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Obstructive sleep apnea does not promote esophageal reflux in fibrosing interstitial lung disease

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Summary
Background: In patients with fibrosing interstitial lung disease (fILD), gastroesophageal reflux (GER) is highly prevalent, perhaps because of the effects of lung fibrosis on altering intrathoracic pressure, diaphragm morphology and lower esophageal sphincter (LES) function. For unclear reasons, obstructive sleep apnea (OSA) is also highly prevalent among patients with fILD. We conducted this study to test our hypothesis that, in patients with fILD, OSA would exacerbate diaphragm/LES dysfunction and increase the propensity for—and severity of – GER.
Methods: We identified patients with fILD who underwent screening polysomnogram and pH or pH/impedence probe at our center during the same week. We examined the association between OSA and GER and used logistic regression to determine independent predictors of OSA or GER.
Results: In 54 included subjects, neither OSA (dichotomous) nor apnea hypopnea index (continuous) predicted the presence of GER. Regardless of body position (upright, recumbent), GER was no more frequent or severe among subjects with OSA vs. those without OSA. Subjects with idiopathic pulmonary fibrosis (IPF) had an odds of GER nearly seven-fold greater than subjects with other forms of fILD (odds ratio = 6.84, 95% confidence interval 1.36–34.43, $p = 0.02$). For the entire cohort and the subgroup with IPF, there was no correlation between pulmonary physiology and GER.
Conclusions: In fILD, OSA does not appear to promote GER. Research is needed to determine if compensatory mechanisms emanating from the crural diaphragm prevent GER in fILD patients with OSA and to sort out whether GER has a role in the pathogenesis of certain forms of fILD.

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Introduction

Fibrosing interstitial lung disease (fILD), regardless of cause, tends to be a progressive condition, to respond poorly to medicinal therapy, and to shorten the lives of patients afflicted with it. One of the most common forms of fILD, idiopathic pulmonary fibrosis (IPF), is particularly lethal, with a median survival around three years from the time of diagnosis.[1] For reasons that have yet to be elucidated, obstructive sleep apnea (OSA) appears to be exceedingly common in patients with IPF(2)—so does gastroesophageal reflux disease (GERD).[3] In fact, investigators have theorized that GERD or more specifically occult, repetitive acidic microaspiration—plays a key role in the pathogenesis of IPF. A competing hypothesis is that microaspiration has nothing to do with IPF, and lung fibrosis itself—by altering intrathoracic pressure and resultant morphologic or mechanistic effects on the diaphragm's esophageal hiatus and the lower esophageal sphincter (LES)—makes GERD more likely in patients with fILD.

The estimated prevalence of obstructive sleep apnea (OSA) in middle-aged U.S. adults is approximately 2–4%.[4,5] Complications of OSA include systemic and pulmonary hypertension, stroke, mood disturbance, and cardiac dysrhythmia.[6] Although the debate is long-standing, many investigators also believe OSA causes GERD. Specifically, respiratory effort in the face of an obstructed upper airway creates a transdiaphragmatic pressure differential (driven by greatly negative intrathoracic pressure) that promotes the reflux of gastric juices into the esophagus and possibly the larynx.[7,8] Other investigators contend the link between OSA and GERD is more circuitous: obesity and hiatal hernia are the common denominators confounding the apparent association between the two.[9,10]

We conducted this study to examine the putative link between OSA and GERD in patients with non-connective tissue disease-related fILD by testing the following two hypotheses: 1) given the theory on lung fibrosis altering the diaphragm/LES apparatus, among patients with fILD, the presence of OSA greatly promotes esophageal reflux; and 2) there is an association between fILD severity (based on pulmonary physiology) and the severity of GERD.

Methods

Subjects

fILD

Potential subjects included patients with fILD first evaluated at National Jewish Health between January 2006 and March 2011 and who underwent both split-night, screening polysomnogram (PSG) and either 24-h esophageal pH or pH/impedence probe at our center as part of their ILD evaluation. The decision to perform the PSG and pH probe was made by the evaluating physicians, of whom certain considered PSG and pH probe components of a standard ILD evaluation. The PSG and probe were done during the same week but not the same night. Pulmonary physiology data were taken from tests performed during the week of the PSG and pH probe testing, and results for forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO) are expressed as percentages of the value predicted for gender, age, and height (e.g., FVC% and DLCO % respectively).

Subjects were identified via ICD-9 codes, and the diagnosis of fILD was confirmed by review of the chart and high-resolution chest computed tomography (HRCT) scan as well as surgical lung biopsy (SLB) specimens where available. In the absence of a SLB, fILD was considered present when slices from an HRCT scan showed traction bronchiectasis along with reticular opacities and/or honeycombing in the face of restrictive pulmonary physiology and/or reduced DLCO. A diagnosis of IPF was rendered in accord with consensus guidelines acceptable for the time.[1] A diagnosis of fibrotic non-specific interstitial pneumonia (fNSIP) was rendered either when SLB specimens confirmed the presence of a fNSIP-pattern or, in the absence of a SLB, when the HRCT pattern suggested fNSIP as the underlying histologic pattern (i.e., when the radiologist identified lower lobe predominant fILD that did not fit a classic UIP-pattern). To avoid issues related to esophageal dysfunction stemming from connective tissue disease (CTD), patients with CTD were excluded.

Controls

We used the control group only as internal validation for certain analyses performed in subjects with fILD. The control group was formed by identifying patients with asthma first evaluated at National Jewish Health over the same time period and who underwent both split-night, screening PSG and either 24-h esophageal pH or pH/impedence probe at our center as part of their asthma evaluation. Patients with asthma were selected as controls for the following reasons: 1) they have lung disease (i.e., their lungs are not normal); and 2) because of the institution-wide, perceived relationship between GERD and asthma, they were the patient group most likely to have undergone both PSG and pH probe at our center.

Definitions for OSA and GERD

All sleep studies were performed in the Sleep Laboratory at National Jewish Health. In our lab, apneas and hypopneas are defined as an absence of flow (apnea) or reduction in flow by 30% (hypopnea) from baseline for 10 s accompanied by a fall in SpO_2 of 4% or greater. Supplemental oxygen was started if the saturation was less than 90% on room air when awake or with desaturation events when asleep. OSA was defined by an apnea hypopnea index (AHI) greater than or equal to five events per hour. The pH probes used were single-use, dual-channel pH or impedence/pH probes by Sandhill Scientific (Sandhill Scientific, Highlands Ranch, CO). The probe was inserted nasally such that the distal channel was located 5 cm above the lower esophageal sphincter (LES), and the proximal channel was located 20 cm above the LES. Proximal acidic GERD was considered present if pH at the proximal channel reading was <4 for $\geq$ 0.9% of the total time; <4 for $\geq$1.2% of the upright time; or <4 for >0% of the recumbent time. Distal acidic GERD was considered present if the pH at the distal channel was <4 for $\geq$4.2% of the total time (if non-medicated) or $\geq$1.3% of the total time (if medicated); <4 for $\geq$6.3% of the upright

time (if non-medicated) or ≥1.5% of the upright time (if medicated); <4 for ≥1.2% of the recumbent time (if non-medicated) or ≥1.3% of the recumbent time (if medicated).[11]

Statistical analysis

Categorical variables are reported as percentages and were analyzed between groups by using Chi-square or Fisher's exact test (where appropriate). Continuous variables are expressed as measures of central tendency and, because they were non-normally distributed, were analyzed between groups by using the Mann–Whitney *U* test. Correlations between continuous variables were analyzed by using Spearman rank coefficients. We examined the relationship between outcome (presence of either GERD or OSA) and predictors in subjects with fILD by using bivariate logistic regression analyses, in which demographic and pulmonary physiology variables were considered candidate predictors. We defined $p < 0.05$ to represent statistical significance for each analysis, except for the correlation and analyses of pH probe variables between subjects with or without OSA. For these, we considered $p \leq 0.001$ to represent statistical significance, to account for multiple comparisons. All statistical testing was performed with SAS (SAS Inc., Cary, NC) Version 9.2. This study was approved by the National Jewish Health Institutional Review Board. Because of the retrospective study design, informed consent was not required.

Results

We enrolled 54 subjects with fILD, the majority of whom were male, and 25% were taking prednisone when the PSG and pH probe were performed (Table 1). Among several pH probe variables assessed, the only difference between fILD subjects and asthma controls was the proportion in each group with abnormal acid at the proximal electrode while upright (fILD 56% vs. asthma 32%, $p = 0.005$). Among those same pH/impedence probe variables, none suggested worse GERD in fILD subjects with OSA vs. those without OSA (Table 2 and Appendix Table 1). Percentage of total time, as well as times in the upright or recumbent position, with abnormal distal esophageal acid exposure was greater in fILD subjects without OSA than those with OSA. In asthma controls, none of the pH/impedence probe outcomes differed significantly between those with vs. those without OSA (Appendix Table 2).

Among subjects with fILD, there was no correlation between FVC%, DLCO%, body mass index, or apnea hypopnea index and any of several pH probe proximal or distal electrode outcomes (e.g., acidic- or non-acidic reflux episodes, time with pH < 4, etc.) (Table 3 and Appendix Table 3). The results of bivariate logistic regression analyses for GERD and OSA are displayed in Tables 4 and 5 respectively. Among several candidates, the only significant predictor of the presence of GERD was having a fILD diagnosis of IPF. In several multivariable models controlling for any combination of age, male gender, DLCO%, distance walked during a 6-min walk test, presence of OSA and nadir SpO_2 during the PSG, having a diagnosis of IPF remained a (and the only) significant independent predictor of GERD. The only significant predictor of OSA was nadir peripheral oxygen saturation during the PSG.

We conducted similar analyses, including the bivariates, correlations, and analyses of the pH/impedence probe

Table 1 Baseline characteristics of subjects with fILD.

	fILD *N* = 54	
Demographics		
Age in years	69.2 ± 7.0	69.0 (65.0–75.0)
Male, %	65	
BMI	30.4 ± 6.9	29.9 (25.8–33.1)
Lung disease data		
FVC%	64.0 ± 15.9	64.0 (52.0–74.0)
DLCO%	43.4 ± 16.5	44.0 (29.0–55.0)
ILD Dx, N		
Asbestosis	2	
cHP	3	
fFIP	6	
fNSIP	19	
IPF	22	
fSarcoidosis	1	
ILD Tx, N		
None	48	
Azathioprine	4	
Mycophenolate mofetil	1	
Cyclophosphamide	1	
On prednisone, %	25	
Supplemental oxygen, N		
24 h	17	
Exertion and sleep	4	
None	33	
Sleep data		
Has OSA		
5 < AHI ≤ 15	15	
15 < AHI ≤ 30	6	
AHI > 30	14	
AHI	23.7 ± 31.2	10.8 (2.5–31.2)
Nadir SpO_2 during PSG	77.5 ± 8.9	79.0 (74.0–83.0)
Epworth Sleepiness Scale (ESS)*	7.9 ± 3.6	9.0 (5.0–10.0)
ESS > 9, %*	37	
% With ESS > 9 and OSA	72	
GERD data		
GERD symptoms, %	17	
On daily anti-reflux Tx, %	44	
On PPI during pH probe, %	21	

Data are mean ± standard deviation, median (interquartile range), other values are percentages or proportions; fILD = fibrotic interstitial lung disease; BMI = body mass index; FVC% = percent predicted forced vital capacity; DLCO % = percent predicted diffusing capacity of the lung for carbon monoxide; ILD = interstitial lung disease; Dx = diagnosis; cHP = chronic hypersensitivity pneumonitis; fFIP = fibrotic familial interstitial pneumonia; fNSIP = fibrotic non-specific interstitial pneumonia; Tx = medication; OSA = obstructive sleep apnea; AHI = apnea hypopnea index; **N* = 49 subjects with fILD; PSG = polysomnogram; SpO_2 = peripheral oxygen saturation; ESS = Epworth Sleepiness Scale; GERD = gastroesophageal reflux disease; Tx = treatment; PPI = proton pump inhibitor.

outcomes, for the following two subgroups: 1) fILD subjects with IPF; 2) fILD subjects not taking anti-reflux medications at the time of the pH probe; and for data from the pH probe limited to recumbent body position. The results for all of these analyses were similar to those described above. Ninety percent of subjects with IPF had GERD; 64% had OSA; and 50% had both GERD and OSA.

Discussion

We identified 54 subjects with non-connective tissue disease-related fILD who underwent PSG and pH probe within the same week at our center between January 2006 and March 2011. Our working hypothesis held that GERD, perhaps stemming from altered intrathoracic pressure and its effects on the diaphragmatic esophageal hiatus and LES, would occur with greater frequency in fILD subjects with OSA than in those without OSA. In contrast, we observed no relationship between the presence of OSA and the presence of GERD in subjects with fILD. Nor did we observe any association between the severity of either fILD or OSA and GERD severity in these subjects.

In this study, our goal was not to derive prevalence estimates for GERD or OSA in fILD; indeed, subjects likely underwent testing for these conditions because their physicians strongly suspected them to be present. Rather, we aimed to begin to explore the potentially intersecting pathways of OSA, GERD and fILD. Other investigators have looked at GERD and OSA separately in samples with fILD. In 1998, Tobin and co-investigators were first to assess the association between GERD and fILD by studying 17 subjects with biopsy-proven IPF; they identified GERD in 16 subjects, only four of whom had GERD symptoms.[12] Given those results, they speculated that GERD may play a significant role in the pathogenesis of IPF.

Raghu and colleagues found that 87% of 65 consecutive IPF patients had GERD, compared with only 68% of asthmatic controls ($p = 0.01$ for the comparison).[3] They also found that 12 of 17 subjects with IPF on a proton pump inhibitor (PPI) during the pH probe had GERD; each of the three of our IPF subjects who took a PPI while the pH probe was in place had GERD. Like Raghu and his colleagues, we discovered that only a minority of subjects with fILD experienced daily GERD symptoms, and like us, they observed no correlation between fILD severity and GERD severity. Sweet and colleagues found GERD to be highly prevalent in IPF patients referred for lung transplantation evaluation,[13] and those with GERD were significantly more likely than those without GERD (65% vs. 10%, $p = 0.004$) to have LES hypotension by esophageal manometry. Their study was not designed to answer the question of whether lung fibrosis (and intrathoracic pressure alterations, etc.) caused the LES hypotension, nor was it designed to assess LES pressures during apneic events. As in the study by Raghu and colleagues, the presence of symptoms did not accurately predict GERD by pH probe.

In a recent publication, Lee and co-authors describe a study in which they observed a risk of death among IPF patients taking daily anti-reflux therapy that was less than half that of IPF patients not taking daily anti-reflux therapy—a risk that held even after adjusting for potentially influential predictor variables like FVC.[14] Although evidence of the inextricable link between fILD and GERD continues to mount, none of the data from these hypothesis-generating studies can inform the question of whether GERD (or occult, repetitive microaspiration) causes fILD.

A number of researchers have examined, in patients with IPF, sleep and sleep-related problems, including nocturnal desaturation, tachypnea, and disrupted sleep architecture[15–19]—this work has also suggested a high prevalence[2] and probable under-recognition[20] of OSA in fILD. Like Lancaster and her colleagues,[2] we found no link between pulmonary restriction and OSA. Although they found a weak, borderline significant relationship between body mass index (BMI) and apnea hypopnea index(AHI) ($r = 0.3$, $p = 0.05$), we observed no significant association between the two in our subjects with fILD.

Studies on the triad of OSA, GERD and fILD are few. Lancaster and colleagues[2] did report the prevalence of GERD among their IPF subjects with or without OSA (50% vs. 70%, p = NS), but pH probes were not done as part of that study, and it is unclear how or whether the diagnosis of

Table 2 Demographic, lung disease, GERD and recumbent body position pH probe outcomes between fILD subjects stratified on the presence of OSA.

	Has OSA $N = 35$	No OSA $N = 19$	p
Demographics			
Age	69.0 (66.0—76.0)	69.0 (65.0—74.0)	0.76
BMI	30.0 (25.1—32.3)	29.9 (25.8—34.0)	0.86
Lung disease data			
FVC%	65.0 (53.0—74.0)	62.0 (47.0—78.0)	0.61
DLCO%	42.5 (31.0—55.0)	44.0 (27.0—57.0)	0.89
pH probe data			
Any GERD	59	41	0.15
Recumbent body position pH probe data			
% On PPI during pH Probe	21	21	0.99
% With Abnormal Proximal Acid Recumbent	26	47	0.11
% With Abnormal Distal Acid Recumbent	39	61	0.15

Data are median (interquartile range); BMI = body mass index; FVC% = percent predicted forced vital capacity; DLCO% = percent predicted diffusing capacity of the lung for carbon monoxide; GERD = gastroesophageal reflux; PPI = proton pump inhibitor.

Table 3 Correlations between clinical and certain pH probe variables in subjects with fILD.

	FVC %	DLCO %	BMI	AHI	Prox acid upright episodes per hr	Prox acid recumb episodes per hr	% Upright time Prox pH < 4	% Recumb time Prox pH < 4	Prox non-acid episodes per Hr total	Distal acid upright episodes per hr	Distal acid recumb episodes per hr	% Upright time distal pH < 4	% Recumb time distal pH < 4	Distal non-acid episodes per hr total
FVC%	1.0	0.53	0.19	−0.04	−0.16	−0.16	0.04	−0.10	0.19	0.02	−0.25	0.10	0.01	0.21
		< 0.0001	0.17	0.79	0.26	0.28	0.78	0.50	0.18	0.88	0.09	0.51	0.93	0.17
DLCO%	—	1.0	−0.07	0.07	−0.31	−0.20	−0.04	−0.07	0.23	−0.31	−0.32	−0.17	−0.11	0.28
			0.62	0.62	0.03	0.17	0.79	0.64	0.10	0.04	0.03	0.27	0.46	0.07
BMI	—	—	1.0	0.03	−0.12	−0.06	−0.05	0.05	0.01	0.11	0.02	0.23	0.20	0.04
				0.85	0.40	0.69	0.71	0.75	0.94	0.47	0.91	0.12	0.19	0.79
AHI	—	—	—	1.0	−0.004	−0.06	−0.07	−0.18	−0.22	−0.07	−0.09	−0.18	−0.30	−0.24
					0.98	0.67	0.61	0.20	0.12	0.64	0.57	0.24	0.05	0.10

Data are correlation coefficients (above) and *p* value (below); Prox = proximal channel of pH probe; Distal = distal channel of pH probe; Recumb = recumbent body position; FVC % = percent predicted forced vital capacity; DLCO% = percent predicted diffusing capacity of the lung for carbon monoxide; BMI = body mass index; AHI = apnea hypopnea index.

Table 4 Bivariate analyses: predictors of GERD among subjects with fILD.

Predictor	Odds ratio (95% CI)	*p*
Age	0.91 (0.80—1.03)	0.1
Male gender	3.10 (0.69—14.08)	0.1
BMI	0.98 (0.89—1.08)	0.7
FVC%	1.02 (0.97—1.06)	0.5
DLCO%	1.04 (0.98—1.10)	0.2
IPF diagnosis	6.84 (1.36—34.43)	0.02
6MWD	1.00 (0.99—1.00)	0.1
Nadir SpO_2 during 6MWT	1.12 (0.87—1.45)	0.4
Daily supplemental O_2 use	0.65 (0.15—2.89)	0.6
Prednisone use	3.20 (0.35—29.00)	0.3
Reported GERD symptoms	1.03 (0.10—10.55)	0.9
Daily anti-reflux therapy	3.31 (0.60—18.19)	0.2
Has OSA	0.35 (0.09—1.48)	0.2
AHI	1.00 (0.97—1.02)	0.7
RERA	0.98 (0.92—1.05)	0.6
Nadir SpO_2 during PSG	1.08 (0.98—1.18)	0.1

BMI = body mass index; FVC% = percent predicted forced vital capacity; DLCO% = percent predicted diffusing capacity of the lung for carbon monoxide; IPF = idiopathic pulmonary fibrosis; SpO_2 = peripheral oxygen saturation; 6MWD = distance walked during the 6-min walk test (6MWT); GERD = gastroesophageal reflux disease; OSA = obstructive sleep apnea; AHI = apnea hypopnea index; RERA = respiratory event arousal index; PSG = polysomnogram.

GERD was confirmed beyond self-report. To our surprise, in our study, we did not find evidence that having OSA increased the propensity for GERD in subjects with fILD. We suspected that if, as theorized, fILD indeed alters the morphology of the esophageal hiatus and the mechanical function of the LES—effects that would decrease the

Table 5 Bivariate analyses: predictors of OSA among subjects with fILD.

Predictor	Odds ratio (95% CI)	*p*
Age	1.01 (0.92—1.12)	0.8
Male gender	1.94 (0.54—7.02)	0.3
BMI	0.96 (0.88—1.05)	0.4
FVC%	1.01 (0.98—1.05)	0.5
DLCO%	1.02 (0.98—1.06)	0.4
IPF diagnosis	0.92 (0.30—2.85)	0.9
6MWD	1.00 (0.99—1.00)	0.5
Nadir SpO_2 during 6MWT	1.04 (0.83—1.31)	0.7
Daily supplemental O_2 use	0.93 (0.26—3.31)	0.9
Prednisone use	0.36 (0.09—1.47)	0.2
Has GERD by pH probe	0.35 (0.09—1.48)	0.2
Daily anti-reflux therapy	0.96 (0.28—3.33)	0.9
Nadir SpO_2 during PSG	0.81 (0.69—0.95)	0.009

BMI = body mass index; FVC% = percent predicted forced vital capacity; DLCO% = percent predicted diffusing capacity of the lung for carbon monoxide; 6MWD = distance walked during the 6 min walk test (6MWT); GERD = gastroesophageal reflux disease; AHI = apnea hypopnea index; SpO_2 = peripheral oxygen saturation; PSG = polysomnogram.

natural anti-reflux barrier and make GER more likely—then the transdiaphragmatic pressure differentials occurring during apneic events would have further increased GER, and this would have been clearly seen in the pH probe data with subjects in the recumbent position (i.e., laying down, sleeping). However, isolating pH probe data from the recumbent position, we observed that subjects with OSA were no more likely than those without OSA to have recumbent GER.

Why might this be? One reason is that diaphragm function is not limited to driving respiration. Using high-resolution manometry, Kuribayashi and co-investigators(10) observed non-respiratory activation of the diaphragm during apneic episodes among their subjects with OSA. Thus, despite a rising abdominal-thoracic pressure differential, stemming from increasingly labored breathing efforts during apneic events, GER was prevented by equally vigorous crural diaphragm contractions that shored-up the anti-reflux barrier. It would be interesting to determine if a similar process occurs in patients with fILD; the results of our study do not refute the possibility that it does. But another study will be needed to address this question directly. Why subjects with IPF were significantly more likely than subjects with other fILDs to have GERD is unclear. Perhaps the crural diaphragm-esophageal hiatus-LES apparatus behaves differently in—or is affected differently by—different types of lung fibrosis. If dysfunction of the entire apparatus (or LES alone) hinges on its proximity to fibrosis, then the usual interstitial pneumonia-pattern of lung injury (as opposed to say upper lobe fibrosis, as occurs in chronic hypersensitivity pneumonitis) would seem most likely to have the greatest influence on LES dysfunction. Obviously, this is purely speculative and would require completion of a different study to sort out.

Our study has several limitations. The first is that the sample size is relatively small and represents a highly-selected and very small fraction of fILD evaluated at our center over the study period. We were not able to determine the number of patients who might have had either a PSG or pH probe ordered but did not end up completing the test. In addition, it is not possible for us to ascertain the circumstances within which either test was ordered. Clearly, for certain subjects, these tests were ordered without regard for a screen that suggested a low probability of disease. For example, PSGs were ordered in 39% of subjects despite Epworth Sleepiness Scale scores of six or less—scores that suggest a low probability of OSA. This reflects the practice by some physicians at our institution of ordering a PSG and pH probe as a routine part of the ILD evaluation. Some subjects took anti-reflux medications during the pH probe study. Recognizing this could influence results, particularly the occurrence of acidic reflux events, we performed a set of analyses after excluding those subjects, and found all the results were similar. Because the PSG and pH probe were not performed the same night, we were not able to directly link the timing of apnea hypopnea and reflux events. We were subject to referral bias, and we can not ignore the fact that the cohort comprises a select group of patients with fILD that may not be representative of fILD patients in the community. However, for the purposes of this hypothesis-generating study, we do not believe these limitations are significant. To study OSA and GERD, we needed subjects who had undergone tests for both conditions; when beginning to dissect the relationship between the two conditions in this patient group, it does not matter why the tests were ordered.

In summary, subjects with fILD and OSA were not more likely to have GERD than those with fILD but no OSA. And we observed no association between the severity of lung fibrosis and the presence of GERD. Additional prospective research is needed to confirm our results, to further clarify why patients with fILD (but interestingly, not especially those with OSA) seem to be prone to GERD, to discern whether GERD and occult microaspiration play a role in the pathogenesis of certain types of fILD, and to determine whether identifying (and subsequently effectively treating) GERD leads to improvements in survival or other meaningful outcomes in this patient group.

Author contributions

Conception and study design: JS, AO, KB, Analysis and interpretation: MP, AO, TH, JSo, EFP, HP, KB, PH, TLC, JSw, Drafting the manuscript for important intellectual content: MP, AO, TH, JSo, EFP, HP, KB, PH, TLC, JSw.

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Conflict of interest

None declared.

Appendix A. Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.rmed.2012.03.014.

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