

Subsequent Identification of a Connective Tissue Disease Amongst Patients with Idiopathic Pulmonary Fibrosis : A Long-term Observational Study in 527 Patients

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Abstract

Background: Connective tissue disease (CTD) might occur during the course of idiopathic pulmonary fibrosis (IPF). Clinical factors associated with CTD development in IPF patients have still not been identified. We investigated which antibodies have a significant association with the development of CTD during the clinical course of IPF.

Methods: We retrospectively reviewed the records of 527 patients with a first diagnosis of IPF between January 2007 and March 2014 and investigated the time to CTD development after IPF diagnosis in these patients.

Results: CTD developed in 15 patients at a median of 2.1 years (range 1.2–4.8) after IPF diagnosis. All patients had anti-neutrophil cytoplasmic antibodies (ANCA) or autoantibodies that met the serology criteria for interstitial pneumonitis with autoimmune features. Survival duration for IPF patients with progression to CTD was 5.3 (3.8, 6.7) years, which was significantly longer than for IPF patients without progression to CTD [2.9 (1.7, 4.8), $p = 0.001$]. Independent risk factors for CTD development in IPF patients included female gender [adjusted hazard ratio (HR) 5.319, $p = 0.0082$], titer of rheumatoid factor (RF; adjusted HR, 1.006; $p = 0.022$), titer of anti-citrullinated protein antibody (ACPA; adjusted HR, 1.009; $p = 0.0011$), and titer of myeloperoxidase (MPO)-ANCA (adjusted HR, 1.02; $p < 0.0001$).

Conclusions: Progression to CTD is uncommon in IPF patients. However, a significant number of IPF patients with high titers of RF, ACPA, or MPO-ANCA progressed to CTD. RF, ACPA, and MPO-ANCA might be significantly associated with CTD development in IPF patients.

Background

Idiopathic pulmonary fibrosis (IPF) is a chronic disease characterized by pulmonary fibrosis and parenchymal destruction.(1, 2) Usual interstitial pneumonia (UIP) is the typical radiological and histopathological pattern of IPF.(2, 3) IPF is, by definition, UIP of unknown cause, and UIP is also observed in patients with connective tissue disease (CTD). Generally, CTD/UIP is diagnosed following investigation of patients with suspected UIP.(1) However, we sometimes encounter patients who progress to CTD during the clinical course of IPF/UIP and whose diagnosis changes to CTD/UIP.(4–7) Because CTD/UIP differs from IPF/UIP in treatment and prognosis, (8–12) it is important to predict the development of CTD during the clinical course of IPF/UIP. However, the cumulative incidence and predictive factors associated with the development of CTD during the clinical course of IPF remain unclear. These factors might be valuable clues for determining the pathogenesis of pulmonary fibrosis in patients with CTD.

Previously, we identified that the autoantibody-positive IPF patients were associated with a good prognosis; moreover, the use of immunosuppressants was associated with a better prognosis in these patients as opposed to the autoantibody-negative patients.(13) At present, autoantibody-positive IPF cases have not been classified as interstitial pneumonitis with autoimmune features (IPAF), and thus, the use of immunosuppressants is not recommended.(14) The clinical characteristics of autoantibody-positive IPF are similar to those of CTD/UIP patients.

We hypothesize that some IPF patients have a clinically significant association with autoimmunity, and that autoantibodies are important biomarkers for identifying these patients. Based on this hypothesis, we investigated whether the serology criteria presented above were associated with the development of CTD during the clinical course of IPF in the patients from our previous study, with a particular focus on which autoantibodies have a significant association with the development of CTD.

Methods

We retrospectively reviewed the records of 527 patients diagnosed with IPF by a multidisciplinary team (pulmonologist, radiologist, rheumatologist, and pathologist) assessing the results of high-resolution computed tomography or lung biopsy in a tertiary hospital from January 2007 through March 2014. The patients were followed up until April 2016 (for 2.4 [IQR, 1.1; 4.2] years). Information regarding demographics, medication, laboratory tests, bronchoscopy, and pulmonary function tests (PFT) was retrospectively collected from the institutional electronic medical records and entered into a database for analysis.

CTD-related symptoms were defined by the IPAF clinical domain. (15) IPF patients with suspected CTD-related symptoms or autoantibodies were evaluated by experienced rheumatologists, and those with CTD-related symptoms confirmed by a rheumatologist at the first visit to the clinic for IPF diagnosis (baseline) were excluded from this study. No clinical or morphologic

manifestation suitable for the IPAF, were identified in the patients included in our study. We investigated the length of time from baseline to CTD diagnosis by an expert rheumatologist in IPF patients. Diagnosis of the specific type of CTD was made in accordance with the criteria from their corresponding societies.(16–20) We defined the survival duration of patients with IPF from their first visit to the clinic for IPF diagnosis to death, and we defined the baseline as the date of the first visit to the clinic for IPF diagnosis. Death was defined as cessation of national health insurance cover. Glucocorticoid (not for management of acute exacerbation) and immunosuppressants for immunomodulation were administered on an individual basis. The present study protocol was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2016 – 0222).

Tests for serologic autoantibodies

The following antibodies were tested; this consisted of tests for anti-citrullinated peptide antibody (ACPA), antinuclear antibody (ANA), rheumatoid factor (RF), anti-dsDNA antibody, anti-Sm antibody, anti-RNP antibody, anti-Ro (SSA) antibody, anti-La (SSB) antibody, anti-Jo-1 antibody, anti-Scl-70 antibody, myeloperoxidase (MPO) anti-neutrophil cytoplasmic antibody (ANCA), and proteinase-3 (PR3) ANCA. Anti-synthetase syndrome Ab (except Jo-1), anti PM-Scl, anti-MDA-5 in the IPAF serologic domain were not tested because that was incompatible with current practice in ASAN Medical Center. Each untested autoantibody was considered autoantibody negative. Autoantibody tests were performed at the time of initial IPF diagnosis in most patients. These autoantibodies were repeatedly tested, usually 1–2 years after the first test in some patients.

Statistical analyses

Continuous variables are reported as means \pm standard deviations or medians and interquartile ranges (IQR), and categorical variables are presented as percentages. Differences between groups were evaluated by the Student's t test or the Mann–Whitney U test for continuous variables, and by the χ^2 or Fisher's exact test for categorical variables. Multivariable Cox proportional-hazards models with backward elimination were used to investigate the risk factors for the development of CTD. The proportional-hazards assumptions were assessed based on Schoenfeld residuals and log-log plots. Statistical significance was set at $p < 0.05$. Statistical analysis was performed with R software (R Foundation for Statistical Computing, Vienna, Austria).

Results

Of the 527 IPF patients in the study, 42% ($n = 221/527$) had autoantibodies, and 29% ($n = 153/527$) had ANCA or autoantibodies that met the IPAF serology criteria. (Fig. 1, Supplementary table 1). CTD developed in 15 (2.8%) IPF patients, at a median of 2.1 [IQR, 1.2–4.8] years after the initial diagnosis of IPF [seven patients with rheumatoid arthritis (RA), one undifferentiated connective tissue disease, two Sjögren syndrome (SJS), one polyarteritis nodosa, and four microscopic polyangiitis (MPA), Tables 1 and 2]. All of these patients who progressed to CTD had either ANCA or any other tested autoantibodies that satisfied the IPAF serology criteria in the clinical course. Two IPF patients who progressed to RA had MPO-ANCA. A significant number of IPF patients with high titers of RF, ACPA, or MPO-ANCA tested at first visit to the clinic progressed to CTD (Fig. 2). Furthermore, four patients (RA case 1, 3, 6, and MPA case 12, Table 2), who initially had either a low titer or absence of RF, ACPA, or MPO-ANCA, were found to have high titers of these autoantibodies following progression to CTD.

Table 1

Clinical features of patients who developed connective tissue disease during the course of idiopathic pulmonary fibrosis

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Age	63	57	66	58	67	48	64	60	66	53	70	56	60	64	69
Gender	F	M	F	M	M	F	F	M	F	F	M	F	M	F	M
Diagnosis of CTD	RA	RA	RA	RA	RA	RA	RA	UCTD	SJS	SJS	PAN	MPA	MPA	MPA	MPA
Time from IPF diagnosis to CTD development (years)	6.6	1.8	2.1	8.8	0.9	5.8	0.6	1.1	1.3	3.8	1.4	3.1	6.1	0.8	2.3
Death	N	Y	N	N	Y	N	Y	Y	Y	N	Y	Y	Y	N	N
Survival duration (years)	7.6	3.8	4.9	10.5	4.4	6.7	1.9	6.3	3.9	6.8	2.2	3.2	6.6	6.8	5.3
FVC%	79	69	80	84	74	80	68	85	83	83	82	102	71	83	53
DLCO%	70	59	72	100	60	63	48	45	64	63	62	110	29	70	50
ESR (mm/h)	47	47	34	19	120	8	9	47	36	36	120	84	23	24	120
CRP (mg/dL)	0.1	0.26	0.1	0.07	0.24	0.1	0.19	8.19	0.22	0.22	1.79	0.1	0.91	0.1	15.57
AZA (before CTD diagnosis)	N	N	Y	N	Y	N	N	N	Y	N	N	N	N	N	N
CYC (before CTD diagnosis)	N	N	N	N	N	N	N	N	N	N	Y	N	N	N	N
CSA (before CTD diagnosis)	N	N	N	N	N	N	N	N	N	Y	N	N	N	N	N
MMF (before CTD diagnosis)	N	N	N	N	N	N	N	N	N	N	N	N	N	N	N
AZA = azathioprine; CTD = connective tissue disease; CYC = cyclophosphamide; CSA = cyclosporine; DLCO = diffusing capacity of the lung for carbon monoxide; ESR = erythrocyte sedimentation rate; CRP = C-reactive protein; FVC = forced vital capacity; IPF = idiopathic pulmonary fibrosis; MMF = mycophenolate mofetil; MPA = microscopic polyangiitis; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; UCTD = undifferentiated connective tissue disease; SJS = Sjögren's syndrome.															

Table 2

Autoantibody profiles in patients who developed connective tissue disease during the course of idiopathic pulmonary fibrosis

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Diagnosis of CTD	RA	RA	RA	RA	RA	RA	RA	UCTD	SJS	SJS	PAN	MPA	MPA	MPA	MPA
RF 1st	-	336	-	-	28	-	548	-	-	NA	34	-	-	-	127
RF on f/u	-	696	513	19	41	325	181	NA	-	-	130	29	NA	32	49
ACPA 1st	-	73	20	> 200	> 340	-	340	-	-	NA	NA	-	-	-	-
ACPA on f/u	14	32	> 340	> 200	> 340	274	340	NA	-	-	-	-	NA	-	-
ANA 1st	1:40	-	-	-	-	-	-	1:640	1:640	1:40	-	1:40	1:40	-	1:40
ANA on f/u	1:80	1:40	1:40	-	-	-	-	1:640	1:320	1:40	-	NA	1:40	-	-
Anti-dsDNA antibody 1st	-	NA	-	-	-	-	-	-	-	-	NA	NA	-	-	-
Anti-dsDNA antibody on f/u	NA	NA	NA	NA	-	NA	-	NA	-	-	NA	-	NA	NA	NA
Anti-RNP antibody 1st	-	-	NA	-	-	-	14	NA	-	-	-	-	-	-	-
Anti-RNP antibody on f/u	NA	NA	NA	NA	NA	-	NA	NA	-	NA	-	-	NA	NA	-
Anti-Sm antibody 1st	-	-	NA	-	-	-	-	-	-	-	-	-	-	-	-
Anti-Sm antibody on f/u	NA	NA	NA	NA	NA	-	NA	NA	-	NA	-	-	NA	NA	-
Anti-Ro antibody 1st	-	-	32	-	-	-	-	-	>240	-	-	-	-	-	-
Anti-Ro antibody on f/u	NA	NA	NA	NA	-	-	NA	NA	>240	NA	-	-	NA	NA	-
Anti-La antibody 1st	-	-	-	NA	-	-	-	-	181	-	-	-	-	-	-
Anti-La antibody on f/u	NA	NA	NA	NA	-	-	NA	NA	144	NA	-	-	NA	NA	-
Anti-Scl antibody 1st	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

ACPA = anti-citrullinated protein antibody; ANA = antinuclear antibody; CTD = connective tissue disease; MPA = microscopic polyangiitis; NA = not available; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; RF = rheumatoid factor; UCTD = undifferentiated connective tissue disease; SJS = Sjögren's syndrome.

Case	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Anti-Scl antibody on f/u	-	NA	NA	-	-	-	NA	NA	-	-	-	-	NA	NA	-
Anti-Jo-1 antibody 1st	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Anti-Jo-1 antibody on f/u	-	NA	NA	-	-	-	NA	NA	-	-	NA	-	NA	NA	-
MPO-ANCA 1st	-	-	-	-	-	19	-	-	-	-	-	-	> 134	174	192
MPO-ANCA on f/u	-	NA	NA	38	-	-	-	NA	-	-	NA	> 134	NA	90	> 134
PR3-ANCA 1st	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PR3-ANCA on f/u	-	NA	NA	-	-	-	-	NA	-	-	NA	-	NA	-	20
ACPA = anti-citrullinated protein antibody; ANA = antinuclear antibody; CTD = connective tissue disease; MPA = microscopic polyangiitis; NA = not available; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; RF = rheumatoid factor; UCTD = undifferentiated connective tissue disease; SJS = Sjögren's syndrome.															

IPF patients with progression to CTD were significantly younger than the IPF patients without progression to CTD, and had a significantly higher proportion of women, rheumatoid factor positivity, ACPA positivity, MPO-ANCA positivity, and presence of lymphocytes in bronchoalveolar lavage (BAL). The survival duration for the IPF patients with progression to CTD was 5.3 [3.8–6.7] years, which was significantly longer than the IPF patients without progression to CTD (2.9 [1.7–4.8] years, $p = 0.001$). The clinical demographic data, baseline results of the PFT, autoantibody profiles, medication, and outcomes for the overall patient group are summarized in Tables 3 and 4.

Table 3
 Characteristics of patients who developed connective tissue disease during the course of idiopathic pulmonary fibrosis

	IPF without progression to CTD (N = 512)	IPF with progression to CTD (N = 15)	P value
Age at baseline	67.0 [61.0–72.0]	63.0 [57.5–66.0]	0.014
Gender, male	412 (80.5%)	7 (46.7%)	0.004
Ever smoked	358 (71.6%)	7 (46.7%)	0.071
IPAF serologic criteria or ANCA			< 0.001
No autoantibody	306 (59.8%)	0 (0.0%)	
Meets criteria	138 (27.0%)	15 100.0%)	
Positive autoantibody but does not meet criteria	68 (13.3%)	0 (0.0%)	
Autoantibody (tested number)			
Rheumatoid factor (n = 520)	56/505 (11.1%)*	9/15 (60.0%)*	< 0.001
ACPA (n = 468)	16/453 (3.5%)*	6/15 (40.0%)*	< 0.001
Antinuclear antibody (n = 525)	44/510 (8.6%)*	4/15 (26.7%)*	0.053
Anti-dsDNA antibody (n = 302)	19/289 (6.6%)*	0/13 (0.0%)*	0.711
Anti-RNP antibody (n = 446)	1/432 (0.2%)*	0/14 (0.0%)*	1.000
Anti-Sm antibody (n = 446)	2/432 (0.5%)*	0/14 (0.0%)*	1.000
Anti-Ro antibody (n = 523)	18/508 (3.5%)*	2/15 (13.3%)*	0.206
Anti-La antibody (n = 523)	1/508 (0.2%)*	1/15 (6.7%)*	0.060
Anti-Scl antibody (n = 518)	1/503 (0.2%)*	0/15 (0.0%)*	1.000
Anti-Jo antibody (n = 514)	1/499 (0.2%)*	0/15 (0.0%)*	1.000
MPO-ANCA (n = 517)	23/502 (4.6%)	6/15 (40.0%)	< 0.001
PR3-ANCA (n = 517)	4/502 (0.8%)	0/15 (0.0%)	1.000
Baseline 6MWT pulse (heart rate /min)	113.5 ± 17.7	112.3 ± 13.3	0.802
Baseline 6MWT SaO ₂ (%)	92.0 [87.0–95.0]	94.0 [89.0–96.0]	0.160
Baseline 6MWT Distance (m)	440.0 [360.0–500.0]	445.0 [390.0–483.5]	0.865
Baseline FVC predicted (%)	68.4 ± 16.6	77.1 ± 11.4	0.046
Baseline DLCO predicted (%)	54.1 ± 17.3	64.3 ± 20.1	0.026
Baseline C-reactive protein (mg/dL)	0.3 [0.1–0.9]	0.2 [0.1–1.1]	0.503
Baseline white blood cell (*10 ³ /μL)	8.0 [6.7–9.8]	7.2 [5.5–9.3]	0.235
BAL fluid nucleated cell count	250.0 [110.0–420.0]	200.0 [100.0–330.0]	0.534
BAL fluid neutrophils (%)	11.0 [4.0–27.5]	6.5 [4.0–55.0]	0.817
BAL fluid lymphocytes (%)	10.0 [4.5–18.0]	20.0 [10.0–24.0]	0.038
6MWT = 6 minute walk test; ANCA = anti-neutrophil cytoplasmic antibodies; BAL = bronchoalveolar lavage; CTD = connective tissue disease; DLCO = diffusing capacity of the lung for carbon monoxide; FVC = forced vital capacity; IPAF = interstitial pneumonitis with autoimmune features; IPF = idiopathic pulmonary fibrosis; SaO ₂ = Oxygen saturation.			
*Meet IPAF serologic domain			

Table 4

Medications and outcomes of idiopathic pulmonary fibrosis patients who developed connective tissue disease during the course of idiopathic pulmonary fibrosis

	IPF without progression to CTD (N = 512)	IPF with progression to CTD (N = 15)	P value
Diagnosis of CTD developed during IPF disease course			
- Rheumatoid arthritis		7 (46.7%)	
- Undifferentiated connective tissue disease		1 (6.7%)	
- Sjögren's syndrome		2 (13.3%)	
- Polyarteritis nodosa		1 (6.7%)	
- Microscopic Polyangiitis		4 (26.7%)	
Time to CTD development after IPF diagnosis (years)		2.1 [1.2–4.8]	
Steroid for immunomodulation	184 (35.9%)	13 (86.7%)	< 0.001
Immunomodulator	130 (25.4%)	12 (80.0%)	< 0.001
- Azathioprine	86 (16.8%)	4 (26.7%)	0.514
- Cyclophosphamide	10 (2.0%)	4 (26.7%)	< 0.001
- Cyclosporin	53 (10.4%)	3 (20.0%)	0.441
- Mycophenolate mofetil	22 (4.3%)	2 (13.3%)	0.305
- Methotrexate	0 (0.0%)	5 (33.3%)	< 0.001
- Sulfasalazine	0 (0.0%)	2 (13.3%)	< 0.001
- Tacrolimus	6 (1.2%)	0 (0.0%)	1.000
- Sirolimus	1 (0.2%)	0 (0.0%)	1.000
Mortality in 5 years	302 (59.0%)	6 (40.0%)	0.228
Survival duration (years)	2.9 [1.7–4.8]	5.3 [3.8–6.7]	0.001
CTD = connective tissue disease; IPF = idiopathic pulmonary fibrosis			

Among the IPF patients, independent risk factors for development of CTD in IPF patients included female gender (adjusted hazard ratio (HR) 5.319, $p = 0.0082$), baseline titer of RF; adjusted HR 1.006, $p = 0.022$), baseline titer of ACPA; adjusted HR 1.009, $p = 0.0011$), and baseline titer of MPO-ANCA (adjusted HR 1.02, $p < 0.0001$).

Discussion

CTD developed in 15 IPF patients during the clinical course of IPF/UIP. All these patients had ANCA or autoantibodies that met the IPAF serology criteria during the clinical course. RF, ACPA, and MPO-ANCA were important risk factors for the development of CTD in IPF patients, but antinuclear antibody (ANA) was not a risk factor. Progression to CTD is uncommon in IPF patients, but a significant number of IPF patients with high titers of RF, ACPA or MPO-ANCA tested at baseline progressed to CTD. Furthermore, there were four patients who initially had low titer or no RF, ACPA, or MPO-ANCA, but had high titers of these autoantibodies when progressed to CTD. This suggests that RF, ACPA, and MPO-ANCA may be significantly associated with the development of CTD/UIP, and that IPF/UIP with high titers of RF, ACPA or MPO-ANCA might be the initial clinical manifestation of CTD.(2, 21–23) High titers of RF, ACPA, or MPO-ANCA might be an important factor in the subsequent identification of CTD among patients with IPF.

Development of CTD during the clinical course of IPF has not been well understood. Among lung disease patients with a high titer of ACPA in a previous study (n = 33), three developed the articular manifestations of RA during a median follow-up of 449 days.(24) Prior studies of patients with MPO-ANCA positive IPF found that 16–33% of patients subsequently developed MPA.(4–7) Similarly, out of 29 IPF patients with MPO-ANCA-positive IPF in our study, 4 (14%) subsequently developed clinical manifestations of MPA. In these previous studies and our study, no IPF patients developed eosinophilic granulomatosis with polyangiitis or granulomatosis with polyangiitis. In our study, 11 of 15 IPF patients with progression to CTD had either RA or MPA. ACPA, RF, and MPO-ANCA were independent risk factors for the development of CTD in IPF patients. Considering this, IPF patients with RF, ACPA, and anti-MPO antibody might be associated with autoimmunity. ACPA, RF, and MPO-ANCA might play an important role in the development of UIP in patients with CTD. Furthermore, there were four patients who initially had low titer or no RF, ACPA, or MPO-ANCA, but had high titers of these autoantibodies when progressed to CTD. Thus, it would be a good option to periodically test these antibodies in IPF patients.

There have been studies on the type of interstitial lung disease (ILD) associated with rheumatic diseases. It is well known that UIP is more frequently observed in RA and MPA, which are associated with RF, ACPA and MPO-ANCA, than in other CTD.(25, 26) In ANCA-associated vasculitis, diffuse alveolar hemorrhage and pulmonary fibrosis are common pulmonary manifestations of MPA, associated with MPO-ANCA, but solitary or multiple nodules are typical chest image findings in patients with eosinophilic granulomatosis with polyangiitis or granulomatosis with polyangiitis.(27–30) It is also known that ILD is more frequently observed in seropositive RA patients than in seronegative RA patients.(31, 32) In addition, UIP is observed at a relatively low frequency in systemic lupus erythematosus, idiopathic inflammatory myopathy, systemic sclerosis, and mixed CTD, all of which have a high frequency of ANA.(26, 33) Considering this, it is reasonable to assume that there is an important association between the specific autoantibody and the type of ILD in CTD. In our study, RF, ACPA, and MPO-ANCA autoantibodies were significant risk factors for development of CTD in IPF patients, but ANA and PR3-ANCA were not. In conclusion, RF, ACPA, and MPO-ANCA might be importantly associated with the development of UIP with CTD. Testing for ANCAs, specifically MPO, is not part of the current major society recommendations for serologic evaluation in patients with suspected IPF or IPAF.(1, 15, 34) Our findings suggest that in addition to testing for ACPA, RF, and ANA, measurement of MPO-ANCA may be indicated in patients with suspected IPF or IPAF.

In a Japanese IPF cohort, CTD developed in 9% of the patients (10/111 patients – 4 RA, 4 MPA, 1 SSc, 1 SSc/SJS) following an initial IPF diagnosis.(35) As in the Japanese IPF cohort, our study showed progression to RA and MPA, rather than the other CTDs, to be more common, with CTD progression more greatly observed among the lower age patients and females. However, they did not find autoantibodies to be significant risk factors for the development of CTD as ACPA was not tested and autoantibodies, with the exception of RF, ANA, and anti-dsDNA antibodies, were tested in only approximately half of the Japanese IPF patients; hence, their study could have a greater number of patients with false negatives compared to our study. Additionally, the Japanese study found that lymphoid aggregates with germinal centers were significant risk factors for development of CTD, which were not collected in our study. Notably, we observed a significantly higher lymphocyte percentage in BAL in IPF patients with CTD progression than in those without progression to CTD. However, we did not include lymphocyte percentage in BAL, which was assessed in approximately half of the patients, in the multivariable analysis. Hence, the factors that may be associated with autoimmunity in the diagnosis of suspected IPF patients include, relatively young age, sex (female), presence of RF, ACPA, or MPO-ANCA, lymphocyte percentages in BAL, and lymphoid aggregates with germinal centers in lung biopsy.

This study has several limitations in addition to those associated with being retrospective. Some patients had not been continuously visiting the hospital before death, and as a result, we may not know about the development of CTD in some cases. Nevertheless, the mean ratio of individual clinic follow-up duration to survival duration was 0.84. The IPF patients with development of CTD had a longer survival, and some patients who had stopped visiting the hospital came back and were diagnosed with CTD. In considering this, it is likely that there were not many cases of unknown CTD.

Conclusions

Autoantibodies have been identified in many IPF patients in previous studies, and some of these patients have been thought to be closely associated with autoimmunity. We observed development of CTD in IPF patients with ANCA or autoantibodies that met the IPAF serology criteria. Among these autoantibodies, RF, ACPA, and MPO-ANCA were significantly associated with the development of CTD in IPF patients. Progression to CTD is uncommon in IPF patients, but a significant number of IPF patients with high titers of RF, ACPA or MPO-ANCA progressed to CTD. IPF/UIP with high titers of RF, ACPA or MPO-ANCA might be the initial clinical manifestation

of CTD. High titers of RF, ACPA, or MPO-ANCA might be an important factor in the subsequent identification of CTD among patients with IPF. Further studies are needed to investigate the role of RF, ACPA, and MPO-ANCA in development of pulmonary fibrosis.

Abbreviations

ACPA: anti-citrullinated peptide antibody; ANA: antinuclear antibody; ANCA: anti-neutrophil cytoplasmic antibody; CTD: connective tissue disease; ILD: interstitial lung disease; IPAF: interstitial pneumonitis with autoimmune features; IPF: Idiopathic pulmonary fibrosis; MPA: microscopic polyangiitis; MPO: myeloperoxidase; RA: rheumatoid arthritis; PR3: proteinase-3; RF: rheumatoid factor; SJS: Sjögren syndrome; UIP: Usual interstitial pneumonia.

Declarations

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Authors' contributions

Study conception and design. BG, BY, and CK

Acquisition of data. BG, SHN and JL

Analysis and interpretation of data. BG, JL, SHN, SHL, SMA, JSO, SH, YGK, JK, BY, and CKL.

All authors read, and the report was approved.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

We retrospectively reviewed the records of IPF patients. The study was approved by the Institutional Review Board of Asan Medical Center (IRB number: 2016-0222).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

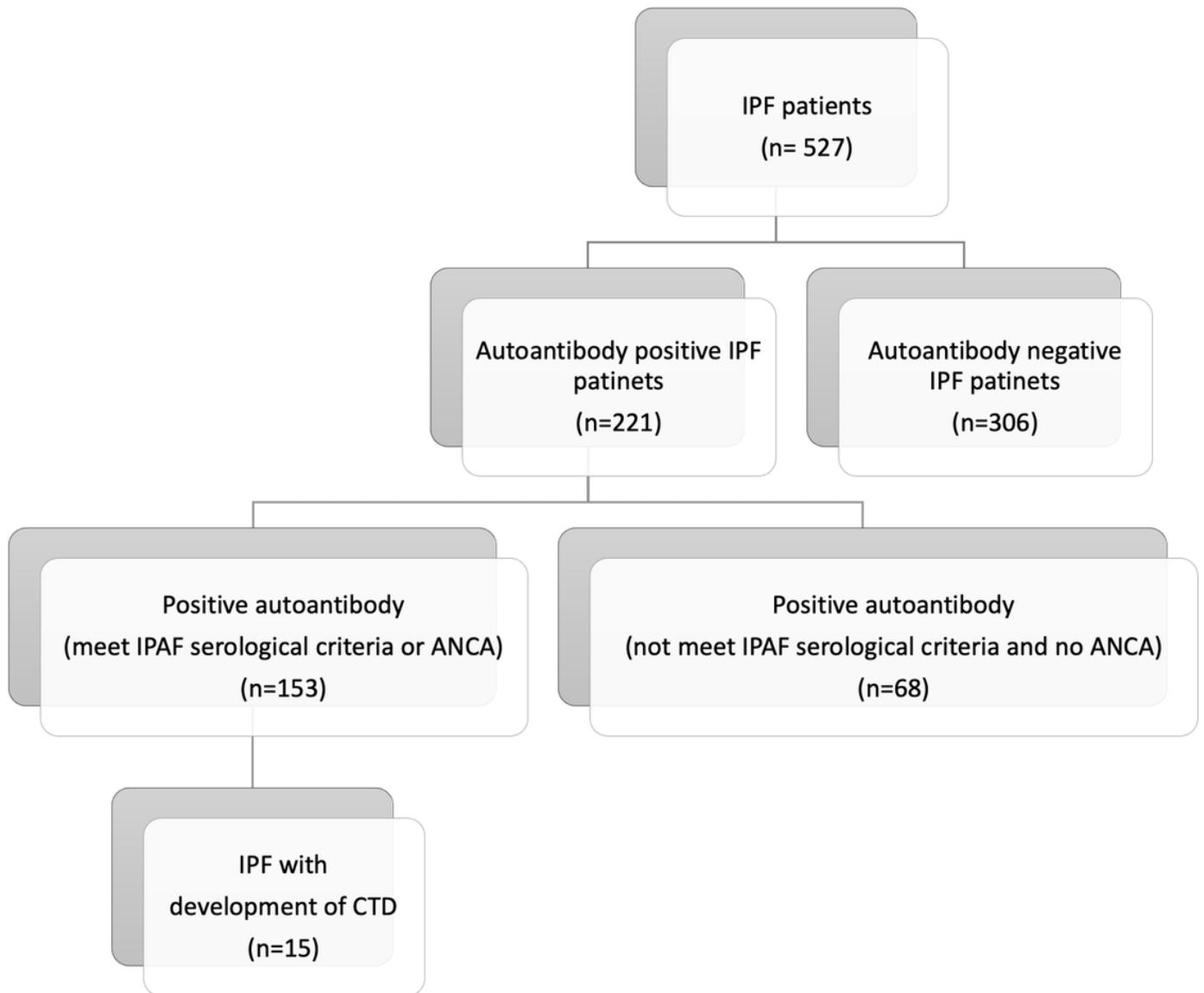


Figure 1

Flowchart representing the differentiation of IPF patients into distinct categories. ANCA = anti-neutrophil cytoplasmic antibodies; CTD = connective tissue disease; IPAF = interstitial pneumonitis with autoimmune features; IPF = idiopathic pulmonary fibrosis;

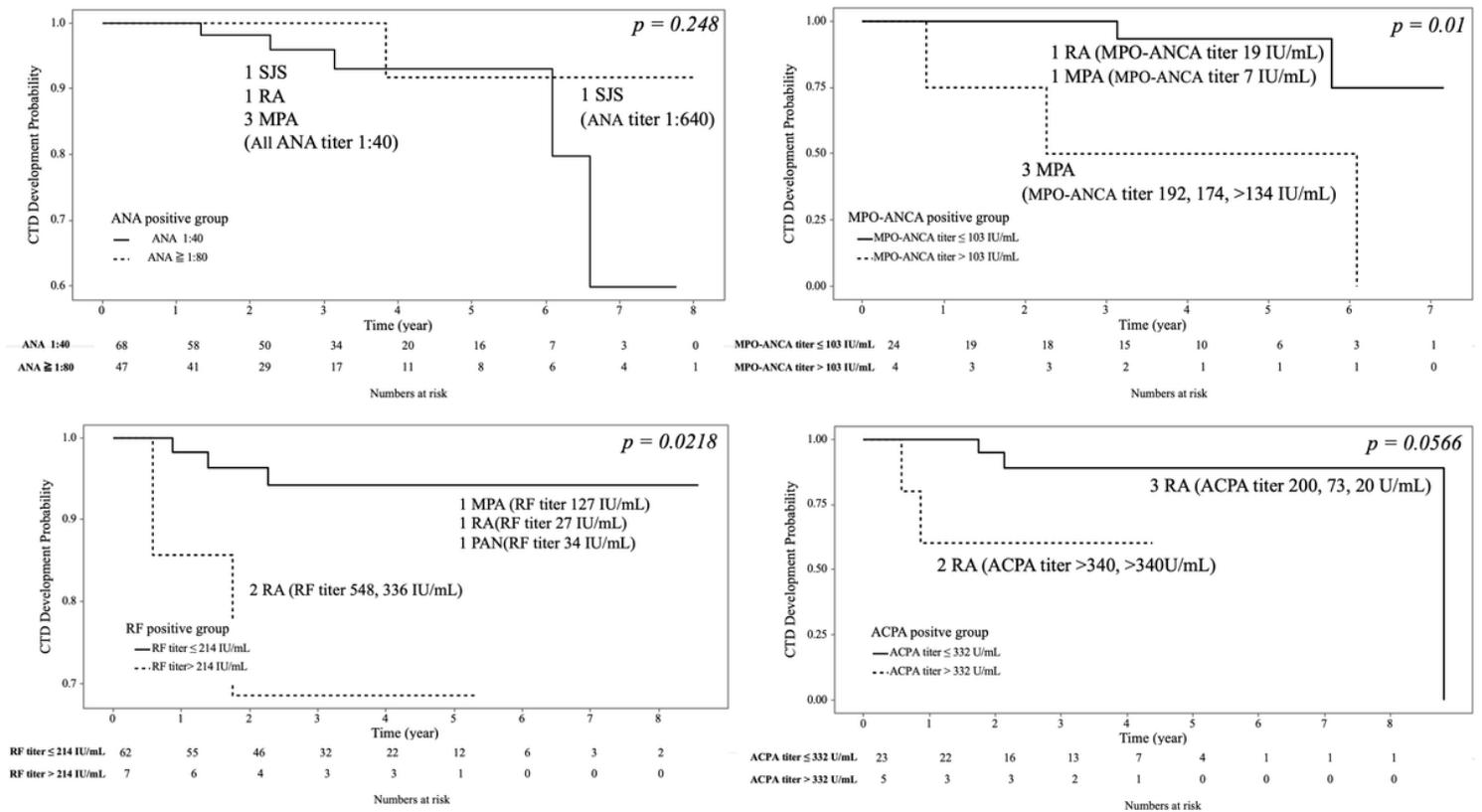


Figure 2

Development of connective tissue disease in each autoantibody-positive idiopathic pulmonary fibrosis patient. (autoantibody tested at baseline) ACPA = anti-citrullinated protein antibody; ANA = antinuclear antibody; CTD = connective tissue disease; MPA = microscopic polyangiitis; PAN = polyarteritis nodosa; RA = rheumatoid arthritis; RF = rheumatoid factor; UCTD = Undifferentiated connective tissue disease; SJS = Sjögren's syndrome.

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