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Research Paper

Prevalence and Effects of Emphysema in Never-Smokers with Rheumatoid Arthritis Interstitial Lung Disease

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ABSTRACT

Aims: Autoimmune conditions such as rheumatoid arthritis-related interstitial lung disease (RA-ILD) have been linked to the existence of emphysema in never-smokers. We aimed to quantify emphysema prevalence in RA-ILD never-smokers and investigate whether combined pulmonary fibrosis and emphysema (CPFE) results in a worsened prognosis independent of baseline disease extent.
Methods: RA-ILD patients presenting to the Royal Brompton Hospital (n = 90) and Asan Medical Center (n = 155) had CT's evaluated for a definite usual interstitial pneumonia (UIP) pattern, and visual extents of emphysema and ILD.
Results: Emphysema, identified in 31/116 (27%) RA-ILD never-smokers, was associated with obstructive functional indices and conformed to a CPFE phenotype: disproportionate reduction in gas transfer (DLco), relative preservation of lung volumes. Using multivariate logistic regression, adjusted for patient age, gender and ILD extent, emphysema presence independently associated with a CT-UIP pattern in never-smokers (0.009) and smokers (0.02).
On multivariate Cox analysis, following adjustment for patient age, gender, DLco, and a CT-UIP pattern, emphysema presence (representing the CPFE phenotype) independently associated with mortality in never-smokers ($p = 0.04$) and smokers ($p < 0.05$).
Conclusion: 27% of RA-ILD never-smokers demonstrate emphysema on CT. Emphysema presence in never-smokers independently associates with a definite CT-UIP pattern and a worsened outcome following adjustment for baseline disease severity.

1. Introduction

In rheumatoid arthritis-related interstitial lung disease (RA-ILD), the prevalence of smoking ranges between 38–72% (Kim et al., 2010; Tsuchiya et al., 2011; Kelly et al., 2014; Antoniou et al., 2013; Saag et al., 1996; Yunt et al., 2017). Smoking has been implicated in the development (Kelly et al., 2014; Saag et al., 1996; Gochuico et al., 2008) and coarsening of ILD (Antoniou et al., 2013) and is associated with the presence of emphysema on CT at lower pack-year ranges than that seen in chronic obstructive pulmonary disease (COPD) controls (Antoniou et al., 2013). A recent large Canadian study demonstrated that RA patients have a 47% adjusted higher risk of hospitalization for COPD than the general population, with results maintained following modelling for potential confounding effects of smoking (McGuire et al., 2017).

Emphysema has previously been identified in never-smokers in an underpowered cohort of patients with rheumatoid lung (8) and in 7.5% of a large cohort of never-smokers with scleroderma-associated pulmonary fibrosis (13). Autoimmune pathways have been linked to the development of emphysema in patients with COPD (Zhang et al., 2014; Feghali-Bostwick et al., 2008; Packard et al., 2013) and may underlie the occurrence of emphysema in never-smokers with fibrosing lung disease (Antoniou et al., 2013; Antoniou et al., 2015).

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It has been suggested that in patients with connective tissue disease related ILD, emphysema adversely affects prognosis by increasing the likelihood of developing pulmonary hypertension (PHT) (Cottin et al., 2011). However, in a contemporary study of IPF patients, combined pulmonary fibrosis and emphysema (CPFE) was not associated with a worsened outcome beyond that explained by the baseline CT disease extents of emphysema and ILD (Jacob et al., 2017).

Prompted by a recent position paper on RA-ILD encouraging future analyses of cohorts from multiple centres (Doyle et al., 2014), and a meta-analysis emphasizing the small sample sizes associated with the majority of prior RA-ILD studies (Assayag et al., 2014), our study examined two large RA-ILD cohorts to answer three questions. Firstly, we quantified emphysema prevalence in never-smokers with RA-ILD. Secondly, in never-smokers, we examined whether the presence of emphysema links to a definite usual interstitial pneumonia (UIP) pattern (Raghu et al., 2011) on CT, identified as being a poor prognostic maker in RA-ILD (Kim et al., 2010; Tsuchiya et al., 2011; Kelly et al., 2014; Yunt et al., 2017; Assayag et al., 2014). Lastly, we investigated whether CPFE has a worsened prognosis in RA-ILD, over and above the extent of emphysema and ILD.

2. Methods

2.1. Clinical Data

A retrospective analysis of an ILD database identified all new consecutive patients presenting between January 2007 to July 2014 to the Royal Brompton Hospital, London, and from May 1995 to May 2015 to the Asan Medical Center, Seoul. Patients with a diagnosis of RA-ILD as confirmed on multidisciplinary team review were identified. The diagnosis of rheumatoid arthritis was made according to the American College of Rheumatology/European League Against Rheumatism criteria (Aletaha et al., 2010). Patients were defined as "ever smokers" following evaluation of clinical notes if they had smoked at least one cigarette per day for at least one year.

Approval for this study of clinically indicated CT and pulmonary function data was obtained from the Institutional Ethics Committee of the Royal Brompton Hospital and the Institutional Review Board of the Asan Medical Center, Seoul, Korea and informed patient consent was not required.

2.2. CT Evaluation

CT and pulmonary function protocols are described in the Supplementary Appendix. Each CT scan was evaluated independently by two radiologists (GC, JB) with 3 and 4 years imaging experience respectively, blinded to all clinical information. Interstitial CT parameters evaluated visually on a lobar basis included ground glass densities, reticular opacities, and honeycombing (Jacob et al., 2017).

Emphysema was classified as being centrilobular and/or paraseptal and as thin-walled cystic lesions within areas of co-existent fibrosis (Inomata et al., 2014). Emphysema was further subcategorized into one of two types: geographically distinct from areas of fibrotic lung (non-admixed emphysema) and as emphysema lying within areas of fibrosis (admixed emphysema) as previously described (Jacob et al., 2017). The total extent of emphysema was quantified on a lobar basis and the proportion of admixed emphysematous lung was recorded. The percentage of admixed emphysema was derived as follows:

$$\text{Percent admixed emphysema} = (\text{total\%emphysema} \times \text{proportion admixed})/100$$

The percentage of non-admixed emphysema represented the remainder of the scored emphysema. All CT variables were expressed as a percentage of the total lung volume. Total ILD extent represented the sum of ground glass opacities, reticulation and honeycombing. A definite radiological UIP pattern was defined using the ATS/ERS/JRS/ALAT consensus statement for IPF (Raghu et al., 2011) and was scored for each CT by a separate scorer (JJ), with 10 years imaging experience blinded to all clinical information.

2.3. Consensus Formulation for Visual Scores

Following visual CT scoring, the identification of systematic biases in visual scores was achieved by plotting the spread of differences in parenchymal pattern scores between observers. The most disparate 5% (two standard deviations) of values were arbitrated by a third scorer (JJ) as was any disagreement between scorers for the presence of either emphysema or honeycombing. Identification of emphysema in never-smokers was verified by the same third scorer (JJ).

2.4. Pulmonary Function Tests

Pulmonary function indices examined in the current study included forced expiratory volume in one second (FEV1), forced vital capacity (FVC), the diffusing capacity for carbon monoxide (DLco) and the carbon monoxide transfer coefficient (Kco).

3. Statistical Analysis

Data are given as means with standard deviations, or numbers of patients with percentages where appropriate. Interobserver variation for visual scores was assessed using the single determination standard deviation for continuous variables and as the Kappa statistic for categorical variables. Mean differences between groups were evaluated using a Chi-squared test for categorical variables or a two-sample *t* test for parametric continuous variables, and the Mann-Whitney U test for medians. Statistical significance was evaluated at a value of $p < 0.05$. Univariate and multivariate linear regression analyses were used to identify relationships between CT and functional indices. Univariate Cox proportional hazards analyses identified variables associated with outcome. Survival estimation was performed via the Kaplan Meier method. Two-sample survival comparisons were performed using the Log rank test.

Four main domains were evaluated in the study: i) prevalence of emphysema in never-smokers, ii) mortality impact of CPFE in never-smokers, iii) association of emphysema with honeycombing (and separately evaluated as IPF-like and non-IPF-like) in never-smokers, iv) an associated CPFE functional profile in never-smokers with emphysema. Analyses performed in never-smokers were compared to parallel analyses in smokers acting as a control group. In all control-group models (smokers), adjustment was made for patient pack-year history.

A multivariate Cox proportional hazard model investigated whether a CPFE phenotype has an independent effect on outcome in never-smokers after adjusting for baseline disease extent (using DLco), patient age, gender, and baseline disease severity (using CT honeycomb presence). Baseline DLco, was used to adjust for baseline disease extent as it captures disease secondary to interstitial fibrosis, emphysema and any associated pulmonary hypertension (Jacob et al., 2017). Baseline disease severity was measured using a CT definite UIP pattern as this has been well recognized as a robust measure of severity in RA-ILD patients.

A multivariate logistic regression model examined variables that were associated with the presence of a) honeycombing on CT in never-smokers and b) an ATS/ERS/JRS/ALAT consensus diagnosis of a definite UIP pattern on CT (Raghu et al., 2011). Both associations of CT honeycombing presence and a definite UIP pattern on CT were separately evaluated in the study to allow consideration of a UIP pattern (evidenced by honeycombing on CT) in RA-ILD, which would not strictly conform to the agreed definition of a UIP pattern in IPF, given differences in disease distribution in RA-ILD (less basal predominant disease, and more peribronchovascular fibrosis) compared to an IPF-like UIP pattern (Raghu et al., 2011). Variables inserted into the regression

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Table 1
Characteristics of RA-ILD patients with (n = 129 unless stated) and without (n = 116 unless stated) emphysema. Variables examined include: patient demographic details, pulmonary function indices and visually scored CT parameters. The t-test was used for continuous variables. *Chi-Square test, ^Mann-Whitney *U* test. Differences in median follow up time were calculated using the Log Rank Test. FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, Kco = carbon monoxide transfer coefficient, ILD = interstitial lung disease.

Variable Units are percentage unless stated	Emphysema absent	Emphysema present	Group comparison
Median age (years)	62	63	=0.86^
Male/female (ratio)	25/91	85/44	<0.0001*
Survival (alive/dead)	80/36	55/74	<0.0001*
Never/ever-smokers (ratio)	85/31	31/98	<0.0001*
FEV1% predicted	79.6 ± 21.1 (115)	76.2 ± 20.7 (121)	=0.21
FVC % predicted	73.4 ± 18.0 (115)	76.6 ± 21.7 (121)	=0.22
DLco % predicted	58.5 ± 19.8 (108)	49.5 ± 20.5 (122)	=0.001
Kco % predicted	82.5 ± 17.8 (71)	65.5 ± 17.7 (93)	<0.0001
Visual ILD extent	26.0 ± 16.9	28.9 ± 18.5	=0.20
Visual honeycombing extent	2.4 ± 4.2	4.8 ± 8.4	=0.006

model included patient age, gender, baseline ILD extent and emphysema presence. Model fit was evaluated using the C-statistic.

Lastly, using multivariate linear regression analyses, we examined whether never-smokers with emphysema displayed a CPFE lung functional profile, characterized by disproportionate DLco reduction and artificially preserved lung volumes. In each model, adjustment was made for patient age, gender, and baseline ILD extent. All positive logistic regression and proportional hazards models were re-run, adjusting for the study center. Assumptions of linearity and proportional hazards were tested by visual inspection of Martingale residuals and scaled Schoenfeld residuals and were satisfied. Statistical analyses were performed with SPSS (IBM SPSS Statistics for Macintosh, Version 20.0. (IBM. Corp., Armonk, NY, USA).

4. Results

4.1. Demographic Data

90 patients presenting to the Royal Brompton Hospital and 155 patients presenting to the Asan Medical Center diagnosed with RA-ILD had vital status completed with no patients lost to follow up. Baseline differences between the populations at the two institutions are demonstrated in Supplementary Table 1. A significant difference in smoking rates between patients at the two institutions (p = 0.0003) [Table 1] was primarily explained by differences in smoking rates between women: female Asan ex-smokers = 7/88 (8%); female Brompton ex-smokers = 25/47 (53%)[p < 0.0001]. Smoking rates were similar amongst men in both institutions: male Asan ex-smokers = 61/67 (91%); male Brompton ex-smokers = 36/43 (84%)[p=0.25].

Differences in baseline variables, across both cohorts, for RA-ILD patients with and without emphysema and between smokers and never-smokers are shown in Tables 1 and 2 respectively. Variation in visual CT scores for continuous variables, as measured by the single determination standard deviation, are shown in Supplementary Table 2. Kappa values for the two scorers for the presence of emphysema were 0.51. Survival curves for patients with and without honeycombing and with and without a definite UIP pattern on CT are shown in Fig. 1a and b respectively.

Across the entire study population, the presence of visually scored emphysema was associated with obstructive FEV1/FVC values on spirometry (β = −7.26, 95%CI −11.48, −3.04, p = 0.001) following adjustment for patient age, gender and baseline ILD extent. When quantified as percentages of the lung, emphysema lying distant to fibrotic lung (β = −0.75, 95%CI −0.96, −0.54, p < 0.0001) and emphysema admixed within fibrotic lung (β = −0.54, 95%CI −0.96, −0.12, p = 0.01) were also associated with obstructive values when inserted separately into the same models adjusted for patient age, gender, and baseline ILD extent.

Across the entire study population, the presence of visually scored honeycombing was associated with restrictive FEV1/FVC values on spirometry (Supplementary Table 3) following adjustment for patient age, gender and visual extents of reticular opacities and total emphysema. Whilst reticular opacities also demonstrated restrictive FEV1/FVC values, emphysema extent demonstrated restrictive FEV1/FVC values

Table 2
Characteristics of never-smokers (n = 116 unless stated) and smokers (n = 129 unless stated) with RA-ILD. Variables examined include: patient demographic details, pulmonary function indices and visually scored CT parameters. The *t*-test was used for continuous variables. *Chi-Square test, ^Mann-Whitney *U* test. Differences in median follow up time were calculated using the Log Rank Test. FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, Kco = carbon monoxide transfer coefficient, ILD = interstitial lung disease, # = only calculated in patients with emphysema.

Variable Units: percentages unless stated	Never-smokers	Smokers	Group comparison
Median age (years)	60	65	=0.01^
Male/female (ratio)	13/103	97/32	<0.0001*
Survival (alive/dead)	77/39	58/71	=0.001*
Median Follow up (months)	75.7 ± 4.2	80.5 ± 9.0	=0.98
FEV1% predicted	79.4 ± 21.7 (115)	76.4 ± 20.2 (121)	=0.27
FVC % predicted	74.1 ± 18.5 (115)	76.0 ± 21.4 (121)	=0.47
DLco % predicted	58.3 ± 21.0 (111)	49.5 ± 19.5 (119)	=0.001
Kco % predicted	79.1 ± 18.4 (70)	68.2 ± 19.3 (94)	=0.0003
Visual ILD extent	26.8 ± 17.4	28.2 ± 18.2	=0.55
Visual Honeycombing extent	3.2 ± 6.0	4.2 ± 7.5	=0.26
Visual Honeycombing presence (Y/N)	71/45	71/58	=0.33*
Visual Emphysema extent#	6.5 ± 11.0 (31)	14.4 ± 15.1 (98)	=0.008
Non-admixed emphysema extent#	2.7 ± 5.5 (31)	8.5 ± 12.2 (98)	=0.01
Admixed emphysema extent#	3.8 ± 5.8 (31)	5.9 ± 6.2 (98)	=0.08

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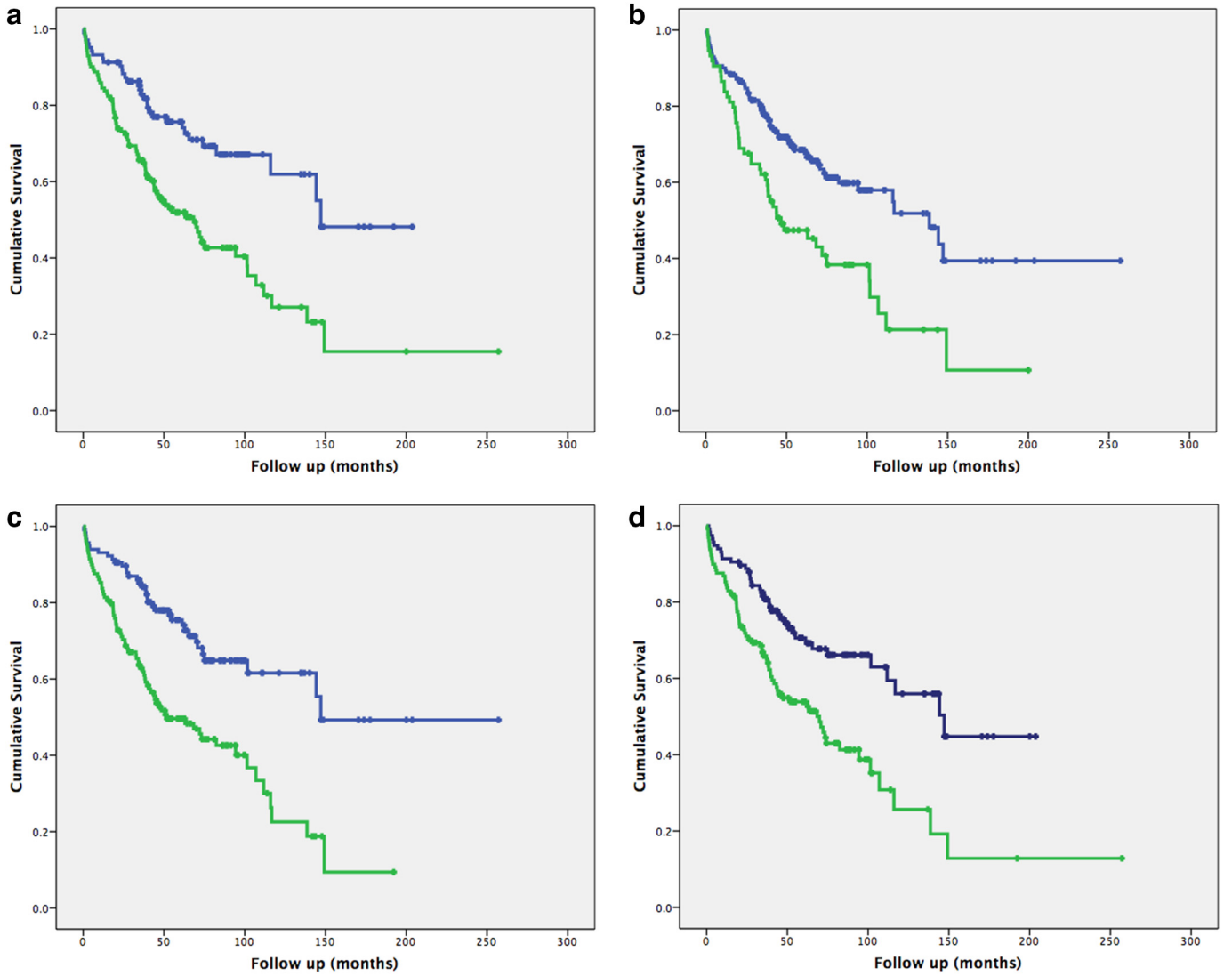

Fig. 1. Kaplan Meier survival curves in subgroups of patients with rheumatoid arthritis related interstitial lung disease. a. Kaplan Meier survival curves were significantly different between RA-ILD patients with honeycombing on CT (green, n = 142, restricted mean survival = 91.0 ± 11.3) and RA-ILD patients without any honeycombing on CT (blue, n = 103, restricted mean survival = 136.1 ± 10.0). Log rank test p < 0.0001. b. Kaplan Meier survival curves were significantly different between RA-ILD patients with a definite UIP pattern on CT (green, n = 74, restricted mean survival = 73.3 ± 9.2), and RA-ILD patients without a definite UIP pattern on CT (blue, n = 171, restricted mean survival = 141.9 ± 11.7 months). Log rank test p = 0.0002. c. Kaplan Meier survival curves were significantly different between RA-ILD patients without any emphysema on CT (blue, n = 116, restricted mean survival = 161.7 ± 13.6), and RA-ILD patients with emphysema scored visually on CT (green, n = 129, restricted mean survival = 75.5 ± 7.1). Log rank test p < 0.0001. d. Kaplan Meier survival curves of RA-ILD patients that were never-smokers (blue; n = 116, restricted mean survival = 129.9 ± 9.3) versus smokers (green; n = 129, restricted mean survival = 87.0 ± 11.5). Log rank test p = 0.0001. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(Supplementary Table 3). The results were maintained in the subgroup of patients with emphysema on CT (Supplementary Table 3).

4.2. Emphysema Presence in Never-Smokers

Emphysema was present on CT in 31/116 (27%, 95% confidence interval = 0.19–0.36) of never-smoking RA-ILD patients compared to 98/129 (76%) control smokers with RA-ILD (p < 0.0001). In never-smokers, emphysema was present in lung regions distant from pulmonary fibrosis (non-admixed) in 30/31 cases. Emphysema was also admixed within areas of pulmonary fibrosis in 25/31 cases. In one never-smoker, emphysema was admixed with fibrosis but was not present in non-fibrotic areas.

When all patients with emphysema were examined, never-smokers were found to have less extensive emphysema than smokers (p = 0.008)[Table 2]. Emphysema occurring separate to fibrotic regions was less extensive in never-smokers than smokers (p = 0.01), and was typically distributed in the upper lobes of the lungs. The proportion of total non-admixed emphysema that was present in the upper lobes did not vary between smokers and never-smokers (p = 0.96). In patients with non-admixed emphysema, coexisting centrilobular and paraseptal emphysema was more common in smokers 71/97 (73%) than never-smokers 11/30 (37%)[p = 0.0003]. In patients with either centrilobular or paraseptal emphysema, paraseptal emphysema 13/30 (43%) was more common than centrilobular emphysema 6/30 (20%) in never smokers, and smokers (paraseptal emphysema: 23/97[24%]; centrilobular emphysema: 3/97 [3%]). Thin walled cystic lesions (Inomata et al., 2014) were more common in smokers 14/97 (14%) than never-smokers 1/30 (3%)[p = 1.00] with non-admixed emphysema. In cases where thin walled cystic lesions were seen, centrilobular and paraseptal emphysema was always present. Admixed emphysema was predominantly identified in the lung bases and of similar extent in smokers and never-smokers (p = 0.08). The results were maintained following adjustment for total emphysema and ILD extents.

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4.3. Outcome Effects of Emphysema in RA-ILD Never-Smokers

Univariate Cox regression analysis demonstrated that increasing emphysema extent, as well as both emphysema subtypes (non-admixed and admixed) were strongly associated with mortality in never-smokers (Table 3). Functional indices did not strongly associate with outcome in never-smokers (Table 3) when compared to smokers (Supplementary Table 4). Outcome differences between patients with and without emphysema and between never-smokers and smokers are shown in Fig. 1c and d respectively.

On multivariate Cox regression analysis, after adjusting for patient age, gender, baseline disease extent using DLco, and a definite UIP pattern on CT, in never-smokers (and separately in smokers), the presence of emphysema (indicating a CPFE phenotype) were independently associated with mortality (Table 4). All models were maintained after adjustment for study center.

4.4. Associations of Honeycombing Presence on CT

In never-smokers, patient age, gender, ILD extent and emphysema presence were inserted into a multivariate logistic regression model (Table 5). The presence of emphysema ($p = 0.005$) was independently associated with the presence of honeycombing on CT (Model C-statistic $= 0.71$). The finding, though weaker in strength, was maintained in smokers ($p = 0.02$), after adjusting for smoking pack year history (Model C-statistic $= 0.78$). Emphysema presence also linked to a definite UIP pattern on CT (Table 5) in never-smokers (model C-statistic $= 0.75$) and smokers (model C-statistic $= 0.77$) when using the same logistic regression models.

The extent of ILD, whilst strongly associated with honeycombing presence in smokers ($p = 0.001$), did not associate with honeycombing presence in never-smokers and demonstrated no linkage to a definite UIP pattern in never-smokers and smokers (Table 5). All models were maintained after adjustment for study center.

4.5. Functional Effects of Emphysema in RA-ILD Never-Smokers

In never-smokers, a classic CPFE functional profile of a disproportionate reduction in DLco and artificially preserved lung volumes was not identified and was thought to be a consequence of the limited extents of emphysema in never-smokers (of the 81 study patients with over 5% emphysema, only 10/81 [12%] were never-smokers). When the functional effects of emphysema presence were examined across the whole study population, a CPFE functional profile was identified with results maintained at a 5% emphysema threshold (Supplementary Table 5). Across the entire study population, emphysema lying distant to fibrotic lung (non-admixed) demonstrated an independent negative association with DLco and Kco. In a similar adjusted model, an independent negative association was identified between admixed emphysema and Kco, but not DLco (Supplementary Table 6).

5. Discussion

Our study has identified several findings in patients with RA-ILD. Firstly, across two independent cohorts of patients, emphysema was identified in 27% of never-smokers. Secondly, in never-smokers, the presence of emphysema was independently associated with the presence of honeycombing on CT and a CT UIP pattern. Lastly, we demonstrated that the presence of emphysema, representing the CPFE phenotype, is independently associated with a worsened outcome in never-smokers and smokers with RA-ILD following adjustment for baseline disease severity.

Our study represents a detailed multicenter evaluation of emphysema and smoking burden in patients with RA-ILD. The primary study aim emerged from limited data in previous analyses of ILD cohorts, whereby emphysema had been identified in life-long never-smokers with IPF (Jacob et al., 2017), RA-ILD (Antoniou et al., 2013), and scleroderma (Antoniou et al., 2015). Since the cardinal question posed by our study revolved around the prevalence of emphysema, to avoid biases in emphysema characterization, all scorers were blinded to all clinical details. Reassuringly, the interobserver agreement for the presence of emphysema in our analyses was similar to previous CT descriptions of emphysema in patients with RA-ILD (Antoniou et al., 2013), scleroderma (Antoniou et al., 2015), and IPF (Jacob et al., 2017).

Four separate observations suggested that the scorers had avoided the misclassification of non-emphysematous lung as emphysema. Firstly, emphysema was scored more extensively in ever-smokers than never-smokers and proportions of emphysema separate to and occurring within fibrotic lung were similar in both patient groups. Secondly, in all but one case, when admixed emphysema was identified, emphysema was identified lying separate to fibrotic lung and was predominantly distributed within the upper lobes of the lung. Thirdly, parenchyma classified as both non-admixed and admixed emphysema was associated with obstructive functional indices. Furthermore, across the whole study population, the CPFE functional profile in RA-ILD mirrored the disproportionate reduction in gas transfer occurring with a relative preservation of lung volumes that has come to define the functional CPFE phenotype in IPF (Jacob et al., 2017; Ryerson et al., 2013; Cottin et al., 2005; Mejía et al., 2009; Bodlet et al., 2013; Mura et al., 2006). Lastly, honeycombing, which represents the CT pattern most likely to be confused with emphysema, was associated with restrictive functional indices when analyzed alongside emphysema extent which maintained its association with obstructive functional indices.

The presence of emphysema in 27% (95% confidence interval = 0.19–0.36) of never-smoker RA-ILD patients, whilst reinforcing observations in IPF (15% emphysema prevalence in never-smokers; measured using contiguous 1.0 mm CT images) (Jacob et al., 2017) and scleroderma (7% emphysema prevalence in never-smokers; measured using 1.5–3.0 mm thickness axial CT images with a 10 mm gap between sections) (Antoniou et al., 2015) was greater than that previously reported in patients with fibrosing lung diseases.

A study by Antoniou et al (Antoniou et al., 2013) identified emphysema in 2/35 (6%) (Antoniou et al., 2013) never-smokers with RA-ILD, and in 22/46 (48%) of smokers with RA-ILD. The comparatively low prevalence of emphysema in never-smokers in the RA-ILD and scleroderma studies of Antoniou et al (Antoniou et al., 2013; Antoniou et al., 2015) are likely to reflect fundamental differences in HRCT acquisition technique. The smaller RA-ILD study population of Antoniou et al

Table 3
Univariate Cox regression analysis demonstrating mortality in never-smokers according to demographic indices (top white), visually derived HRCT indices (light grey), pulmonary function tests (dark grey). ILD = Interstitial lung disease, FVC = forced vital capacity, DLco = diffusing capacity for carbon monoxide, Kco = Carbon monoxide transfer coefficient.

Variable (Units are percentage unless specified)	Patient number	Hazard ratio	95.0% confidence interval		*P* value
			Lower	Upper	
Age (years)	116	1.05	1.02	1.08	0.001
Gender (M = 1, F = 0)	116	1.49	0.57	3.84	0.41
Visual CT scores					
ILD extent	116	1.03	1.02	1.05	<0.0001
Honeycombing extent	116	1.08	1.05	1.12	<0.0001
Honeycombing presence	116	2.90	1.36	6.21	0.006
Non-admixed emphysema	116	1.08	1.02	1.15	0.009
Admixed emphysema	116	1.11	1.04	1.18	0.002
Total emphysema	116	1.05	1.02	1.08	0.003
Emphysema presence	116	1.51	0.78	2.95	0.23
Emphysema > 5%	116	2.34	0.88	6.17	0.09
Emphysema > 10%	116	6.84	2.00	23.42	0.002
Pulmonary Function Tests					
FVC	115	0.97	0.95	0.99	0.009
DLco	111	0.98	0.96	1.00	0.02
Kco	70	0.97	0.95	1.00	0.03

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Table 4
Multivariate Cox proportional hazards regression models associated with mortality in never-smokers (Model 1) and smokers (Model 2) with RA-ILD, following correction for patient age, gender, a CT definite usual interstitial pneumonia (UIP) pattern and baseline disease extent using DLco (diffusing capacity for carbon monoxide). Unadjusted hazard ratios are shown in brackets.

Multivariate Model	Baseline severity and emphysema models	Hazard ratio ((unadj), adj)	95.0% confidence interval		P value
			Lower	Upper	
Model 1	Age	(1.05) 1.06	1.02	1.09	0.003
	Gender	(1.49) 0.86	0.29	2.55	=0.78
	DLco	(0.98) 0.98	0.96	1.00	=0.02
	Emphysema presence	(1.51) 2.30	1.02	5.16	=0.04
	CT definite UIP pattern	(1.71) 1.54	0.72	3.32	=0.27
Model 2	Age	(1.04) 1.04	1.01	1.07	0.006
	Gender	(1.35) 0.85	0.44	1.66	0.64
	DLco	(0.97) 0.97	0.95	0.98	<0.0001
	Emphysema presence	(2.59) 2.16	1.01	4.62	=0.047
	CT definite UIP pattern	(2.26) 2.13	1.24	3.65	=0.006

(Antoniou et al., 2013), was evaluated using 1.5–3.0 mm thickness axial CT slices acquired at −30 mm intervals. Accordingly, mild extents of emphysema in the RA-ILD (Antoniou et al., 2013) and scleroderma (Antoniou et al., 2015) studies may have been missed on individual CT series when compared to the 1mm thickness slices acquired volumetrically in the Brompton population and the 10mm intervals in the Asan population.

The presence of emphysema in never-smokers, though limited in extent and quantified in a discrete population (31/116 patients), was independently associated with both the presence of honeycombing on CT and a definite CT UIP pattern (Raghu et al., 2011). Whilst passive smoking is one explanation for emphysema in never-smokers, the much higher prevalence of emphysema in never-smokers in the current study, when compared to never-smoker IPF patients (Jacob et al., 2017) who are on average much older and far more likely to be exposed to the effects of passive smoking, suggests that passive smoking alone cannot be the sole explanation for the presence of emphysema in never-smokers with RA-ILD.

Several independent reports have demonstrated linkages between RA and COPD prevalance (McGuire et al., 2017; Bieber et al., 2013; Shen et al., 2014) and RA and COPD hospitalization (McGuire et al., 2017; Shen et al., 2014). There findings argue strongly for common shared, automimmue pathways (Zhang et al., 2014; Feghali-Bostwick et al., 2008; Packard et al., 2013) that may activate protein citrullination (Rocha-Muñoz et al., 2015; Makrygiannakis et al., 2008; Rangel-Moreno et al., 2006; Scally et al., 2013), oxidative stresses (Vuorinen et al., 2008; Volonte et al., 2009), and matrix remodeling (Zandvoort et al., 2008) all of which have been implicated in the etiology of both emphysema and fibrosis.

The presence of emphysema was linked to an adverse outcome in both never-smokers and smokers with RA-ILD and runs counter to a recent report in IPF patients where, following analogous correction for baseline disease extent, CPFE was shown to have no added mortality effect in IPF (Jacob et al., 2017). Patients with IPF have more extensive fibrotic disease, and die rapidly as a consequence of their lung fibrosis. In patients with RA-ILD however, a more limited extent of ILD, and a longer disease course may result in emphysema and the impact of smoking related co-morbidities having a greater influence on patient outcome. The lack of a linkage between ILD extent on CT and CT honeycombing presence/definite CT UIP pattern (Raghu et al., 2011) may be explained by RA-ILD patients with extensive disease that have a non-specific interstitial pneumonia rather than a UIP pattern of fibrosis.

There were limitations to the current study. We examined two distinct populations of patients with RA-ILD and identified fundamental demographic differences between the populations, such as the low rate of smoking within the Korean female population when compared to British women with RA-ILD. Yet, we would argue that the use of disparate RA-ILD populations are a fundamental strength of our study and confer a robustness to our results when cardinal observations such as the occurrence of emphysema in never-smokers are replicated across both study cohorts. The relatively small sample size of 116 never-smoker RA-ILD patients in our study resulted in the relatively wide 95% confidence intervals for the presence of emphysema in never-smokers. Whilst our study remains one of the largest detailed

Table 5
Multivariate logistic regression models associated with a) the presence of honeycombing on CT b) an IPF-like definite UIP pattern on CT, in never-smokers and smokers. IPF = idiopathic pulmonary fibrosis, ILD = interstitial lung disease extent. Unadjusted odds ratios are shown in brackets.

Smoking status	Dependent variable	Variable	Odds ratio ((unadj)/adj)	95.0% confidence interval		P value
				Lower	Upper	
Never smoker	Honeycombing presence (Yes = 1, No = 0)	Age (years)	(1.04) 1.06	1.02	1.10	0.005
		Gender (Male = 1)	(2.30) 0.90	0.19	4.21	0.89
		ILD extent (%)	(1.01) 1.01	0.99	1.03	0.42
		Emphysema presence (Yes = 1)	(3.53) 5.05	1.64	15.56	0.005
Smoker	Honeycombing presence (Yes = 1, No = 0)	Age (years)	(1.03) 1.03	0.99	1.08	0.17
		Gender (Male = 1)	(2.59) 2.04	0.78	5.30	0.15
		ILD extent (%)	(1.05) 1.04	1.02	1.07	0.001
		Emphysema presence (Yes = 1)	(3.46) 3.23	1.21	8.62	0.02
		Smoking pack year history	(1.02) 1.01	0.99	1.03	0.29
Never smoker	IPF Definite CT UIP pattern (Yes = 1, No = 0)	Age (years)	(1.06) 1.09	1.04	1.14	0.0004
		Gender (Male = 1)	(0.70) 0.27	0.06	1.32	0.11
		ILD extent (%)	(0.98) 0.97	0.94	1.00	0.05
		Emphysema presence (Yes = 1)	(1.81) 4.36	1.44	13.20	0.009
Smoker	IPF Definite CT UIP pattern (Yes = 1, No = 0)	Age (years)	(1.01) 0.99	0.95	1.04	0.79
		Gender (Male = 1)	(9.66) 7.61	1.62	35.79	0.01
		ILD extent (%)	(1.02) 1.01	0.98	1.03	0.66
		Emphysema presence (Yes = 1)	(3.92) 4.64	1.24	17.36	0.02
		Smoking pack year history	(1.02) 1.02	1.00	1.04	0.06

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examinations of emphysema extent on CT in RA-ILD patients, larger multicentred studies would be important to validate our observations.

As we examined a respiratory and not a rheumatological database for our study, we were limited with regard to the serological information we were able to analyze. We had no information on patient symptom duration (both respiratory and rheumatological) prior to presentation to either tertiary center, or information on the cause of death in the study population. Furthermore, as tertiary care centers, we do not always receive comprehensive information regarding patient management at local primary or secondary base care centres, where treatment regimens such as dose and duration of steroid treatment, and choice of steroid sparing agents can vary widely. As an a priori decision, we intentionally chose not to try to quantify steroid dosages at the time of presentation with RA-ILD as many patients may have had RA pre-existing for some years before the development of symptomatic ILD. During this pre-symptomatic period, patients may have received steroids and steroid sparing agents for some time, with the result that knowledge of steroid use at a single point in time, or for the duration of symptomatic ILD, is likely to have only provided part of the patients treatment profile, and its effect on lung disease.

In conclusion, our study has demonstrated that 27% of RA-ILD patients that have never-smoked have emphysema visible on CT. We have shown that in both never-smokers and smokers, the presence of emphysema independently associates with the presence of honeycombing on CT and the negatively-prognostic CT-UIP pattern. We have also demonstrated that CPFE is associated with a worsened outcome in RA-ILD, following correction for baseline disease severity, when compared patients without emphysema.

Declaration of Interests

Dr. Jacob reports personal fees from Boehringer Ingelheim outside the current work.

Prof Maher has, via his institution, received industry-academic funding from GlaxoSmithKline R&D, UCB and Novartis and has received consultancy or speakers fees from Apellis, Astra Zeneca, Bayer, Biogen Idec, Boehringer Ingelheim, Cipla, GlaxoSmithKline R&D, Lanthio, InterMune, ProMetic, Roche, Sanofi-Aventis, Takeda and UCB outside the current work.

Dr. Renzoni reports personal fees from Roche, Boehringer Ingelheim, and Takeda, outside the submitted work.

Dr. Devaraj reports personal fees from Roche and Boehringer Ingelheim, outside the submitted work.

Prof Wells reports personal fees from Intermune, Boehringer Ingelheim, Gilead, MSD,

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Authors Contributions

JJ, JWS, HYY, DSK, AD, MK, TM, GC, JB, WLW, FA, ER, AUW were all involved in data collection, analysis and interpretation for the study.

JJ and AUW were also involved in the conception and design of the study and writing of the manuscript.

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Appendix A. Supplementary data

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