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ORIGINAL ARTICLE

Association of rheumatoid arthritis-related autoantibodies with pulmonary function test abnormalities in a rheumatoid arthritis registry

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Abstract

Introduction We investigated whether rheumatoid arthritis (RA)-related autoantibodies were associated with abnormalities on pulmonary function tests (PFTs).

Methods We studied RA serostatus and PFT abnormalities within a RA registry. RA serostatus was assessed by research assays for cyclic citrullinated peptide (CCP) and rheumatoid factor (RF). Outcomes were abnormalities on clinically indicated PFTs, including restriction, obstruction, and diffusion abnormality. Logistic regression was used to obtain ORs and 95% CIs for the PFT abnormalities by RA serologic phenotypes independent of lifestyle and RA characteristics.

Results Among 1272 analyzed subjects, mean age was 56.3 years (SD 14.1), 82.2% were female, and 69.5% were seropositive. There were 100 subjects with abnormal PFTs. Compared with seronegativity, seropositivity was associated with increased odds of any PFT abnormality (multivariable OR 2.29, 95% CI 1.30–4.03). When analyzing type of PFT abnormality, seropositivity was also associated with restriction, obstruction, and diffusion abnormalities; multivariable ORs were 2.48 (95% CI 1.26–4.87), 3.12 (95% CI 1.28–7.61), and 2.30 (95% CI 1.09–4.83), respectively. When analyzing by CCP and RF status, the associations were stronger for RF+ than for CCP+ (any PFT abnormality OR 1.99, 95% CI 1.21–3.27 for RF+ vs. RF−; OR 1.67, 95% CI 1.03–2.69 for CCP+ vs. CCP−) with a dose effect of higher RF titer increasing odds for each PFT abnormality (p for trend < 0.05).

Conclusions Seropositive RA patients had two-fold increased risk for abnormalities on PFTs performed for clinical indications compared with seronegative RA. Patients with seropositive RA, particularly those with high-titer RF positivity, may be more likely to have obstructive and restrictive abnormalities, independent of smoking.

Key points

- *Due to the known excess pulmonary morbidity/mortality in RA, we studied the relationship of rheumatoid arthritis (RA)-related autoantibodies with pulmonary function test (PFT) abnormalities using a large RA registry.*
- *We evaluated whether presence and levels of cyclic citrullinated peptide (CCP) and rheumatoid factor (RF) were associated with restriction, obstruction, and diffusion abnormalities on PFTs among 1272 subjects with RA.*
- *Seropositivity was associated with two-fold increased risk for any PFT abnormality, independent of confounders including smoking. Higher titers of RF conferred greatest risk for all PFT outcomes: obstruction, restriction, and diffusion abnormality.*
- *These results provide evidence that patients with RA should be closely monitored for pulmonary involvement, particularly those with high-titer RF seropositivity.*

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Keywords CCP · Pulmonary disease · RF · Rheumatoid arthritis · Serostatus

Introduction

Extra-articular manifestations affect nearly 40% of patients with rheumatoid arthritis (RA) [1]. Pulmonary involvement in RA is associated with high morbidity and mortality, affecting pleura, airways, parenchyma, blood vessels, and respiratory muscles [2, 3]. RA-associated interstitial lung disease (RA-ILD) is a well-described restrictive lung disease with median survival of less than 3 years after clinical diagnosis [4]. RA may also be associated with increased risk for obstructive pulmonary diseases such as chronic obstructive lung disease (COPD) and asthma, as well as other airway diseases particularly bronchiectasis [5–7]. Patients with RA have been shown to have increased risk of pulmonary function test (PFT) and chest computed tomography (CT) abnormalities compared with non-RA controls, but less is known about RA-specific risk factors for pulmonary abnormalities [8].

Despite the morbidity and mortality associated with RA-associated pulmonary disease, there is limited understanding of the clinical characteristics associated with PFT abnormalities in RA. Seropositivity for cyclic citrullinated peptide antibody (CCP) or rheumatoid factor (RF) is an established risk factor for RA-ILD, increasing risk by nearly two-fold compared with seronegativity [4, 9, 10]. However, risk factors associated with other types of RA-associated pulmonary diseases remain poorly understood [11–13]. Prior studies suggested both CCP and RF seropositivity may be associated with increased risk for structural pulmonary abnormalities, while others focused mostly on CCP [12, 14, 15]. However, these studies were focused on specific pulmonary structures affected in RA, and most focused solely on CCP or RF, limiting investigation of whether these autoantibodies had differential effects on the pulmonary outcomes. PFTs have been used to monitor disease progression in rheumatologic lung disease [16]. Studying PFT abnormalities allows assessment of a wide range of pulmonary manifestations of RA, broadly characterized as restrictive or obstructive.

We aimed to investigate whether RA-related autoantibodies were associated with abnormalities on PFTs. We hypothesized that seropositivity for CCP or RF would be associated with increased risk for PFT abnormalities compared with seronegative RA since presence of these RA-related autoantibodies may be associated with abnormalities in pulmonary interstitium, alveoli, and airways. We further hypothesized that there would be a dose effect of higher titers of CCP and RF increasing risk for restrictive as well as obstructive lung disease.

Methods

Study population and design

We investigated RA-related autoantibodies and PFT abnormalities using the Brigham Rheumatoid Arthritis Sequential Study (BRASS). BRASS is a single-center, prospective, observational, longitudinal registry of more than 1500 adults with RA that was commenced in 2003 at Brigham and Women's Hospital (BWH) in Boston, MA. All subjects in BRASS have RA according to the treating rheumatologist with 99% meeting accepted ACR/EULAR criteria [17, 18]. Details regarding the design of the BRASS registry have been reported previously [19]. CCP and RF were tested at enrollment on all subjects.

Patient-reported data collected every 6 months include demographics, smoking status, and RA medications. Physician-reported disease activity measures (disease activity score in 28 joints using the C-reactive protein level (DAS28-CRP)) were collected annually at a study visit. In addition, the electronic medical record is available to obtain clinical data. RA-ILD cases were identified from clinically indicated chest CTs by three independent adjudicators as previously described [20, 21]. The study protocol and informed consent document were reviewed and approved by the Partners HealthCare Institutional Review Board. All subjects provided written informed consent before participating in the BRASS registry.

We performed an analysis within BRASS investigating whether RA-related autoantibodies were associated with presence of abnormalities on clinically indicated PFTs among patients with RA without PFT abnormalities prior to RA diagnosis. The study sample was composed of patients with RA enrolled in BRASS until June 1, 2017, when PFT results were last extracted. We excluded subjects that were missing CCP or RF data or had any PFT abnormalities prior to RA diagnosis. Many subjects had established RA at baseline. CCP and RF were tested for research purposes at time of BRASS enrollment. Subjects with PFT abnormalities after RA diagnosis but prior to enrollment in BRASS were included since RA serostatus is usually stable after diagnosis, although the levels may change slightly over time or with therapy and/or disease activity [22].

Exposures: CCP and RF serostatus

The primary exposure was seropositive RA compared with seronegative RA. Seropositive RA was defined as either CCP or RF positivity (> upper limit of normal (ULN)) vs. seronegative (both CCP and RF negative, ≤ ULN). These tests

were performed at a CLIA-certified laboratory using commercial assays. Third-generation CCP measurements were performed using validated enzyme-linked immunosorbent assays (ELISAs) from Inova Diagnostics (San Diego, CA) and Euro Diagnostica (Minneapolis, MN) with ULN of 19.9. RF measurements were performed by an immunoturbidimetric technique on the Cobas Integra 700 analyzer (Roche Diagnostics; Indianapolis, IN), using reagents and calibrators from Roche with ULN of 15. We defined CCP and RF levels as low positive (> 1 to 3× ULN) or high positive (> 3× ULN) based on cutoffs used in the 2010 ACR/EULAR criteria for RA classification [18].

We performed the following secondary analyses: (1) CCP positive vs. CCP negative (reference group); (2) RF positive vs. RF negative (reference group); (3) CCP high positive vs. CCP low positive vs. CCP negative (reference group); (4) RF high positive vs. RF low positive vs. RF negative (reference group); and (5) CCP positive and RF positive vs. CCP positive and RF negative vs. CCP negative and RF positive vs. CCP negative and RF negative (reference group).

Outcomes: abnormalities on clinically indicated PFTs

The primary outcome of the study was a composite of any abnormality on PFTs. The PFT abnormalities were identified from the electronic medical record and included all clinically indicated PFTs performed on BRASS subjects. Numeric and free-text PFT data were extracted and verified by two independent reviewers. Any PFT abnormality was defined as a composite of the following: obstruction (ratio of forced expiratory volume in 1 s to forced vital capacity (FEV_1/FVC) < 0.7 on any PFT), restriction (% predicted FVC < 80 on any PFT), or diffusion abnormality (% predicted diffusing capacity of the lungs for carbon monoxide corrected for hemoglobin (D_{LCO}[Hb]) < 70 on any PFT; uncorrected D_{LCO} was used if D_{LCO}[Hb] was unavailable). These definitions for PFT abnormalities are consistent with clinical and research definitions for defining presence or absence of obstruction, restriction, and diffusion abnormality [23, 24]. If a subject had more than one PFT performed during routine clinical care, the subject was classified based on the lowest values. The specific reason for ordering PFTs was unable to be captured in this study.

The secondary outcomes were the individual components of the composite outcome: obstruction, restriction, and diffusion abnormality. Subjects that had no clinically indicated PFTs performed were allowed in the primary analysis and secondary analyses were restricted to those who had PFTs performed.

Covariates

We considered covariates that may be commonly associated with CCP/RF positivity and PFT abnormalities. Covariates were measured at baseline in BRASS. These included sociodemographic variables such as age (continuous in years), sex, race (White/non-White), and education (college degree or higher/less education). Lifestyle factors included body mass index (BMI, continuous in kg/m^2) and smoking (never/past/current). Clinical variables included the multimorbidity index previously validated for RA as a categorical variable (0, 1, > 1) [25] and physical activity (metabolic equivalent of task (MET), hours per week) [26]. RA characteristics included RA duration, disease activity score 28 (DAS28) (high-moderate/remission-low) [27], multidimensional health assessment questionnaire (MD-HAQ) score [28], ever methotrexate use, ever other non-biologic and biologic disease-modifying antirheumatic drug (DMARD) use, and ever glucocorticoid use.

Statistical analysis

Descriptive statistics for the study sample at BRASS baseline were reported overall and according to RA serologic status. Among the subset that had PFTs ordered through routine clinical care, we reported the median and interquartile range of % predicted FEV_1, FVC, and D_{LCO} as well as FEV_1/FVC, overall and by RA serologic status. We compared subjects with seropositive and seronegative RA using Wilcoxon rank sum tests.

We used logistic regression to obtain odds ratios (OR) and 95% confidence intervals (CI) for the PFT abnormality outcomes by RA serologic phenotypes. The reference group in all models was seronegative (or CCP/RF negative depending on the exposure of interest). For the three-level CCP and RF variables, the p value for trend was obtained by using the median value for each category and using this in the model as a continuous variable. We adjusted for possible confounders in multivariable logistic regression models by including age, sex, education, BMI, smoking status, and RA duration at baseline. We did not include RA severity factors such as disease activity, erosions, and rheumatoid nodules in the multivariable models since these may be causally related to RA serostatus.

We performed additional sensitivity analyses to assess for the robustness of our primary analyses. First, we restricted the analysis to only the subset of subjects who had PFTs performed ($n = 188$). Second, we performed an incident PFT analysis after BRASS baseline among this subset ($n = 1214$) to examine the time-to-event association. We used Cox regression in this analysis with these censoring variables: date of initial PFT abnormality (outcome), death, or end of study (June 1, 2017), whichever came first, and reported the hazard ratio (HR) and 95% CI for any PFT abnormality by RA serologic status. Third, we reclassified mild PFT abnormalities ($FEV_1 \geq 70\%$ predicted for obstruction, $FEV_1 \geq 70\%$ predicted for restriction, D_{LCO}[Hb] ≥ 60% predicted for diffusion) as not being an outcome, since these mild PFT abnormalities

may be clinically asymptomatic and may not have serious clinical consequences compared with more severe PFT abnormalities [29]. Using this strategy, 25 subjects were reclassified for the primary analyses; for the secondary analyses, 10, 27, and 19 subjects were reclassified in the obstruction, restriction, and diffusion abnormality groups, respectively. Fourth, we further adjusted our multivariable model for baseline ever use of methotrexate since some patients may rarely develop pneumonitis or fibrosis after methotrexate use which may result in PFT abnormalities [30]. Fifth, to investigate the role of smoking on RA serologic status and risk of PFT abnormalities, we performed the primary analysis stratified by smoking status (ever vs. never smokers) and tested for an interaction. Sixth, we further adjusted our restriction model with baseline RA-ILD to investigate if the association with restrictive PFT changes can be explained by ILD. Finally, we further adjusted our obstruction model with baseline RA-related airway disease (bronchiectasis and bronchiolitis obliterans) to investigate if the association with obstructive PFT abnormalities can be explained by known airway disease.

Statistical significance was defined as a two-sided p value less than 0.05. Analyses were performed using SAS, version 9.4.

Results

Study sample characteristics

Baseline characteristics of the subjects meeting the inclusion and exclusion criteria ($n = 1272$) are shown in Table 1. The mean age was 56.3 (SD 14.1) and the subjects were predominantly female (82.2%). Most of the subjects were seropositive (884, 69.5%) and 388 (30.5%) were seronegative. The seropositive subjects tended to have a longer median RA duration and higher disease activity with erosive and nodular disease, as well as were more likely to have ever been on DMARDs. Among the seropositive subjects, 71.8% had CCP level above 3× ULN, and 61.2% had RF level above 3× ULN. There were 11.0% of the seropositive subjects with CCP+ but RF−, and 11.5% with CCP− but RF+.

RA-related autoantibodies and restriction

Table 4 shows the association of RA serostatus with restriction on clinically indicated PFTs (defined as FVC < 80% predicted). Seropositivity was associated with 2.48-fold (95% CI 1.26–4.87) increased odds of restriction compared with seronegativity, after multivariable adjustment. CCP and RF positivity were also significantly associated with restriction, with OR 1.95 (95% CI 1.09–3.47) and 2.34 (95% CI 1.28–4.27) compared with CCP and RF negativity, respectively. There were statistically significant dose effects on risk for restriction for both CCP and RF titers, $p = 0.016$ and 0.002, respectively.

RA-related autoantibodies and obstruction

The association of RA serostatus with obstruction on clinically indicated PFTs (defined as $FEV_1/FVC < 0.7$) is shown in Table 5. Seropositivity was associated with 3.12 (95% CI 1.28–7.61) times the odds of obstruction compared with seronegative subjects, after multivariable adjustment. CCP and RF positivity were also significantly associated with obstruction, with OR 2.04 (95% CI 1.00–4.15) and 2.60 (95% CI 1.22–5.56) compared with CCP and RF negativity, respectively. No statistically significant dose effect was seen for CCP (p for trend 0.072). However, there was a statistically significant dose effect with RF titer, with $p = 0.003$ for trend. Subjects with high-titer RF had three-fold higher odds of obstruction (OR 3.10, 95% CI 1.42–6.76) than RF− subjects.

RA-related autoantibodies and diffusion abnormality

Table 6 shows the association of RA serostatus with diffusion abnormality on PFTs (defined as D_{LCO}[Hb] < 70% predicted). Seropositivity was associated with 2.30 (95% CI 1.09–4.83) times the odds of diffusion abnormality compared with seronegative subjects, after multivariable adjustment. RF positivity was also significantly associated with diffusion abnormality, with OR 2.01 (95% CI 1.05–3.85), with higher titer RF increasing risk in a dose-dependent manner (p for trend of 0.012). There was no statistical association of CCP positivity with diffusion abnormality (OR 1.47, 95% CI 0.80–2.71).

Sensitivity analyses

When restricting the analysis to only the subjects who had PFTs performed for clinical indication ($n = 188$, Supplemental Table 1), seropositivity remained significantly associated with any PFT abnormality (multivariable OR 2.40, 95% CI 1.07–5.35) compared with seronegativity. The point estimates for the secondary exposures based on CCP, and RF status were also similar in this subgroup, but some did not reach statistical significance.

We analyzed serostatus and incident PFT abnormality occurring after BRASS baseline among this subset ($n = 1214$) using a time-to-event Cox regression analysis (Supplemental Table 2). There were a total of $n = 85$ incident PFT abnormalities in this analysis during 12,538 person years of follow-up (mean 10.3 (SD 4.2) years/subject). Seropositivity was significantly associated with increased risk of PFT abnormality (multivariable HR 1.97, 95% CI 1.11–3.49), compared with seronegativity. RF positivity was significantly associated with increased risk of PFT abnormality (HR 1.66, 95% CI 1.01–

2.74), similar to the primary analysis though some of the findings did not reach statistical significance likely due to restricted sample size.

Since mild PFT abnormalities may not be clinically significant, we reclassified mild PFT abnormalities as non-cases in an additional sensitivity analysis. The strengths of the

Table 1 Baseline characteristics of subjects in BRASS overall and by serologic status ($n = 1272$)

	All ($n = 1272$)	Seropositive ($n = 884$)	Seronegative ($n = 388$)
Sociodemographics			
Mean age, years (SD)	56.3 (14.1)	56.5 (13.9)	55.7 (14.5)
Female, *n* (%)	1046 (82.2)	737 (83.4)	309 (79.6)
White, *n* (%)	1165 (91.6)	802 (90.7)	363 (93.6)
College degree or more, *n* (%)	703 (55.3)	471 (53.3)	232 (59.8)
Serologic status			
Seropositive, *n* (%)	884 (69.5)	884 (100.0)	0 (0.0)
CCP+, *n* (%)	782 (61.5)	782 (88.5)	0 (0.0)
RF+, *n* (%)	787 (61.9)	787 (89.0)	0 (0.0)
CCP+ and RF+, *n* (%)	685 (53.9)	685 (77.5)	0 (0.0)
CCP+ and RF−, *n* (%)	97 (7.6)	97 (11.0)	0 (0.0)
CCP− and RF+, *n* (%)	102 (8.0)	102 (11.5)	0 (0.0)
CCP level, *n* (%)			
≤ ULN	490 (38.5)	102 (11.5)	388 (100.0)
> 1 to 3× ULN	147 (11.6)	147 (16.6)	0 (0.0)
> 3× ULN	635 (49.9)	635 (71.8)	0 (0.0)
RF level, *n* (%)			
≤ ULN	485 (38.1)	97 (11.0)	388 (100.0)
> 1 to 3× ULN	246 (19.3)	246 (27.8)	0 (0.0)
> 3× ULN	541 (42.5)	541 (61.2)	0 (0.0)
Lifestyle and clinical			
Mean body mass index (kg/m^2, SD)	26.8 (5.8)	26.7 (5.8)	27.2 (5.7)
Smoking status, *n* (%)			
Never	606 (47.6)	415 (47.0)	191 (49.2)
Past	466 (36.6)	333 (37.7)	133 (34.3)
Current	89 (7.0)	57 (6.5)	32 (8.3)
Mean MET-hours/week (SD)	4.8 (5.3)	4.8 (5.3)	5.0 (5.1)
Multimorbidity index count, *n* (%)			
0	870 (68.4)	594 (67.2)	276 (71.1)
1	195 (15.3)	141 (16.0)	54 (13.9)
> 1	206 (16.2)	148 (16.7)	58 (15.0)
RA characteristics			
Median RA duration, years (IQR)	9.0 (3.0, 21.0)	11.0 (4.0, 23.0)	4.0 (2.0, 11.5)
DAS28-CRP3 moderate/high, *n* (%)	736 (57.9)	531 (60.1)	205 (52.8)
Methotrexate use, *n* (%)	941 (74.0)	693 (78.4)	248 (63.9)
Non-biologic DMARD use, *n* (%)	1192 (93.7)	849 (96.0)	343 (88.4)
Biologic DMARD use, *n* (%)	574 (45.1)	447 (50.6)	127 (32.7)
Glucocorticoid use, *n* (%)	1004 (78.9)	700 (79.2)	304 (78.4)
RA-ILD, *n* (%)	86 (6.8)	76 (8.6)	10 (2.5)
RA-related airway disease*, *n* (%)	18 (1.4)	17 (1.9)	1 (0.3)

Missing data not reported

*Bronchiectasis or bronchiolitis obliterans

CCP, cyclic citrullinated peptide antibody; *CRP*, C-reactive protein; *DAS*, disease activity score; *DMARD*, disease-modifying antirheumatic drug; *IQR*, interquartile range; *MDHAQ*, multidimensional health assessment questionnaire; *MET*, metabolic equivalent; *RA*, rheumatoid arthritis; *RF*, rheumatoid factor; *SD*, standard deviation; *ULN*, upper limit of normal

Table 2 Pulmonary function test results overall and by serologic status, among the subset of subjects who had testing performed through routine clinical care ($n = 188$)

	All ($n = 188$)	Seropositive ($n = 146$)	Seronegative ($n = 42$)	p value
FEV_1 (% predicted)	81.5 (61–96)	80 (59–93)	89.5 (70–101)	0.034
FVC (% predicted)	84 (66–97)	82.5 (63–96)	88 (75–105)	0.055
FEV_1/FVC	76 (68–80.5)	76 (68–81)	76.5 (72–80)	0.352
D_{LCO} (% predicted)	71 (53–85)	68 (53–82)	78 (58–90)	0.060

D_{LCO}, diffusing capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity

associations were similar to the primary analyses, with seropositive subjects having ORs of 2.24 (95% CI, 1.17–4.30) for any PFT abnormality, 3.42 (95% CI, 1.31–8.94) for restriction, 2.93 (95% CI, 1.10–7.80) for obstruction, and 1.83 (95% CI, 0.78–4.30) diffusion abnormality, when compared with seronegative subjects.

We also assessed the impact of methotrexate use on any PFT abnormality by additionally including this in the multivariable model of our primary analysis. The association between RA serostatus and any PFT abnormality remained statistically significant (OR 2.42, 95% CI 1.36–4.29) in this model. Ever use of methotrexate was not significantly associated with any PFT abnormality (OR 0.73, 95% CI 0.45–1.17) compared with non-use as a covariate in this model.

We assessed the impact of smoking on the association of RA serologic status and any PFT abnormality using a stratified model by smoking status (ever vs. never smokers) (Supplemental Table 3). In each stratum, a significant

Table 3 Unadjusted and multivariable odds ratios for any clinically-indicated pulmonary function test abnormality (restriction, obstruction, or diffusion abnormality) according to RA-related autoantibody status ($n = 1272$).

	Unadjusted OR (95%CI)	**Multivariable* adjusted OR (95%CI)**
Seronegative	1.00 (REF)	1.00 (REF)
Seropositive	2.44 (1.41−4.23)	2.29 (1.30−4.03)
CCP negative	1.00 (REF)	1.00 (REF)
CCP positive	1.87 (1.18−2.96)	1.67 (1.03−2.69)
RF negative	1.00 (REF)	1.00 (REF)
RF positive	2.18 (1.35−3.52)	1.99 (1.21−3.27)
CCP negative	1.00 (REF)	1.00 (REF)
CCP > 1 to ≤ 3× ULN	1.88 (0.95−3.70)	1.78 (0.89−3.57)
CCP > 3× ULN	1.86 (1.16−3.00)	1.64 (1.00−2.69)
p for trend	0.012	0.061
RF negative	1.00 (REF)	1.00 (REF)
RF > 1 to ≤ 3× ULN	1.30 (0.67−2.55)	1.32 (0.67−2.62)
RF > 3× ULN	2.60 (1.58−4.27)	2.29 (1.37−3.84)
p for trend	< 0.001	0.001
CCP−/RF−	1.00 (REF)	1.00 (REF)
CCP+/RF−	1.81 (0.72−4.53)	1.91 (0.75−4.87)
CCP−/RF+	2.53 (1.11−5.75)	2.78 (1.20−6.44)
CCP+/RF+	2.52 (1.44−4.41)	2.28 (1.27−4.07)

*Adjusted for age (continuous, years), sex (male, female), education (less than college degree, college degree or higher), smoking status (never, past, current), body mass index (continuous, kg/m^2), and RA duration at study baseline (continuous, years).

CCP: cyclic citrullinated peptide antibody; CI; confidence interval; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; ULN: upper limit of normal

Table 4 Unadjusted and multivariable odds ratios for restriction (% predicted FVC <80) on clinically-indicated pulmonary function testing according to RA-related autoantibody status (n = 1272).

	Unadjusted OR (95%CI)	Multivariable* adjusted OR (95%CI)
Seronegative	1.00 (REF)	1.00 (REF)
Seropositive	2.63 (1.37–5.05)	2.48 (1.26–4.87)
CCP negative	1.00 (REF)	1.00 (REF)
CCP positive	2.19 (1.26–3.81)	1.95 (1.09–3.47)
RF negative	1.00 (REF)	1.00 (REF)
RF positive	2.54 (1.42–4.53)	2.34 (1.28–4.27)
CCP negative	1.00 (REF)	1.00 (REF)
CCP > 1 to ≤ 3× ULN	1.60 (0.68–3.79)	1.51 (0.62–3.67)
CCP > 3× ULN	2.33 (1.32–4.09)	2.04 (1.14–3.68)
p for trend	0.003	0.016
RF negative	1.00 (REF)	1.00 (REF)
RF > 1 to ≤ 3× ULN	1.61 (0.74–3.49)	1.67 (0.75–3.69)
RF > 3× ULN	2.98 (1.65–5.40)	2.64 (1.42–4.90)
p for trend	< 0.001	0.002
CCP–/RF–	1.00 (REF)	1.00 (REF)
CCP+/RF–	1.47 (0.46–4.73)	1.56 (0.48–5.13)
CCP–/RF+	2.14 (0.77–5.94)	2.46 (0.87–6.97)
CCP+/RF+	2.87 (1.48–5.57)	2.61 (1.31–5.20)

*Adjusted for age (continuous, years), sex (male, female), education (less than college degree, college degree or higher), smoking status (never, past, current), body mass index (continuous, kg/m^2), and RA duration at study baseline (continuous, years).

CCP: cyclic citrullinated peptide antibody; CI; confidence interval; FVC: forced vital capacity; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; ULN: upper limit of normal

association remained between seropositivity and any PFT abnormalities. We also performed an analysis to investigate if there is an interaction between RA serostatus and smoking, which was not statistically significant (p for interaction 0.328, Supplemental Table 3).

We investigated if the association between RA serostatus and restrictive PFT abnormalities can be explained by ILD by further adjusting the model with baseline RA-ILD diagnosis. The OR for seropositivity decreased minimally from 2.48 (95% CI 1.26–4.87) to 2.25 (95% CI 1.14–4.42) while maintaining statistical significance (Supplemental Table 4). The significant associations with CCP+ and RF+ were also preserved. The previously observed dose-response with RF and CCP remained significant. We also investigated if the association between RA serostatus and obstructive PFT abnormalities can be explained by baseline RA-related airway disease. The OR after additionally adjusting for baseline bronchiectasis or bronchiolitis obliterans changed minimally from 3.12 (95% CI 1.28–7.61) to 3.01 (95% CI 1.24–7.35) (Supplemental Table 4).

Discussion

In this large registry of RA subjects, we observed that seropositivity for CCP or RF was associated with increased risk of abnormalities on clinically indicated PFTs. Ours is one of the first studies to demonstrate the importance of high-titer RF positivity, rather than CCP, for the pulmonary function test abnormalities. In addition, we report that RA-related autoantibodies are associated with obstructive changes, not only restrictive changes that may have been expected due to RA-ILD. We showed that seropositive subjects had two-fold increased odds of having any PFT abnormality. This association was also observed for the individual components of the primary composite outcome: restriction, obstruction, and diffusion abnormality. These results suggest that RA seropositivity is not only associated with restrictive changes as previously shown in RA-ILD [9, 10], but these RA-related autoantibodies may also be important in the development of obstructive pulmonary disease. We observed that both CCP and RF positivity were associated with increased risk for PFT abnormalities. Interestingly, RF tended to have a stronger, titer-related impact

Table 5 Unadjusted and multivariable odds ratios for obstruction (FEV_1/FVC <0.7) on clinically-indicated pulmonary function testing according to RA-related autoantibody status (n = 1272).

	Unadjusted OR (95%CI)	Multivariable* adjusted OR (95%CI)
Seronegative	1.00 (REF)	1.00 (REF)
Seropositive	3.34 (1.41–7.89)	3.12 (1.28–7.61)
CCP negative	1.00 (REF)	1.00 (REF)
CCP positive	1.87 (1.18–2.96)	2.04 (1.00–4.15)
RF negative	1.00 (REF)	1.00 (REF)
RF positive	2.91 (1.40–6.03)	2.60 (1.22–5.56)
CCP negative	1.00 (REF)	1.00 (REF)
CCP > 1 to ≤ 3× ULN	2.18 (0.83–5.72)	2.14 (0.79–5.79)
CCP > 3× ULN	2.31 (1.15–4.63)	2.01 (0.97–4.18)
p for trend	0.018	0.072
RF negative	1.00 (REF)	1.00 (REF)
RF > 1 to ≤ 3× ULN	1.55 (0.57–4.21)	1.52 (0.54–4.22)
RF > 3× ULN	3.55 (1.68–7.47)	3.10 (1.42–6.76)
p for trend	< 0.001	0.003
CCP–/RF–	1.00 (REF)	1.00 (REF)
CCP+/RF–	2.03 (0.50–8.27)	2.27 (0.54–9.54)
CCP–/RF+	3.28 (0.98–10.98)	3.56 (1.03–12.29)
CCP+/RF+	3.53 (1.47–8.46)	3.17 (1.28–7.86)

*Adjusted for age (continuous, years), sex (male, female), education (less than college degree, college degree or higher), smoking status (never, past, current), body mass index (continuous, kg/m^2), and RA duration at study baseline (continuous, years)

CCP: cyclic citrullinated peptide antibody; CI; confidence interval; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; ULN: upper limit of normal

compared with CCP on PFT abnormalities, for restriction as well as obstruction. Overall, these results suggest that RA-related autoantibodies may have important effects on restrictive and obstructive abnormalities among patients with RA beyond the effect of other risk factors, including smoking, and that patients with high-titer RF positivity may be particularly susceptible.

Prior studies suggest that PFT and CT chest imaging abnormalities in RA can occur both in the presence and absence of respiratory symptoms [8, 11, 31, 32]. The lung has also been suggested to be a site of initiating the production of RA autoantibodies [33]. A meta-analysis pooling eight studies reported that CCP positivity had an OR of 2.62 for RA-related pulmonary disease [34]. This study focused on the effect of CCP positivity, and the effect of RF on RA-related pulmonary disease was not found to be statistically significant. However, only five out of eight included studies included RF positivity. In a Japanese study of 356 RA patients with RA, RF positivity, but not CCP positivity, was associated with RA-ILD [35]. Seropositivity for both RF and CCP was associated with airway diseases of bronchiectasis and bronchiolitis as measured on high-resolution chest CT scans [35]. In a cross-sectional study of 252 patients with RA, increased CCP levels, but not RF levels, were associated with increased risk for lung abnormalities on high-resolution chest CT scans [15]. In both of these studies, structural pulmonary disease was categorized based on imaging studies, but functional measures by PFTs were not the focus. Interestingly, both CCP and RF positivity have been shown to be associated with the development of pulmonary diseases such as ILD and bronchiectasis in the absence of clinical RA with articular manifestations [36–39]. The RA shared epitope (SE) is known to be associated with increased RA risk and dose-dependent CCP and RF titers [40, 41]. It is possible that patients with SE are more susceptible to PFT abnormalities given the known interaction between SE and smoking [42].

The association between seropositivity and development of RA-ILD has been established. A possible framework for RA-ILD susceptibility has been proposed related to interactions between smoking, presence of the *HLA-DRB1* shared epitope, and the development of CCP antibodies [43], but it did not include RF. In a Finnish study of 71 RA subjects, RF

Table 6 Unadjusted and multivariable odds ratios for diffusion abnormality (% predicted D_{LCO} <70) on clinically-indicated pulmonary function testing according to RA-related autoantibody status (n = 1272).

	Unadjusted OR (95%CI)	Multivariable* adjusted OR (95%CI)
Seronegative	1.00 (REF)	1.00 (REF)
Seropositive	2.31 (1.12–4.77)	2.30 (1.09–4.83)
CCP negative	1.00 (REF)	1.00 (REF)
CCP positive	1.56 (0.86–2.81)	1.47 (0.8–2.71)
RF negative	1.00 (REF)	1.00 (REF)
RF positive	2.05 (1.09–3.85)	2.01 (1.05–3.85)
CCP negative	1.00 (REF)	1.00 (REF)
CCP > 1 to ≤ 3× ULN	1.71 (0.72–4.07)	1.66 (0.68–4.01)
CCP > 3× ULN	1.52 (0.82–2.81)	1.43 (0.76–2.69)
p for trend	0.197	0.301
RF negative	1.00 (REF)	1.00 (REF)
RF > 1 to ≤ 3× ULN	1.22 (0.50–2.99)	1.32 (0.53–3.26)
RF > 3× ULN	2.44 (1.27–4.67)	2.31 (1.18–4.53)
p for trend	0.004	0.012
CCP–/RF–	1.00 (REF)	1.00 (REF)
CCP+/RF–	1.81 (0.55–6.01)	1.87 (0.55–6.29)
CCP–/RF+	3.10 (1.13–8.55)	3.45 (1.23–9.65)
CCP+/RF+	2.27 (1.08–4.77)	2.20 (1.03–4.73)

*Adjusted for age (continuous, years), sex (male, female), education (less than college degree, college degree or higher), smoking status (never, past, current), body mass index (continuous, kg/m^2), and RA duration at study baseline (continuous, years).

CCP: cyclic citrullinated peptide antibody; CI; confidence interval; D_{LCO} diffusing capacity of the lungs for carbon monoxide; OR: odds ratio; RA: rheumatoid arthritis; RF: rheumatoid factor; ULN: upper limit of normal

positivity was correlated with lower D_{LCO} [44]. However, only D_{LCO} was measured in that study without the other components of PFTs such as FEV_1 and FVC which are important clinical measures used to detect and evaluate the presence and severity of restriction and obstruction. In a large, multicenter UK study that included 230 RA-ILD cases and 230 RA controls without ILD, both CCP and RF were found to be significantly associated with RA-ILD, and CCP titers conferred highest risk for RA-ILD [9]. That study focused on subjects with proven RA-ILD, while our current study focused on any pulmonary abnormalities among all patients with RA, not restricted to patients diagnosed with RA-ILD. Since only 86 (6.8%) subjects out of 1272 had RA-ILD, it is unlikely that our findings are explained solely by RA-ILD.

Since we investigated both CCP and RF, we were able to study their differential associations with PFT outcomes, unlike previous studies. Compared with CCP positivity, RF positivity tended to be more strongly associated with both the primary outcome and its individual components along with clear dose effects with higher RF levels associated with increased risk for PFT abnormalities. In comparison, a CCP titer dose-associated effect was only observed for restrictive abnormalities, but not in the primary outcome or obstructive changes. In CCP/RF discordant subjects, CCP−/RF+ subjects tended to have higher ORs for having PFT abnormalities compared with CCP+/RF− subjects. This provides further support for our finding that RF positivity appears more strongly associated with PFT abnormalities than CCP positivity. In a sensitivity analysis, we found that RA seropositivity was also associated with incident PFT abnormalities. Inclusion of methotrexate use in our models did not seem to significantly alter the association between RA seropositivity and PFT abnormalities. Stratification by smoking status did not significantly alter the OR demonstrating the association was not explained by smoking. Inclusion of RA-ILD in the restriction model did not significantly alter the association. Hence RA-ILD did not explain the observed associations. Similarly, we found that RA-related airway diseases did not explain the observed association between RA seropositivity and obstructive PFT abnormalities. The findings suggest that clinicians should have increased vigilance in screening for pulmonary abnormalities particularly in seropositive RA patients. Caution should be exercised when using medications with known pulmonary toxicity. However, inclusion of methotrexate in our model

did not significantly alter the association between serostatus and PFT abnormalities. The results from our study suggest close monitoring of seropositive RA patients, particularly those with high-titer RF, for pulmonary disease with PFTs, which has been shown to correlate with structural abnormalities on chest CT [12]. Future studies should investigate the biologic effects of RF on pulmonary involvement in RA. Our observation cannot establish causality, so further research is required to confirm these findings.

However, our study has several limitations. We studied abnormalities captured on clinically indicated PFTs. Thus, it is possible that some subjects with subclinical PFT abnormalities were not tested or that PFTs were performed at other institutions. However, the sensitivity analysis restricting the study sample to only those who had PFTs performed demonstrated similar associations of seropositivity and RF positivity with PFT abnormalities, similar to the primary analysis. Further, analyzing subjects without PFTs performed would misclassify true cases as non-cases which should bias the effect size toward the null. In addition, the tests were ordered for clinical reasons which we were unable to ascertain and may have affected the associations we found. Future studies should investigate the effect of RA-related autoantibodies on PFT abnormalities among asymptomatic patients measured for research purposes to determine the utility of screening RA patients with PFTs. In this study, we utilized PFT instead of imaging to assess for lung disease. PFTs have been shown to be well-correlated with imaging abnormalities in a wide range of pulmonary disease [45]. The BRASS registry consisted mostly of subjects with established RA instead of those who were newly diagnosed. However, the association remained after adjusting for RA disease duration. While our results were adjusted for important covariates including smoking status, many were self-reported, which can be subject to recall bias or misclassification. For example, adjustment for smoking pack-years could have affected results. As the patients in the BRASS registry are older adults, E-cigarette use was not measured. Future studies would be necessary to investigate the association of E-cigarettes and other inhalants with pulmonary outcomes in RA. BRASS is a single-center study at a tertiary care center of mostly white and educated patients, which may not be representative of the general RA population. Future studies should investigate the effects of RA-related autoantibodies in more diverse populations.

A major strength of our study is using a large registry of RA subjects with access to both research data and electronic medical record data, which provided us with a rich source of information over time. Nearly all the subjects in BRASS fulfilled the ACR/EULAR RA classification criteria, so all subjects analyzed truly had RA. In addition, all subjects had CCP and RF measurements at BRASS enrollment using research assays, which provided a complete dataset and allowed comparison of autoantibody titers. We investigated PFT abnormalities since this provides a broad assessment of types of functional abnormalities that are prevalent in RA, rather than only focusing on restriction or obstruction. We were able to study details of the subjects' PFTs as well as rich covariates and biomarker data. The ability to link to the electronic medical record also allowed us to assess the time to developing PFT abnormalities. Since all the PFTs in this study were clinically indicated, they are reflective of real-world practice since not all patients with RA are screened with PFTs.

In conclusion, we found that RA-related seropositivity was associated with increased risk for abnormalities on PFTs that were performed for clinical indications. This association was also seen in specific patterns of PFT abnormalities including restriction, obstruction, and diffusion abnormalities. These results suggest that RA-related autoantibodies may be associated with risk for obstructive lung disease in addition to the previously known effects on restrictive lung disease. Unlike CCP, RF had clear dose effects for the association with PFT abnormalities with increasing titers. Future studies should assess the value of screening for pulmonary function abnormalities in seropositive RA patients, particularly those who are RF positive at high titer.

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Author contributions All authors were involved in drafting the article or revising it critically for important intellectual contact, and all authors approved the final version to be published. Huang, He, Shadick, and Sparks were involved in the study conception and design; Huang, Zaccardelli, Marshall, Friedlander, Blaustein, Smith, Cui, Iannaccone, Mahmoud, Weinblatt, Shadick and Sparks in acquisition of data; and Huang, He, Doyle, Zaccardelli, Marshall, Friedlander, Cui, Iannaccone, Mahmoud, Weinblatt, Dellaripa, Shadick and Sparks in data analysis and interpretation. Dr. Huang had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Compliance with ethical standards

The study protocol and informed consent document were reviewed and approved by the Partners HealthCare Institutional Review Board. All subjects provided written informed consent before participating in the BRASS registry.

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