Thyroid Disease Is Prevalent and Predicts Survival in Patients With Idiopathic Pulmonary Fibrosis

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BACKGROUND: A significant minority of patients with idiopathic pulmonary fibrosis (IPF) display features of autoimmunity without meeting the criteria for overt connective tissue disease. A link between IPF and other immune-mediated processes, such as hypothyroidism (HT), has not been reported. In this investigation, we aimed to determine whether HT is associated with IPF and if outcomes differ between patients with IPF with and without HT.

METHODS: A retrospective case-control analysis was conducted. Of 311 patients referred to the University of Chicago Interstitial Lung Disease Center with an initial diagnosis of IPF, 196 met the inclusion criteria and were included in the final analysis. Each case was matched 1:1 by age, sex, and race to a control subject with COPD.

RESULTS: HT was identified in 16.8% of cases and 7.1% of control subjects (OR, 2.7; 95% CI, 1.31-5.54; $P = .01$). Among patients with IPF, HT was associated with reduced survival time ($P < .001$) and was found to be an independent predictor of mortality in multivariable Cox regression analysis (hazard ratio, 2.12; 95% CI, 1.31-3.43; $P = .002$). A secondary analysis of two IPF clinical trial datasets supports these findings.

CONCLUSIONS: HT is common among patients with IPF, with a higher prevalence than in those with COPD and the general population. The presence of HT also predicts mortality in IPF, a finding that may improve future prognostication models. More research is needed to determine the biologic link between IPF and HT and how the presence of thyroid disease may influence disease progression.

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ABBREVIATIONS: ACE-IPF = Anticoagulant Effective in Idiopathic Pulmonary Fibrosis; AIF-ILD = autoimmune-featured interstitial lung disease; CAD = coronary artery disease; CTD = connective tissue disease; D_{LCO} = diffusion capacity of the lung for carbon monoxide; DM = diabetes mellitus; GAP = gender, age, physiology; GER = gastroesophageal reflux; HR = hazard ratio; HRCT = high-resolution CT; HT = hypothyroidism; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; IPFnet = Idiopathic Pulmonary Fibrosis Network; PAN = prednisone/azathioprine/N-acetylcysteine; PANTHER = Prednisone, Azathioprine and N-acetylcysteine for Pulmonary Fibrosis; RAI = radioactive iodine; SLB = surgical lung biopsy; SP = surfactant protein; TSH = thyroid-stimulating hormone; TTF-1 = thyroid transcription factor-1; UCTD = undifferentiated connective tissue disease; UIP = usual interstitial pneumonia

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Idiopathic pulmonary fibrosis (IPF) is a fibrosing interstitial lung disease (ILD) of unknown cause. It has a median survival of 3 to 5 years and a heterogeneous natural history, and research has focused on identifying unique IPF subgroups.[1,2] Individuals with IPF and other ILDs who exhibit the features of autoimmunity, but who fail to meet the established rheumatologic criteria for connective tissue disease (CTD) compose one such group.[3-5] Those who have interstitial pneumonia with autoimmune features, referred to as undifferentiated connective tissue disease (UCTD) and autoimmune-featured ILD (AIF-ILD), account for a significant minority of patients with IPF and other idiopathic interstitial pneumonias.[3-5]

UCTD and AIF-ILD criteria focus on CTD-related physical signs and serologies but do not address non-CTD autoimmune disease processes, several of which are common in the general population. Chronic autoimmune thyroiditis, also known as Hashimoto thyroiditis, is one such process and is characterized by T-cell and autoantibody-mediated destruction of the thyroid gland, leading to hypothyroidism (HT).[6] Although congenital and postpartum forms of HT exist, and HT may be caused by iodine deficiency and some medications, the overwhelming majority of HT cases in developed nations have an autoimmune cause, which is estimated to affect 5% to 9% of women and 1% to 2% of men.[6-8]

The prevalence of HT and other non-CTD autoimmune processes among patients with IPF and other ILDs is currently unknown. We hypothesized that (1) HT is more common in patients with IPF than in matched control subjects and (2) clinical characteristics, including outcomes, differ between patients with IPF with and without HT. To test these hypotheses, we conducted a case-control analysis and then analyzed datasets from two randomized clinical trials conducted by the Idiopathic Pulmonary Fibrosis Network (IPFnet) to determine whether our results could be replicated.[9-11]

Materials and Methods

Study Design

This retrospective investigation was conducted at the University of Chicago and was approved by our institutional review board (IRB protocol 13-1180). A case-control analysis was conducted using patients with IPF referred to the University of Chicago ILD center along with age-, sex-, and race-matched control subjects with COPD. Of 311 individuals evaluated at the University of Chicago from 2004 to 2012 with an initial diagnosis of IPF based on *International Classification of Diseases, Ninth Revision* code (Fig 1), 247 met the criteria for IPF according to the 2011 American Thoracic Society/European Respiratory Society criteria.

Of those failing to meet the criteria for IPF, 30 had possible IPF but declined surgical lung biopsy (SLB) after high-resolution CT (HRCT) scanning failed to demonstrate usual interstitial pneumonia (UIP), 14 were missing the clinical information needed to confirm the diagnosis (HRCT scan or SLB), and 20 were given a diagnosis of an alternative ILD. Patients with a diagnosis of IPF who exhibited features of autoimmunity according to previously suggested criteria[3-5] (n = 38) were excluded from the analysis, as were 13 patients who participated in the clinical trials used for our replication cohort, leaving 196 cases for the primary analysis. Of these 196 cases, 155 (79%) demonstrated UIP on HRCT scan, whereas the remainder demonstrated histopathologic UIP after SLB.

The control group was composed of individuals with COPD who had been referred to the University of Chicago general pulmonary clinic from 2006 to 2014. Patients with an *International Classification of Diseases, Ninth Revision* code for COPD were systematically identified by the University of Chicago Center for Research Informatics and were matched according to age, sex, and race/ethnicity in a sequential fashion starting at the top of the alphabet by last name.

All data were extracted retrospectively from the electronic medical record using the initial clinic visit. These data included demographic information (age, race/ethnicity, sex), patient-reported medical/surgical history (HT, gastroesophageal reflux [GER], diabetes mellitus [DM], coronary artery disease [CAD], tobacco use, hyperthyroidism, thyroid ablation, thyroidectomy), patient-reported medications (thyroid replacement, GER and statin therapy, lithium, amiodarone, systemic corticosteroids, azathioprine, N-acetylcysteine, radioactive iodine [RAI] history), physical examination findings (BMI, clubbing, crackles), laboratory studies (antinuclear antibody with staining pattern, rheumatoid factors, anticitrullinated protein antibody, myositis-specific antibodies, antineutrophil cytoplasmic antibody, anti-Ro/SSA antibody, anti-La/SSB antibody, anti-Scl-70 antibody, aldolase, thyroid-stimulating hormone [TSH], and free thyroxine), and diagnostic studies (HRCT scan, SLB, pulmonary function testing, including FVC, FEV_1, and percent predicted diffusion capacity of the lung for carbon monoxide [DLCO]).

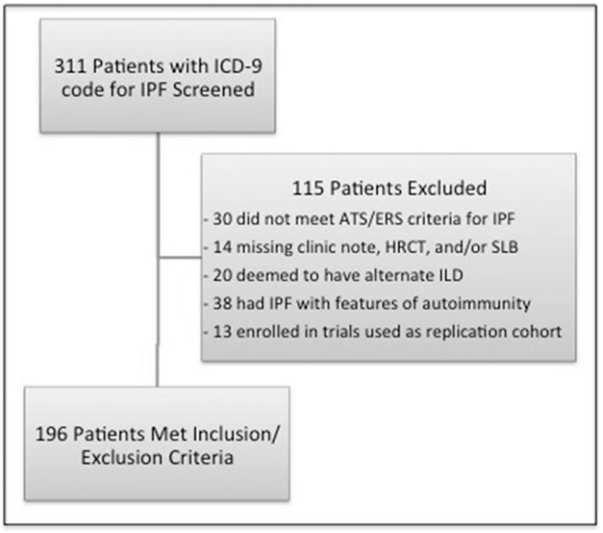

Figure 1 – *Consort diagram outlining case-finding methodology. ATS = American Thoracic Society; ERS = European Respiratory Society; HRCT = high-resolution CT; ICD-9* = International Classification of Disease, Ninth Revision*; ILD = interstitial lung disease; IPF = idiopathic pulmonary fibrosis; SLB = surgical lung biopsy.*

TABLE 1] Baseline Characteristics

Characteristic	IPF Case Patients (n = 196)	Control Subjects With COPD (n = 196)[a]	*P* Value
Age, y	68.1 ± 8.6	69 ± 9	.35
Male	146 (74.5)	146 (74.5)	1
Race/ethnicity			1
White	157 (80.1)	157 (80.1)	
Black	16 (8.2)	16 (8.2)	
Hispanic	18 (9.2)	18 (9.2)	
Asian	5 (2.5)	5 (2.5)	
BMI	30.2 ± 5.4	28.5 ± 7.5	.01
Ever smoker	145 (74)	178 (91)	< .001
Gastroesophageal reflux	87 (44.4)	85 (43.4)	.84
Diabetes mellitus	41 (20.9)	43 (21.9)	.81
Systemic corticosteroid use	25 (12.8)	31 (15.8)	.39

Data are presented as mean ± SD or No. (%). IPF = idiopathic pulmonary fibrosis.
[a]Exception for number of patients: BMI (n = 195).

HT was recorded when a patient reported the use of thyroid replacement therapy and did not report a previous history of thyroidectomy or RAI ablation. No patients reported the use of medications known to alter thyroid function, including lithium, amiodarone, or interferon-γ. No patients were immediately postpartum or endorsed a history of congenital HT. No patients lived outside the United States.

We then analyzed datasets from two IPFnet randomized clinical trials, Anticoagulant Effective in Idiopathic Pulmonary Fibrosis (ACE-IPF)[9] and Prednisone, Azathioprine and N-acetylcysteine for Pulmonary Fibrosis (PANTHER),[10,11] to determine whether our findings could be replicated. HT was recorded when a patient reported the use of thyroid replacement therapy.

Statistical Analysis

Continuous variables are reported as means with SD and are compared using a two-tailed Student *t* test. Categorical variables are reported as counts and percentages and were compared using the χ^2 test or Fisher exact test, as appropriate. Conditional logistic regression was performed to compare the proportion of HT between cases and control subjects. Survival analysis was performed using univariate and multivariable Cox regression together with the unadjusted log-rank test and was plotted using the Kaplan-Meier survival estimator. Survival time was defined as the time from diagnostic test (SLB or HRCT scan) to death, transplant, loss to follow-up, or end of study period. Patients undergoing lung transplant were censored at the time of transplant. All statistical analyses were performed using Stata 12 (StataCorp LP).

Results

One hundred ninety-six patients with IPF were matched 1:1 by age, sex, and race/ethnicity to a control patient with a diagnosis of COPD. A comparison of baseline characteristics between case patients and control subjects is shown in Table 1. Case patients and control subjects were similar in terms of age (68.1 years vs 69 years, respectively), sex (74.5% male), and race/ethnicity (80.1% white, 8.2% black, 9.2% Hispanic, and 2.5% Asian), as specified by the study design. Compared with control subjects, case patients had a higher BMI (30.2 vs 28.5, $P = .01$) and fewer ever smokers (74% vs 91%, $P < .001$). No significant differences between case patients and control subjects were observed regarding GER (44.4% vs 43.4%, respectively), DM (20.9% vs 21.9%, respectively) or chronic systemic corticosteroid use (12.8% vs 15.8%, respectively).

When comparing the proportion of patients with HT between cases and control subjects (Table 2), HT was found to be significantly associated with IPF in univariate analysis (OR, 2.72; 95% CI, 1.37-5.44; $P = .004$).

TABLE 2] Hypothyroidism and IPF Risk

Characteristic	IPF Case Patients (n = 196)	Control Subjects With COPD (n = 196)	Unadjusted Results			Adjusted Results[a]		
			OR	*P* Value	95% CI	OR	*P* Value	95% CI
Hypothyroidism	33 (16.8)	14 (7.1)	2.72	.004	1.37-5.44	2.7	.01	1.31-5.54
Male	19 (13)	6 (4.1)						
Female	14 (28)	8 (16)						

Data are presented as No. (%). See Table 1 legend for expansion of abbreviation.
[a]Adjusted for BMI, smoking history, diabetes mellitus, gastroesophageal reflux, and corticosteroid use.

In multivariable analysis adjusting for variables previously associated with IPF, HT, or both, including BMI,[12] smoking history,[13,14] DM,[15] and GER,[16] along with chronic corticosteroid use, HT remained significantly associated with IPF (OR, 2.7; 95% CI, 1.31-5.54; $P = .01$). HT was identified in 13% of male case patients compared with 4.1% of male control subjects and 28% of female case patients compared with 16% of female control subjects.

We then stratified patients with IPF based on HT status (Table 3). Significantly fewer men were observed among those with IPF/HT compared with IPF alone (57.6% vs 77.9%, $P = .02$). Those with IPF/HT were also found to have a significantly lower mean Dlco % predicted compared with those with IPF alone (43.3 vs 50.4, $P = .05$), but 8.7% (n = 17) of individuals in the overall cohort could not perform this maneuver. No significant differences were observed between groups with respect to the following: age; race/ethnicity; BMI; crackles; clubbing; smoking history; GER; DM; the use of corticosteroid monotherapy, azathioprine monotherapy,

TABLE 3] Characteristics of Patients With IPF Stratified by HT Status (N = 196)[a]

Characteristic	IPF/HT (n = 33)	IPF Alone (n = 163)	*P* Value
Age, y	70.6 ± 8.1	67.6 ± 8.6	.07
Male	19 (57.6)	127 (77.9)	.02
Race/ethnicity			.7
White	28 (84.9)	129 (79.1)	
Black	1 (3)	15 (9.2)	
Hispanic	3 (9.1)	15 (9.2)	
Asian	1 (3)	4 (2.4)	
BMI	30 ± 5.6	30.2 ± 5.4	.77
Crackles	31 (93.9)	152 (95.6)	.68
Clubbing	3 (9.4)	35 (23.8)	.07
Ever smoker	22 (66.7)	123 (75.5)	.29
Gastroesophageal reflux	14 (42.4)	73 (44.8)	.8
Diabetes mellitus	7 (21.2)	34 (20.9)	.96
Corticosteroid monotherapy	6 (18.2)	27 (16.6)	.8
Azathioprine monotherapy	1 (3)	5 (3.1)	1
PAN triple therapy	1 (3)	4 (2.5)	1
GER therapy	14 (42.4)	65 (39.9)	.79
FVC % predicted	59.5 ± 12.2	65.4 ± 18.1	.07
Dlco % predicted	43.3 ± 16.3	50.4 ± 17.6	.05
Radiographic UIP	26 (78.8)	129 (81.7)	.7
ANA seropositivity[b]	12 (37.5)	34 (23.1)	.09
RF or aCCP seropositivity	7 (22.6)	25 (17)	.46
≥ 1 autoantibody	16 (50)	51 (34.5)	.1
TSH	3.1 ± 5.1	2.2 ± 1.6	.25
GAP stage[c]			.14
I	9 (27.3)	63 (38.7)	
II	13 (39.4)	70 (42.9)	
III	11 (33.3)	30 (18.4)	
Lung transplant	1 (3)	17 (10.4)	.32

aCCP = anticitrullinated protein antibody; ANA = antinuclear antibody; Dlco = diffusion capacity of the lung for carbon monoxide; GAP = gender, age, physiology; GER = gastroesophageal reflux; HT = hypothyroidism; PAN = prednisone/azathioprine/N-acetylcysteine; RF = rheumatoid factor; TSH = thyroid-stimulating hormone; UIP = usual interstitial pneumonia. See Table 1 legend for expansion of other abbreviation.

[a]Exceptions for number of patients: crackles (n = 192); clubbing (n = 179); Dlco (n = 179); radiographic UIP (n = 191); ANA (n = 179); RF/aCCP (n = 178); any autoantibody (n = 180); TSH (n = 79).

[b]Titer > 1:320 or nucleolar pattern.

[c]Based on Ley et al.[17]

prednisone/azathioprine/N-acetylcysteine (PAN) triple therapy, or GER therapy (proton pump inhibitor or histamine-2 blocker); FVC % predicted; radiographic UIP; antinuclear antibody seropositivity; rheumatoid factor/anticitrullinated protein antibody seropositivity; >1 autoantibody seropositivity; TSH; gender, age, physiology (GAP)[17] stage; or lung transplant.

In unadjusted survival analysis, those with IPF/HT demonstrated significantly shorter survival compared with those with IPF alone ($P<.001$) (Fig 2). Substratifying by HT status and sex (Fig 3) shows that men and women with IPF/HT demonstrated significantly shorter survival compared with their counterparts with IPF alone ($P=.001$), with women without HT having the best overall survival. Univariate and multivariable Cox regression was performed (Table 4) to identify predictors of mortality in this cohort. In univariate analysis, HT was found to be a significant predictor of mortality (hazard ratio [HR], 2.1; 95% CI, 1.34-3.28; $P=.001$), as was each increase in GAP stage (HR, 2.06; 95% CI, 1.56-2.73; $P<.001$) and PAN triple therapy (HR, 2.60; 95% CI, 1.07-6.49; $P=.04$).

Other variables that may influence survival in IPF, including corticosteroid monotherapy,[11] azathioprine monotherapy,[11] GER therapy,[18] smoking history,[19] and CAD,[20] did not predict survival in univariate analysis. A multivariable model that included these variables, along with race/ethnicity and BMI, showed that HT remained a significant predictor of mortality (HR, 2.12; 95% CI, 1.31-3.43; $P=.002$), as did each increase in GAP stage (HR, 1.91; 95% CI, 1.42-2.58; $P<.001$). PAN triple therapy no longer predicted survival after multivariable adjustment. These conclusions held when transplant-free, transplant-excluded, and transplant-as-a-competing-event Cox regression models were constructed (e-Tables 1-3). The GAP stage was chosen rather than individual pulmonary function metrics to account for individuals unable to perform the DLCO maneuver. A multivariable model using age, sex, FVC % predicted, and DLCO % predicted rather than the GAP stage was also constructed with missing DLCO values imputed to 7 (equal to the lowest recorded value in the cohort), but did not significantly change the overall conclusions (e-Table 4).

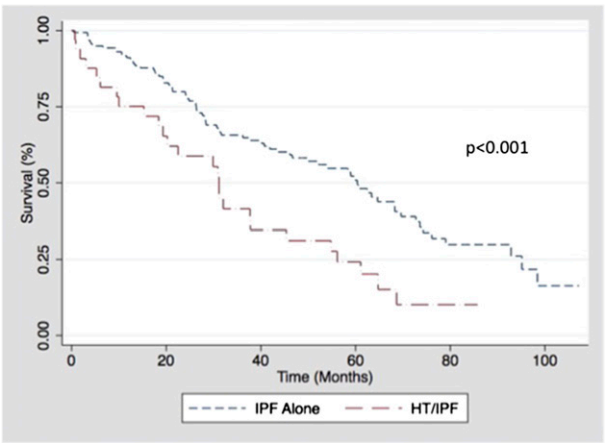

Figure 2 – *Survival among patients with IPF stratified by HT status. Those with combined HT and IPF demonstrate significantly reduced survival time compared with those with IPF alone (P < .001). HT = hypothyroidism. See Figure 1 legend for expansion of other abbreviation.*

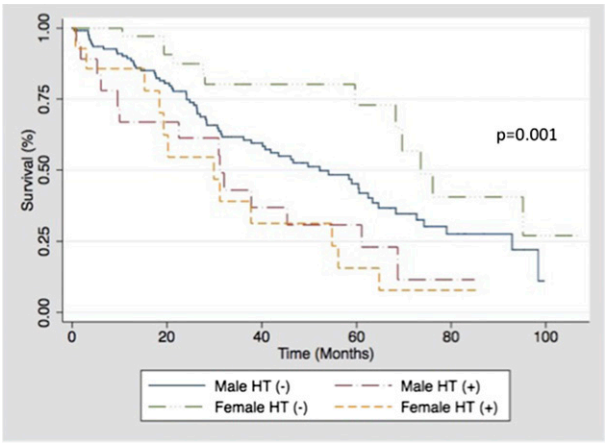

Figure 3 – *Survival among patients with IPF stratified by sex and HT status. Men and women with combined HT and IPF demonstrate significantly shorter survival time compared with their counterparts with IPF alone (P = .001). See Figure 1 and 2 legends for expansion of abbreviations.*

Similar methods were used with the ACE-IPF and PANTHER clinical trial datasets. HT was present in 9.4% (n = 10) and 11.7% (n = 31) of men and 15.4% (n = 6) and 23.4% (n = 18) of women in ACE-IPF and PANTHER trials, respectively (Table 5). These cohorts were combined, and univariate and multivariable Cox regression was performed to determine predictors of transplant-censored survival (Table 6). In univariate analysis, each increase in GAP stage along with PAN triple therapy and warfarin therapy were found to be significant predictors of mortality. A multivariable model was constructed that adjusted for race, BMI, GER therapy, smoking history, the ACE-IPF and PANTHER treatment arms, concurrent prednisone and azathioprine use in the ACE-IPF trial, and concurrent warfarin use in the PANTHER trial. In this multivariable model, HT was found to be a significant predictor of mortality (HR, 3.36; 95% CI, 1.4-8.05; $P=.007$), as was each increase in GAP stage along with PAN and warfarin therapy.

Discussion

In this investigation, we report, to our knowledge for the first time, an association between HT and IPF. HT was

TABLE 4] Variables Predicting Survival in Patients With IPF

Characteristic	Unadjusted (n = 196)			Adjusted[a] (n = 196)		
	HR	*P* Value	95% CI	HR	*P* Value	95% CI
Hypothyroidism	2.1	.001	1.34-3.28	2.12	.002	1.31-3.43
GAP stage	2.06	< .001	1.56-2.73	1.91	< .001	1.42-2.58
Corticosteroid monotherapy	1.3	.27	0.81-2.1	1.65	.08	0.95-2.89
Azathioprine monotherapy	0.96	.94	0.3-3.01	0.77	.66	0.23-2.5
PAN triple therapy	2.6	.04	1.07-6.49	1.99	.17	0.75-5.26
GER therapy	0.97	.88	0.66-1.45	0.85	.48	0.53-1.34
Smoking history	1.12	.6	0.73-1.72	1.02	.9	0.66-1.61
CAD	1.45	.08	0.96-2.18	1.03	.71	0.95-1.04

CAD = coronary artery disease; HR = hazard ratio. See Table 1 and 3 legends for expansion of other abbreviations.
[a]Adjusted for race/ethnicity, BMI, and variables listed above.

found in 16.8% of our IPF cohort, including 13% of men and 28% of women. The proportion of IPF cases with HT was significantly higher than that found among matched control subjects with COPD and was markedly higher than the estimated prevalence of HT in the general population. A similar conclusion was reached with two IPFnet clinical trial datasets, supporting the association between HT and IPF. Although few phenotypic differences exist between patients with IPF with and without HT, survival analysis shows that HT was an independent predictor of mortality in our University of Chicago cohort, as well as in a combined cohort of patients enrolled in the ACE-IPF and PANTHER clinical trials. This finding may help improve future prognostication models.

The mechanism by which HT may contribute to IPF pathogenesis and mortality is unclear. A case series of two patients suggested a link between severe untreated HT and radiographic ILD that improved upon return to a euthyroid state.[21] However, induction of HT in mice appears to prevent the pulmonary fibrosis associated with systemic sclerosis[22] and to accelerate the recovery of liver fibrosis,[23] raising doubt that biochemical HT itself could contribute to IPF onset or progression. Among those with thyrotropin data in our cohort (n = 79), all but four patients were biochemically euthyroid at the time of presentation. Furthermore, TSH level itself did not predict survival (e-Table 5). Longitudinal changes in thyroid state were not assessed in this investigation; therefore, any alteration in thyroid function at the time of IPF progression could not be determined.

A possible link between HT and IPF mortality lies in thyroid transcription factor-1 (TTF-1) expression. This transcription factor binds to the promoter regions of genes encoding surfactant protein (SP)-A, SP-B, and SP-C and is integral to lung development.[24] Increased levels of alveolar and serum SP-A have been reported in patients with IPF and may predict survival.[25-28] High levels of TTF-1 expression, as seen in some forms of lung cancer, may result in increased production of SP-A and other SPs and have been shown to cause pulmonary inflammation and fibrosis in mice.[29-32] Increased TTF-1 expression has been demonstrated in patients with chronic autoimmune thyroiditis,[33] raising the question of whether increased TTF-1 related to HT may contribute to the increased SP production observed in some patients with IPF.

Immune dysregulation provides another possible link between HT and IPF. A gene expression analysis of peripheral blood mononuclear cells in patients with IPF using an RNA microarray platform identified

TABLE 5] Prevalence of HT by Study

Sex	Idiopathic Pulmonary Fibrosis			General Population[a]
	ACE-IPF (n = 145)	PANTHER (n = 341)	University of Chicago (n = 196)	
Male	9.4 (10 of 106)	11.7 (31 of 264)	13 (19 of 146)	1.2-2.3
Female	15.4 (6 of 39)	23.4 (18 of 77)	28 (14 of 50)	5-9.4

Data are presented as %. ACE-IPF = Anticoagulant Effective in Idiopathic Pulmonary Fibrosis; PANTHER = Prednisone, Azathioprine and N-acetylcysteine for Pulmonary Fibrosis. See Table 3 legend for expansion of other abbreviation.
[a]Based on Garber et al,[6] Sawin et al,[7] and Vanderpump et al.[8]

TABLE 6] Variables Predicting Survival in Patients Enrolled in ACE-IPF and PANTHER Trials

	Unadjusted (n = 482)			Adjusted[a] (n = 481)		
Characteristic	HR	*P* Value	95% CI	HR	*P* Value	95% CI
Hypothyroidism	1.82	.14	0.82-4.02	3.36	.007	1.4-8.05
GAP stage	4.29	< .001	2.47-7.42	3.99	< .001	2.17-7.38
Study medications						
PAN triple therapy	11.2	< .001	4.18-29.7	5.71	.002	1.89-17.3
NAC monotherapy	1.31	.64	0.42-4.05	1.36	.61	0.42-4.42
Warfarin therapy	5.64	.001	1.95-16.3	7.86	< .001	2.55-24.2
Smoking history	0.76	.46	0.37-1.56	1.19	.67	0.52-2.73
GER therapy	0.93	.83	0.46-1.87	0.82	.61	0.38-1.77

NAC = N-acetylcysteine. See Table 3-5 legends for expansion of other abbreviations.
[a]Adjusted for race, BMI, CAD history, azathioprine use (ACE-IPF cohort), prednisone use (ACE-IPF cohort), and warfarin use (PANTHER cohort).

several differentially expressed genes, including *CTLA-4*, *ICOS*, and *CD28*, within the T-cell biocarta pathway.[34] Reduced expression of each of these genes was associated with an increased hazard of death in two IPF cohorts. Genes encoding *CTLA-4*, *ICOS*, and *CD28* lie within 300kb on the long arm of chromosome 2, and polymorphisms at this locus have been linked previously to autoimmune thyroid disease.[35,36] Polymorphisms in *CTLA-4* have also been shown to correlate with thyroid autoantibody production and may explain the increased risk of death in some patients with IPF and HT.[37,38]

A substantially higher proportion of control subjects had HT compared with that reported in the general population. An immunologic contribution to COPD pathogenesis has been described,[39] and Karadag et al[40] showed that thyroid dysfunction may occur in COPD, but nonthyroidal illness syndrome predominates over overt HT. However, an earlier case series by Dimopoulou et al[41] did not support this correlation. Although COPD may be linked to thyroid dysfunction, active smoking has been shown to be protective against HT in several large population studies.[42,43] We explored this association among control subjects but found no difference in the proportion of HT among those with a smoking history and never smokers (data not shown).

There were several limitations in this study. First, because of its retrospective design, causality could not be assessed and our findings represent only an association between HT and IPF. Second, biochemical confirmation of autoimmune thyroiditis was not possible for the majority of patients, because most individuals had received a diagnosis of HT years to decades prior to referral to our institution. We, therefore, chose to refer to the more broad diagnosis of HT rather than chronic autoimmune thyroiditis. By excluding other possible causes of nonautoimmune thyroid disease through our protocol, we feel confident that the overwhelming majority of cases of HT identified were indeed of autoimmune origin, as is the case among the general population.[6] We were unable to apply these strict criteria to the IPFnet clinical trial datasets, because a history of RAI or thyroidectomy was not possible to ascertain, so the true proportion of patients with HT with an autoimmune cause may be somewhat lower.

Another limitation was the use of patient-reported medical history and medications. A minority of patient charts contained objective data confirming diagnoses such as GER or CAD, and medication administration could not be verified. We also chose to exclude those patients meeting the proposed criteria for UCTD and AIF-ILD. Validation of the criteria for UCTD/AIF-ILD is lacking and needs further research to determine the validity of such criteria. As such, we also performed survival analysis on the patients with UCTD/AIF-ILD included in our transplant-censored univariate and multivariable Cox models (n = 36; two were excluded because of ACE-IPF enrollment), but this did not change our findings (e-Table 6).

Conclusions

In conclusion, we demonstrate that HT, a largely autoimmune process, is common among patients with IPF and may represent an additional feature of autoimmunity in this patient population. Despite the paradigm shift away from an immunologic or inflammatory driver to that of alveolar injury and aberrant cellular repair, mounting evidence suggests involvement of the immune system in IPF pathogenesis and progression. Further investigation is needed to determine whether common pathogenic pathways exist between autoimmune thyroid disease and IPF and why the presence of HT is associated with the increased mortality risk observed in these cohorts.

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