and/or interpretation of data: GYL, IC, NAZ, BME, KDJ, PJW, AA, BL
- Drafting of manuscript and/or critical revision of major intellectual content: All authors
- Final approval of the version to be published: All authors

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