Association between chronic obstructive pulmonary disease, smoking, and interstitial lung disease onset in rheumatoid arthritis

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Abstract

Objective

In rheumatoid arthritis (RA), respiratory manifestations include chronic obstructive pulmonary disease (COPD) and interstitial lung disease (ILD). We assessed whether baseline COPD and smoking were associated with RA-ILD onset.

Methods

We identified new-onset ILD in incident RA subjects within the MarketScan Commercial Claims database, using physician and/or hospitalisation diagnostic codes. Smoking data (current, past, never) were available for a subset via a health questionnaire. Kaplan-Meier analyses assessed time to ILD onset, stratified by prior COPD and smoking. Multivariate Cox regression models were adjusted for age, sex, and (in the subset) smoking. Sensitivity analyses adjusted for past RA drugs.

Results

Among 373,940 new RA subjects, 6343 (1.7%) developed ILD (8.1 events per 1000 person-year, 95% CI 7.9, 8.3). ILD was more common among subjects with baseline COPD. Adjusting for age and sex, the hazard ratio (HR) between baseline COPD and incident ILD was 2.15, 95% CI 1.93, 2.39. We could not establish a clear relationship between current smoking and ILD; in the subset with smoking data, the HR point estimate for COPD was similar but the 95% CI was wider (due to fewer subjects) and included the null value. Adjusting for baseline RA drugs did not change results.

Conclusion

Pre-existing COPD in incident RA subjects was associated with higher risk of future ILD. While a trend persisted after adjusting for smoking, we were limited by reduced sample size. Our study highlights the importance of ongoing assessments of potentially complicated relationships between smoking, COPD, and other factors in RA-associated ILD.

Key words

rheumatoid arthritis, interstitial lung disease, smoking, risk factors, chronic obstructive pulmonary disease

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Introduction

Rheumatoid arthritis (RA) is the most frequent autoimmune rheumatic disease, affecting 1% of adults (1) and co-occurring lung disease represents a significant cause of morbidity and mortality. It is estimated that ~5% of RA patients develop clinically significant interstitial lung disease (ILD) associated with a 50% five-year mortality rate (2). The risk of RA-ILD is increased in the presence of rheumatoid factor and anti-citrullinated peptide antibody (ACPA) positivity. Other risk factors for RA-ILD are older age, male sex, disease duration, and chronically high disease activity (3, 4). Smoking, associated with increased ACPA titres, has been implicated as another risk factor for RA-ILD. However, the association between smoking and clinically significant RA-ILD has been inconsistently identified in observational cohorts (2, 5).

Smoking is also a key cause of chronic obstructive pulmonary disease (COPD), an inflammatory, destructive airway disease that can manifest as bronchitis and/or emphysema. RA patients have an increased risk of COPD even with low cumulative smoking exposure (6). Both ILD and COPD have an inflammatory component, although affecting different lung tissues with increased cellular infiltrates in the airways in COPD (7) and increased $CD4^+$ T cell infiltrates in the parenchymal interstitium in RA (8). It is unknown whether COPD associated with RA would represent an additional risk factor for ILD or if RA patients with lung involvements might share an underlying susceptibility beyond smoking. Our goal was to examine COPD and smoking as risk factors for RA-ILD in a large population-based dataset. We hypothesised that both COPD and smoking would be independently associated with RA-ILD onset.

Methods

Data source

This retrospective longitudinal study used the IBM MarketScan Commercial Claims administrative database (2010-2018) containing healthcare data from employer-sponsored insurance plans. Linked to this database is a sub-cohort of subjects in the MarketScan Health Risk Assessment (HRA) database with self-reported health insurance questionnaires on smoking exposure. This study was approved by the McGill University ethics committee (no. A04-M47-12B).

Subject selection

Adults with new-onset RA were identified in the presence of ≥2 physician claims and/or ≥1 hospitalisation(s) with a RA principal diagnosis within 2 years using International Classification of Diseases-9-Clinical Modification (ICD-9-CM) codes 714 and ICD-10 codes M05, M06. Subjects must have ≥12 months of continuous plan enrolment without prior RA diagnoses. The first RA diagnosis date was considered the index date.

Variable definitions

ILD was identified in the presence of ≥2 claims for pulmonary fibrosis and/or rheumatic lung disease at least 1 month apart (ICD-9-CM codes 515, 516.3, 714.81 and ICD-10 J84.1, M05.1). Pre-existing ILD was excluded based on a one-year look-back period. Co-existing COPD was identified in the presence of ≥1 claim(s) of ICD-9-CM codes 491, 492, 496 and ICD-10 codes J41-J44, assessed up to one year before the index date. In the smoking sub-cohort, smoking was classified as current, past, or never. Other covariates were sex, age at the index date, and ever use of RA related medications: systemic corticosteroids, disease modifying anti-rheumatic drugs (DMARDs: methotrexate, leflunomide, sulfasalazine, hydroxychloroquine), and biologic agents (anti-TNF agents, tocilizumab, abatacept, tofacitnib, rituximab).

Statistical analysis

Time to ILD onset was estimated using Kaplan-Meier curves and compared between those with and without pre-existing COPD, as well as by smoking status in the smoking sub-cohort. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ILD onset were obtained using Cox proportional hazards models adjusted for age and sex, and smoking in the sub-cohort. In sensitivity analyses we also adjusted for prior RA related medication use to control for possible misclassification

Table I. Baseline characteristics of RA subjects in the full MarketScan and HRA smoking sub-cohort.

Full MarketScan cohort	All RA subjects (n=373,940)	RA-ILD (n=6,343)	RA no ILD (n=367,597)	Difference (95% CI)
Mean age, years (SD)	50.5 (10.9)	51.3 (11.1)	50.4 (10.9)	
Female, n (%)	280,469 (75.0)	4,655 (73.4)	275,814 (75.0)	-1.64 (-0.56, -2.75)
COPD, n (%)	11,396 (3.1)	406 (6.4)	10,990 (3.0)	3.41 (2.83, 4.04)
Drugs prior to RA claim, n (%)				
Biologic	23,450 (6.3)	302 (4.8)	23,148 (6.3)	-1.54 (-0.09, -2.04)
DMARD	60,414 (16.2)	906 (14.3)	59,508 (16.2)	-1.90 (-1.01, -2.75)
Corticosteroids	133,654 (35.7)	2,540 (40.0)	131,114 (35.7)	4.38 (3.17, 5.60)
Smoking sub-cohort	**All RA subjects (n=18,808)**	**RA-ILD (n=288)**	**RA no ILD (n=18,520)**	**Difference (95% CI)**
Mean age, years (SD)	50.7 (9.9)	51.8 (9.2)	50.7 (9.9)	
Female, n (%)	13,739 (73.1)	202 (70.1)	13,537 (73.1)	3.00 (-2.00, 8.51)
Smoking, n (%)				
Current	1,444 (9.4)	19 (8.3)	1,425 (9.5)	1.10 (-2.40, 3.46)
Past	2,103 (13.7)	32 (14.0)	2,071 (13.7)	0.07 (-4.11, 3.24)
Never	11,762 (76.8)	178 (77.7)	11,584 (76.8)	0.74 (-4.72, 6.52)
COPD, n (%)	704 (3.7)	16 (5.6)	688 (3.7)	1.84 (-0.29, 5.13)
Drugs prior to RA claim, n (%)				
Biologic	1,091 (5.8)	14 (4.9)	1,077 (5.8)	0.95 (-2.19, 2.93)
DMARD	3,346 (17.8)	46 (16.0)	3,300 (17.8)	1.85 (-2.86, 5.67)
Corticosteroids	9,985 (53.1)	175 (60.8)	9,810 (53.0)	7.79 (2.00, 13.30)

95% CI: 95% confidence interval; SD: standard deviation; ILD: interstitial lung disease; COPD: chronic pulmonary obstructive disease; Biologic: anti TNF agents, tocilizumab, abatacept, tofacitinib, rituximab; DMARD: disease-modifying anti-rheumatic drugs and includes methotrexate, leflunomide, sulfasalazine, hydroxychloroquine.

of pre-existing RA as incident RA. An exploratory *post-hoc* analysis was performed to examine the use of methotrexate and anti-TNF separately from the other medications given concerns of these drugs being potentially associated with ILD exacerbations (9, 10).

Results

373,940 incident RA subjects were identified in the MarketScan database, with a mean follow-up time of 2.1 (standard deviation, SD, 1.8) years. 1.7% developed ILD, with an incidence rate of 8.1 per 1000 person-year (95% CI 7.9, 8.3). 18,808 incident RA subjects were identified in the smoking sub-cohort and 1.5% developed ILD over a mean follow-up time of 2.6 (SD 1.8) years, with an incidence rate of 5.9 per 1000 person-year (95% CI 5.2, 6.6). In both cohorts the majority were women, with a mean age of ~50 years (Table I). Baseline COPD was present in 6.4% of those who developed ILD *versus* 3.0% of those who did not (Table I).

In the Kaplan-Meier survival analysis, subjects with COPD had a higher risk of ILD onset (Fig. 1) and this finding persisted after adjusting for age and sex (HR 2.15, 95% CI 1.93, 2.39, Table II). In the HRA sub-cohort, smoking questionnaires were filled on average 1.0 (SD 1.1) years before the index date. 76.8% were never smokers (Table I). Among those with COPD, 55% self-reported as never smokers and 45% as a past and/or current smoker. The correlation between ever smoking and COPD was weak (Cramer's V = 0.12, 95% CI 0.10, 0.14). The time to ILD onset between RA subjects with different smoking histories were similar on Kaplan-Meier analyses and there was no association between ILD and smoking on multivariate analysis. The adjusted HR estimate for COPD suggested a positive association with ILD in the sub-cohort, although the 95% CI was wider and included the null (Table II).

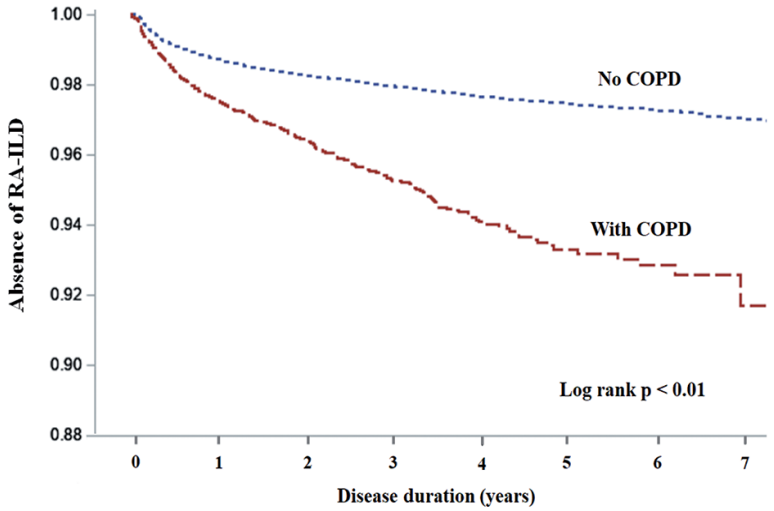

Fig. 1. Kaplan-Meier curves for time to ILD onset stratified by co-existing COPD in the overall MarketScan RA cohort.

The inclusion of RA related medication in the Cox models did not impact the HRs between COPD and ILD. However, past corticosteroid use was associated with ILD onset in both the full (HR 1.21, 95% CI 1.15, 1.28) and sub-cohort (HR 1.54, 95% CI 1.18, 2.02, Table II). Of those previously

Table II. Multivariate Cox regression models of the likelihood of RA-ILD onset in the full MarketScan and HRA smoking sub-cohort.

	Model without baseline medication use	Model with baseline medication use
Full MarketScan cohort	Hazard ratio (95% CI)	Hazard ratio (95% CI)
COPD	2.15 (1.93, 2.39)	2.10 (1.89, 2.32)
Female	0.93 (0.88, 0.99)	0.93 (0.88, 0.98)
Age at RA onset	1.00 (1.00, 1.01)	1.00 (1.00, 1.01)
Drugs prior to RA claim		
Biologic		0.76 (0.67, 0.85)
DMARD		0.85 (0.80, 0.92)
Corticosteroids		1.21 (1.15, 1.28)
Smoking sub-cohort	Hazard ratio (95% CI)	Hazard ratio (95% CI)
Smoking		
Current *vs*. never	0.80 (0.49, 1.29)	0.77 (0.48, 1.27)
Past *vs*. never	0.99 (0.68, 1.44)	1.01 (0.69, 1.48)
COPD	1.67 (0.94, 2.93)	1.68 (0.93, 2.89)
Female	0.83 (0.62, 1.11)	0.82 (0.61, 1.09)
Age at RA onset	1.01 (1.00, 1.03)	1.01 (0.99, 1.03)
Drugs prior to RA claim		
Biologic		0.73 (0.38, 1.38)
DMARD		0.88 (0.62, 1.25)
Corticosteroids		1.54 (1.18, 2.02)

95% CI: 95% confidence interval; RA: rheumatoid arthritis; ILD: interstitial lung disease; COPD: chronic pulmonary obstructive disease; Biologic: anti TNF agents, tocilizumab, abatacept, tofacitinib, rituximab; DMARD: disease-modifying anti-rheumatic drugs and includes methotrexate, leflunomide, sulfasalazine, hydroxychloroquine.

exposed to DMARDs, 28,535 (47.2%) had been exposed to methotrexate. Of those previously exposed to biologics 21,576 (92.0%) had been exposed to anti-TNFs. *Post-hoc* analysis specifically examining previous MTX and anti-TNF use found a lower likelihood of ILD onset among patients exposed to methotrexate compared to patients exposed only to other DMARDs (HR 0.78, 95%CI 0.68, 0.90) and a lower likelihood of ILD onset among patients exposed to anti-TNF compared to other biologics (HR 0.58, 95% CI 0.41, 0.82), after adjusting for age, sex, and COPD status in the overall MarketScan cohort.

Discussion

This is the first population-based study of COPD and RA-ILD and we found that COPD was associated with RA-ILD in incident RA patients. However, it is difficult to separate the effects of smoking which could not be reliably assessed in our sub-cohort with self-reported smoking questionnaires. The majority was never smokers and participants may have under-reported smoking behavior given that these were healthcare insurance plan questionnaires. This may explain the poor correlation between COPD and smoking and the low sample sizes that limited the analyses in this sub-cohort. Thus, it is difficult to interpret the loss of statistical significance in the association between COPD and ILD in the multivariate model with smoking status. While the trend towards increased ILD among those with pre-existing COPD remained, the widened confidence interval may be due to a lack of power. It is feasible that COPD and ILD share common aetiologic pathways in RA as COPD occurs even at low levels of smoking exposure in RA (11) and obstructive lung changes are more frequent in the presence of ACPA (12), which are antibodies associated with RA-ILD pathogenesis. In fact, emphysema, found in COPD, is co-present with ILD on lung imaging in 27% of RA patients who never smoked (13).

While few studies have examined the link between COPD and RA-ILD, various RA cohorts have examined smoking. Some were unable to establish any association (2, 5, 14) while others have found that cumulative smoking exposure was associated with increased risk of RA-ILD (15), subclinical lung imaging abnormalities (16), as well as pulmonary function test changes and increased symptoms (17). The absence of cumulative smoking information in our study could also have led to under-ascertainment of smoking and further biased our estimates between smoking and ILD towards the null.

In sensitivity analyses, past corticosteroid use was associated with RA-ILD. Because corticosteroids can be used to treat COPD or acute ILD flares, this potentially represents protopathic bias, where initiation of a drug occurs in response to symptoms of a latent diagnosis. Because corticosteroids are also used in RA that is poorly controlled despite DMARD or biologic therapy, this association may represent confounding by disease activity since active RA is associated with RA-ILD (4). This also explains why DMARDS and biologics were associated with lower HR for RA-ILD in our study. It is also conceivable that the prevalent RA patients on treatment were misclassified as incident RA by our algorithm *because* they were so stable that they did not consult physicians for RA during our 1-year look-back period, leading to an appearance of reduced RA-ILD risk in this treated group. Finally, patients exposed to methotrexate had a lower HR for ILD onset than patients treated with other DMARDs. This finding is in keeping with recent data that methotrexate use is in fact associated with reduced RA-ILD onset (18). As an alternate possibility, the lower HRs for ILD associated with methotrexate and anti-TNF may be due to the fact that physicians tend to avoid these medications in patients with ILD (19).

Although use of a large population-based database is a strength, the validity of ICD codes to detect disease is dependent on accurate physician coding. For RA, physician and hospitalisation codes have been validated to have a sensitivity/specificity of 97% and 77%, respectively (20) and RA identification algorithms show better sensitivity and specificity when at least two claims were required (21), as we did. The demographics of our RA cohort correspond with the expected RA sex and age distribution, as does our incidence of RA-ILD (2, 22,

23). While ICD codes do not map well to current ILD classification, the coding for RA-ILD has recently been validated in the Veterans Affairs database examining various algorithms, including of our ICD-9 definition which performed favourably, with a specificity of 97.1% and PPV of 72.1% (24). Our definition also followed those used in previous RA-ILD studies (22, 25, 26). The definition we used for COPD coding has been validated to have a sensitivity/specificity of 85.0% and 78.4% respectively for ICD 10 coding (27) and a sensitivity/specificity of 79% and 62%, respectively for ICD 9 coding (28).

The imperfect diagnostic ascertainment may result in imprecision from non-differential misclassification of outcome, thus contributing to the wide confidence intervals for some of our estimates. It is also important to note that ILD could have initially been misdiagnosed as COPD, which may have contributed to our association between COPD and ILD, although COPD and ILD diagnoses are largely temporally separated. There may also have been a detection bias, given that COPD patients may be more closely monitored for lung diseases by their physicians, leading to earlier ILD detection. Another potential limitation is that subjects are no longer identifiable after they change insurance status, which is why we needed to adjust for potential misclassification of prevalent RA. Other residual confounding that could not be accounted for include autoantibody seropositivity. However, it is unclear if these are part of the causal pathway linking smoking and RA-ILD; in which case they should not be adjusted for (29).

Conclusions

In a large US based administrative claims database, we found that COPD was associated with ILD onset in incident RA. We saw trends for an association between smoking and ILD, but (due in part to power issues), we could not definitively comment on a unique role for this potential risk factor in ILD. Corticosteroid use prior to RA diagnosis was also associated with ILD, potentially related to confounding/protopathic bias. Further studies are needed to validate our findings and to better evaluate the effects of smoking in the relationship between COPD and RA-ILD onset, as well as to understand underlying pathogenic mechanisms.

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