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Decline of Pulmonary Function Is Associated With the Presence of Rheumatoid Factor in Korean Health Screening Subjects Without Clinically Apparent Lung Disease

A Cross-Sectional Study

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Abstract: Although higher-than-normal levels of rheumatoid factor (RF) are often observed in subjects without specific medical problems, little is known about the influence of RF on pulmonary function in health screening subjects. This study aimed to determine the association between the presence of RF and decreased pulmonary function in Korean health screening subjects without any history of joint disease or clinically apparent lung disease.

A total of 115,641 study subjects (age range, 18–88 years) participated in the health checkup program. We excluded subjects who did not have pulmonary function test, as well as those with abnormal chest radiographs. Subjects with medical history of arthritis including rheumatoid arthritis, and lung disease based on the self-reported questionnaire. Final analysis was performed on 94,438 Koreans (41,261 women).

RF-positive subjects had a lower forced vital capacity (FVC) predicted value and forced expiratory volume in 1 s (FEV1) predicted value than RF-negative subjects ($82.8 \pm 11.5\%$ vs $83.8 \pm 11.4\%$ for FVC% predicted and $83.5 \pm 13.0\%$ vs $85.1 \pm 12.9\%$ for FEV1% predicted, $P < 0.001$ for both). RF positivity was significantly associated with the decline of FEV1% predicted regardless of smoking history (adjusted odds ratio [OR] = 1.289 [95% confidence interval [CI] 1.163–1.429], $P < 0.001$ for nonsmokers and adjusted OR = 1.138 [95% CI 1.004–1.289], $P < 0.001$ for smokers) while the decline of FVC% predicted only in nonsmokers (adjusted OR = 1.251 [95% CI 1.133–1.382], $P < 0.001$). Our results suggest that the presence of RF could impact pulmonary function in apparently healthy subjects.

A follow-up study to investigate serial changes in pulmonary function may reveal the actual influence of raised RF titers.

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Abbreviations: AFL = airflow limitation, BMI = body mass index, CCP = cyclic citrullinated protein, CI = confidence interval, CRP = C-reactive protein, DLCO = diffusion capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, HBsAb = hepatitis B surface antibody, HBsAg = hepatitis B surface antigen, HCV Ab = hepatitis C antibody, HRCT = high-resolution computed tomography, OR = odds ratio, PFT = pulmonary function test, RA = rheumatoid arthritis, RF = rheumatoid factor.

INTRODUCTION

Rheumatoid factor (RF) is an autoantibody directed against the Fc portion of immunoglobulin G, and could aid in diagnosis and prognosis of rheumatoid arthritis (RA) patients. RF is present in approximately 70% to 80% of RA patients and also found nonspecifically in other inflammatory condition such as sarcoidosis, hepatitis B and C infection, and tuberculosis. False positive reactions for RF in the general population range from 1% to 5%.^{1,2}

Meanwhile, RF or anticyclic citrullinated protein (CCP) antibodies, so-called RA-related antibodies, have been found in subjects with lung diseases such as cystic fibrosis, cryptogenic fibrosing alveolitis, pigeon hypersensitivity pneumonitis, and interstitial lung disease, even without clinical evidence of RA.^{3–6} In a case–control study, subjects without inflammatory arthritis who had RA-related antibodies showed a significantly higher frequency of inflammatory airway abnormalities such as bronchial wall thickening, bronchiectasis, centrilobular opacities, and air trapping in high-resolution computed tomography (HRCT) scans compared to those without RA-related antibodies.⁷ Moreover, an inverse relationship was observed between RF titer and the diffusion capacity for carbon monoxide in smoking patients with RA.⁸ In an old Mini-Finland health survey study, a decreased ratio of forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) in nonarthritic women was significantly associated with RF positivity, regardless of age and smoking history.⁹ Some researchers have asserted that several mucosal surfaces, such as those of the lungs, are potential sites for the initiation of an inappropriately modulated immune reaction.^{6,10} These findings, taken together, suggest that the lung may be an important site for generating or sequestering autoantibodies produced as a result of immune dysregulation and that RF might be responsible for structural changes and/or functional abnormalities of the lung.

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Although higher-than-normal levels of RF are often observed in subjects without specific medical problems, very few researchers have examined the influence of RF in these subjects on conditions other than arthritis, such as pulmonary function, even though it is well known that RA-related antibodies can be present for up to 10 years before symptomatic RA develops.^{11,12}

We hypothesized that the lungs are potential sites of RF-related injury caused by chronic immune stimulation in subjects without clinically apparent lung disease. Thus, this study was performed to determine the association between the presence of RF and decreased pulmonary function in Korean health screening subjects without any history of joint disease or clinically ostensible lung disease.

METHODS

Subjects

A total of 115,641 study subjects (age range, 18–88 years) participated in the health checkup program held at the Total Healthcare Center, Kangbuk Samsung Hospital, Seoul, South Korea between January 2010 and December 2010. All subjects completed a self-reported questionnaire to document medical history, current use of regular medications, any clinical symptoms, and lifestyle factors including history of smoking and drinking habits. We excluded subjects who did not have pulmonary function test (PFT) ($n = 762$) or RF ($n = 4,648$) test results, as well as those with abnormal chest radiographs ($n = 15,091$). In addition, subjects with arthralgia, medical history of arthritis including RA, and lung disease based on the self-reported questionnaire ($n = 697$) as well as those with an extremely high RF titer ($> 1,000$) ($n = 5$) were excluded because of high suspicion of developing RA. Final analysis was performed on 94,438 subjects. Ethics approval for patient recruitment and data analyses was obtained from the institutional review board of Kangbuk Samsung Hospital (#KBC14046). The institutional review board exempted the requirement for informed consent for this study because for data analysis, we accessed a deidentified database retrospectively. In addition, the study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Measurement of Pulmonary Function

Spirometry was performed as recommended by the American Thoracic Society^{13,14} using the Vmax22 system (Sensor-Medics, Yorba Linda, CA). The percentage predicted values (% predicted) for FEV1 and FVC were calculated from the obtained absolute values of FEV1 and FVC using the following equations that were derived from a representative Korean population sample:¹⁵

$$\text{Predicted FVC} = -4.8434 - (0.00008633 \times \text{age}^2 [\text{y}]) + (0.05292 \times \text{height} [\text{cm}]) + (0.01095 \times \text{weight} [\text{kg}])$$

$$\text{Predicted FEV1} = -3.4132 - (0.0002484 \times \text{age}^2 [\text{y}]) + (0.04578 \times \text{height} [\text{cm}]).$$

Among 3 or more tests with satisfactory curves, the highest values of FEV1 and FVC were chosen for further analyses. Regarding FVC (predicted %) and FEV1 (predicted %), the formula for predicted % was to divide the measured value (L) by the predicted value (L) then converted into a percentage. Study subjects were categorized into 4 groups according to the quartiles of baseline predicted % for FVC or FEV1 as used previously.¹⁶ The resulting 4 groups of FVC (predicted %) or FEV1 (predicted %) were meant to contain 25% of subjects in

each quartile. Each group of FVC (predicted %) was as follows: $\geq 91.56\%$ in quartile 1, 83.46% to 91.55% in quartile 2, 75.77% to 83.45% in quartile 3, and $\leq 75.76\%$ in quartile 4 while each group of FEV1 (predicted %) as follows: $\geq 93.58\%$ in quartile 1, 84.64% to 93.57% in quartile 2, 76.17% to 84.63% in quartile 3, and $\leq 76.16\%$ in quartile 4. Airflow limitation (AFL) was defined as FEV1/FVC $< 70\%$.

Anthropometric Measurements and Laboratory Tests

We included the following variables in our analyses: height (m), weight (kg), body mass index (BMI) (kg/m^2), smoking status as packs-year, drinking habit, medical history including hypertension, coronary artery disease, diabetes, chronic liver disease, and malignancy. Laboratory tests also included such as lipid profile, fasting glucose, homocysteine, C-reactive protein (CRP), RF, and hepatitis B and C levels.

Blood samples were taken uniformly in the morning from the antecubital vein of participants who had fasted for at least 12 h. RF and the serological test for hepatitis B and C virus were measured by the identical method used in previous study:² RF by an immunoturbidimetric assay with Modular P800 (Roche Diagnostics, Basel, Switzerland), hepatitis B surface antigen (HBsAg) and antibody (HBsAb) by a chemiluminescent micro-particle immunoassay (Architect i2000SR; Abbott Laboratories, Abbott Park, IL), and hepatitis C antibody (HCV Ab) by radioimmunoassay (RIAKEY_anti-HCV IRMA tube; Shin Jin Medics, Goyang, Korea). The RF titer ≥ 20 IU/mL was considered positive.

Statistical Analysis

Continuous variables were presented as the mean \pm standard deviation or median with interquartile ranges (IQRs), and categorical variables were reported as numbers and percentages. The normality of the distribution for all variables was assessed by the statistic of skewness and its standard error, the statistic of kurtosis and its standard error, and the Kolmogorov–Smirnov test. Comparisons between the 2 groups were done by Student *t* test or chi-squared test. For skewed variables, comparisons were done by Mann–Whitney *U* test. The parameters of pulmonary function were not normal in distribution and therefore the association of RF and other covariates was examined by multivariable binary logistic regression models for the binary outcomes of pulmonary function. The strength of associations was estimated with odds ratio (OR) and 95% confidence interval (CI). All covariates were treated as categorical variables; highs or lows, or with or without. For multivariate analysis, univariate analyses were performed first and variables with *P* values < 0.1 were included in the multivariate models. In order to demarcate the potential confounding effects of smoking and RF to the decline of lung function, the analyses were performed separately in smoke-exposed subjects (past and current smokers) and smoke-naïve subjects (nonsmokers ever). Multivariate analyses were adjusted in a stepwise manner, in which a logistic model was designed as good as fit to the data so the most exclusive sets of variables were selected to investigate the association of RF but gender was treated as an equivalent of age despite of the risk for unmet goodness of fit. Covariates considered in the final adjusted models included gender, age, CRP, RF, and comorbidities, and smoking of 20 pack-years or more was included in the analyses for the smoke-exposed subjects. In model 1, RF positivity was adjusted by age and gender. Model 2 included CRP in addition to the variables included in model 1, and smoking of 20 pack-years or more was

added in the model 2 of the smoke-exposed subjects. For final adjustment, variables in model 3 comprised the variables in model 2 and comorbidities including hypertension, coronary artery disease, diabetes, and malignancy. Evaluation of the goodness of fit of each logistic regression model was based on receiver operating characteristics curve, the area under the curve (AUC), and the Hosmer and Lemeshow test. *P* value <0.05 was considered statistically significant. PASW Statistics 18.0 (Predictive Analytics Software, SPSS Inc., Chicago, IL, USA) was used for all analyses.

RESULTS

Characteristics of Study Subjects

The characteristics of the eligible 94,438 subjects are summarized in Table 1. Mean age (\pm standard deviation) was 41.3 (\pm 8.3) years (IQR, 35–46 years), and 41,261 subjects were female (43.7%). About one-third of subjects (34.1%) were obese or overweight. Three thousand three hundred twenty-six subjects (3.52%) were positive for RF. A smoking history was available in 93,793 subjects (99.3%); the proportion of heavy smokers (\geq 20 pack-years) was larger in the RF-positive group than the RF-negative group (7.9% vs 6.9%, *P* = 0.021). Drinking habit was documented in 73,372 (78.0%) subjects. There were more nondrinkers in the RF-positive group than the RF-negative group (22.5% vs 20.8%, *P* = 0.033). In terms of

medical history, there were no significant differences between groups except for hypertension, which was more prevalent in the RF-positive group than the RF-negative group (11.5% vs 9.7%, *P* < 0.001). Hepatitis B and C infection rates were significantly higher in the RF-positive group than the RF-negative group (12.1% vs 3.5%, *P* < 0.001 for HBsAg and 0.5% vs 0.1%, *P* < 0.001 for HCV Ab). The measured values of RF were asymmetrically distributed with a long tail to the left, and the median was 6.90 IU/mL (IQR, 4.67–8.80). The median level of CRP in the 2 groups was comparable (*P* = 0.074).

Association Between RF Positivity and Pulmonary Function

PFT results in the RF-negative and RF-positive subjects groups are compared in Table 2. RF-positive subjects had lower FVC and FEV1 predictive percentages than RF-negative subjects: FVC (% predicted), 82.8 \pm 11.5% versus 83.8 \pm 11.4%, *P* < 0.001 and FEV1 (% predicted), 83.5 \pm 13.0% versus 85.1 \pm 13.0%, *P* < 0.001. According to the quartiles for both FVC (% predicted) and FEV1 (% predicted), the lower quartiles (quartiles 3 and 4) had more RF-positive subjects than the higher quartiles (quartiles 1 and 2). Correspondingly, the proportion of subjects with an FVC (% predicted) of 82% or less was significantly higher in the RF-positive group than the RF-negative group (50.7% vs 46.6%, *P* < 0.001), and the proportion of patients with

TABLE 1. Demographics and Clinical Characteristics of the Study Subjects (n = 94,438)

	RF(–) (n = 91,112)	RF(+) (n = 3,326)	<i>P</i> Value
Age, y	41.3 \pm 8.2	41.3 \pm 8.3	0.678
Female	39,804 (43.7)	1457 (43.8)	0.891
BMI \geq 25, kg/m ²	31,150 (34.2)	1084 (32.6)	0.059
Smoking status (n = 93,987)			
Ever-smoker	37,398 (41.2)	1290 (39.0)	0.009
In males	20,676 (22.8)	706 (21.2)	
In females	16,722 (18.4)	584 (17.8)	
Median pack-years [IQR]	0 [0–5.5]	0 [0–5.0]	0.021
Pack-years of smoking \geq 20 (n = 93,793)	6235 (6.9)	262 (7.9)	0.021
Alcohol use (n = 73,372)	56,152 (79.2)	1948 (77.5)	0.033
Comorbidities			
Hypertension (n = 94,208)	8805 (9.7)	383 (11.5)	<0.001
Coronary artery disease (n = 94,208)	493 (0.5)	25 (0.8)	0.107
Diabetes mellitus (n = 94,208)	2797 (3.1)	111 (3.3)	0.384
Chronic liver disease (n = 94,208)	13,098 (14.4)	474 (14.3)	0.829
Malignancy (n = 94,208)	1845 (2.0)	75 (2.3)	0.359
Laboratory findings			
HBsAg(+)	3145 (3.5)	403 (12.1)	<0.001
HCV(+) (n = 93,398)	132 (0.1)	15 (0.5)	<0.001
RF titer [IQR], IU/mL	6.80 [4.67–8.50]	33.20 [24.50–55.47]	<0.001
Total cholesterol, mg/dL	196.0 \pm 34.2	194.8 \pm 33.8	0.091
LDL, mg/dL	117.9 \pm 30.9	115.9 \pm 30.3	<0.001
HDL, mg/dL	55.8 \pm 13.8	56.7 \pm 14.2	0.001
Homocysteine	11.1 \pm 4.7	11.2 \pm 4.6	0.734
Fasting glucose	93.6 \pm 14.5	94.1 \pm 16.0	0.613
CRP [IQR], mg/dL	0.02 [0.02–0.10]	0.02 [0.02–0.10]	0.074

Values represent mean \pm standard deviation, median with interquartile range (IQR), or frequencies (number of subjects) with percentages. *P* values were determined with chi-squared test for categorical variables; and the Student *t* test or Mann–Whitney *U* test, which was for skewed continuous variables.

BMI = body mass index, CRP = C-reactive protein, HBsAg = surface antigen of hepatitis B virus, HCV = hepatitis C virus, HDL = high-density lipoprotein, LDL = low-density lipoprotein, RF = rheumatoid factor.

TABLE 2. Comparison of Pulmonary Function According to RF Positivity in the Study Subjects

	RF(−) (n = 91,112)	RF(+) (n = 3,326)	P Value
FVC, L	3.87 ± 0.83	3.79 ± 0.83	<0.001
Mean predicted FVC%	83.8 ± 11.4	82.8 ± 11.5	<0.001
Predicted FVC% ≤ 82%	42,434 (46.6)	1686 (50.7)	<0.001
Quartile for predicted FVC%			<0.001*
Q1 ≥ 91.56%	22,851 (25.1)	758 (22.8)	
Q2 83.46–91.55%	22,835 (25.1)	775 (23.3)	
Q3 75.77–83.45%	22,768 (25.0)	842 (25.3)	
Q4 ≤ 75.76%	22,658 (24.9)	951 (28.6)	
FEV1, L	3.26 ± 0.67	3.17 ± 0.66	<0.001
Mean predicted FEV1%	85.1 ± 12.9	83.5 ± 13.0	<0.001
Predicted FEV1% ≤ 84%	45,031 (49.4)	1814 (54.5)	<0.001
Quartile for predicted FEV1%			<0.001*
Q1 ≥ 93.58%	22,896 (25.1)	713 (21.4)	
Q2 84.64–93.57%	22,822 (25.0)	787 (23.7)	
Q3 76.17–84.63%	22,752 (25.0)	857 (25.8)	
Q4 ≤ 76.16%	22,642 (24.9)	969 (29.1)	
AFL, %	84.3 ± 6.6	84.2 ± 6.7	0.562
AFL < 70%	1403 (1.5)	46 (1.4)	0.470

Values represent mean ± standard deviation or frequencies (number of subjects) with percentages. *P* values were determined with chi-squared test for categorical variables; and the Student *t* test or Mann–Whitney *U* test, which was for skewed continuous variables.

AFL = airflow limitation, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, RF = rheumatoid factor.

**P* value calculated by chi-squared test for linear trend.

FEV1 (% predicted) of 84% or less was higher in the RF-positive group than the RF-negative group (54.5% vs 49.4%, *P* < 0.001). AFL, however, was similar between the 2 groups, indicating that RF levels were not elevated in patients with PFT results consistent with obstruction.

According to quartiles of FVC (% predicted), the incidence of RF positivity was 4.0% (951/23,609) in the lowest quartile (quartile 4), 3.6% (842/23,610) in the third (quartile 3), 3.3% (775/23,610) in the second (quartile 2), and 3.2% (758/23,609) in the highest quartile (quartile 1) (*P* for trend < 0.001). A similar trend was observed for the FEV1 (% predicted) quartiles: 4.1% (969/23,609) in quartile 4, 3.6% (857/23,610) in quartile 3, 3.3% (787/23,609) in quartile 2, and 3.0% (713/23,610) in quartile 1 (*P* for trend < 0.001). In addition, the median RF titer decreased as the values of each quartile in both FVC (% predicted) and FEV1 (% predicted) increased (*P* < 0.001, respectively) (Figure 1). FVC (% predicted) and FEV1 (% predicted) values tended to decrease as the RF titer, which was grouped into 4 categories (<20, 20–59.99, 60–119.99, and 120 IU/mL or more) increased (*P* for trend = 0.001, respectively) (Figure 2).

Impact of RF on a Decline in Pulmonary Function

To investigate the influence of RF as a risk factor for a decline in pulmonary function, we performed binary logistic regression analysis. First, 3 parameters of decreased pulmonary function were analyzed as dependent variables in univariate analyses: FVC (% predicted) below 82%, FEV1 (% predicted) below 84%, and AFL below 70%. There was no difference in RF positivity between groups with AFL below 70% or not (1.4% vs 3.5%, *P* = 0.47), so we excluded AFL from subsequent analyses. Tables 3 and 4 show the impact of RF positivity in smoke-exposed subjects (past and current smokers) and smoke-naïve subjects (nonsmokers) (adjusted OR with 95% CIs) on FVC (% predicted) below 82% and FEV1 (% predicted) below

84%. Model 3 of each table displayed the final result of multivariate logistic regression analyses.

RF positivity was significantly associated with a decline of FEV1 (% predicted) in multiple logistic regression analysis of both smoke-exposed subjects (past and current smokers) and smoke-naïve subjects (nonsmokers). Regarding FVC (% predicted), RF positivity demonstrated the significant association only in smoke-naïve subjects (adjusted OR = 1.251, 95% CI 1.133–1.382, *P* < 0.001), while in smoke-exposed subjects the association was not significant. Instead, heavy smoking was strongly associated with lowered pulmonary function in smoke-exposed subjects (adjusted OR = 1.331, 95% CI 1.254–1.414, *P* < 0.001), while heavy drinking was less strongly associated.

DISCUSSION

Herein, we examined the relationship between RF positivity and pulmonary function as assessed by FVC and FEV1. We used a large sample of Korean adults representative of the general population who were not selected based on either extraordinary health or certain underlying diseases. We found that RF-positive subjects had lower FVC and FEV1 values than RF-negative subjects, and that both FVC and FEV1 decreased as RF titer increased. Notably, RF positivity was significantly associated with a decline in FVC and FEV1 in fully adjusted logistic regression analyses except that of FVC in smokers.

Approximately 3.5% of the study cohort was seropositive for RF. This proportion is generally comparable to those reported in other studies in non-RA populations (3–5% reported prevalence).^{2,17} Some studies have suggested that the prevalence of RF positivity in the general population increases with age and smoking status.^{18,19} RF positivity has been observed to antedate the clinical course of RA based on long-term research (up to 28 years) in the Danish general population.¹⁷ While RF is detected in the “preclinical” phase of seropositive RA, it can

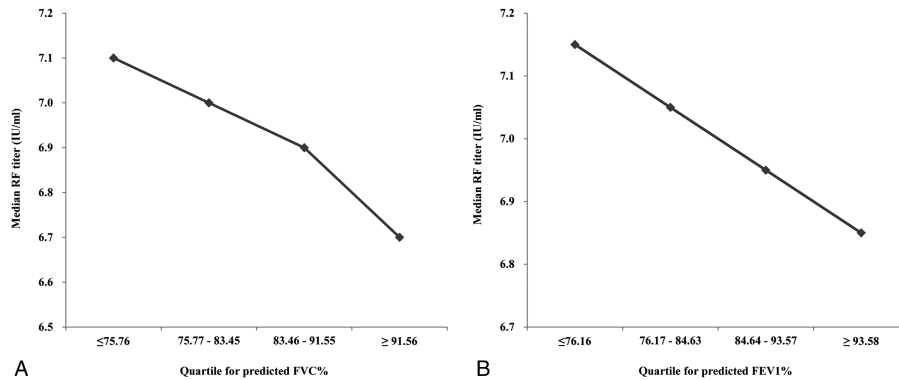


FIGURE 1. Change of median RF titer according to quartiles of lung function (FVC and FEV, % predicted). The median RF titer is shown as an closed square for each quartile of both FVC (% predicted) and FEV1 (% predicted) and the solid line connects individual squares to highlight the decreasing tendency of median RF titer according to raising of pulmonary function. (A) Median RF titer according to quartiles of predicted FVC%. As values of each quartile of FVC (% predicted) are increased, the median RF titer significantly decreases (P for trend < 0.001). (B) Mean RF titer according to quartiles of predicted FEV1%. As values of each quartile of FEV1 (% predicted) are increased, the median RF titer significantly decreases (P for trend < 0.001). FEV = forced expiratory volume, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, RF = rheumatoid factor.

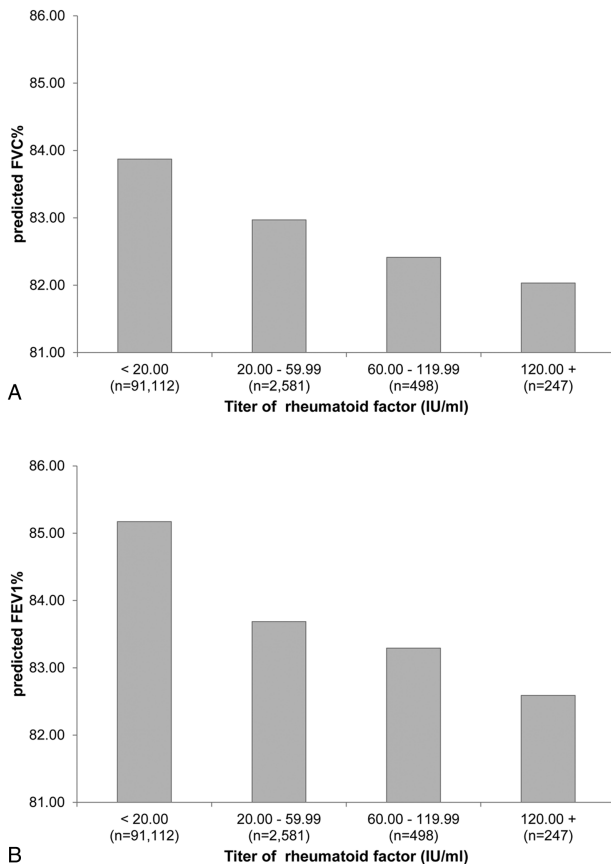


FIGURE 2. Decline in pulmonary function according to RF titer. The mean predicted value of FVC and FEV1 is shown as bar for each group of the RF titer, which was categorized into 4 groups: < 20 IU/mL, 20 to 59.99 IU/mL, 60 to 119.99 IU/mL, and 120 IU/mL or more. (A) Mean predicted FVC%. FVC (% predicted) values tend to decrease as the RF titer is increased (P for trend = 0.001). (B) Mean predicted FEV1%. FEV1 (% predicted) values tend to decrease as the RF titer is increased (P for trend = 0.001). FEV = forced expiratory volume, FEV1 = forced expiratory volume in 1 s, FVC = forced vital capacity, RF = rheumatoid factor.

also be detected in a number of chronic inflammatory conditions, including rheumatic conditions such as Sjogren syndrome, systemic sclerosis, and systemic lupus erythematosus as well as nonrheumatic conditions including infectious diseases such as hepatitis and tuberculosis, and malignancies such as colon cancer and leukemia at frequencies ranging from 10% to 70%.^{20,21} These immunological abnormalities suggest that RF plays an important role in normal immune defense mechanisms and that elevated levels of RF may reflect inflammatory conditions.

The lack of specificity of RF makes it difficult to determine potential initiating sites for RF. Nevertheless, systemic autoimmunity appears to precede the incidence of synovial inflammation, even in subjects who are at risk of progression to RA; an extra-articular site has therefore been assumed to be the site of RA-related autoimmunity initiation.²² Several mucosal surfaces such as the gums, lungs, and gut have been proposed as initiating sites.¹⁰ Recent study also suggested that RA-associated autoantibodies were associated with lung mucosal inflammation in patients with cystic fibrosis and bronchiectasis and may be associated with oral mucosal inflammation in patients with periodontitis.²³ The assumption that the lung may be a potential site for the initiation of immune dysregulation and RA-related autoimmunity is based on several factors: A subset of arthritis-free individuals were shown to have RF and/or anti-CCP antibodies present in their sputum that were not present in their serum, or that were present in higher levels in their sputum compared with their serum²⁴; symptomatic lung disease and RF positivity have been reported to precede clinically apparent articular RA^{6,25,26}; inhaled factors such as smoke and dust are associated with an increased risk of RA^{27,28}; and organized lymphatic tissue has been identified in the lungs of patients with different interstitial lung diseases and established RA, referred to as inducible bronchus-associated lymphatic tissue.²⁹

Meanwhile, a relationship between RF and pulmonary structural abnormalities in healthy subjects has been reported, in which a higher prevalence of inflammatory airway disease was shown by HRCT in RA-related autoantibody-positive individuals ($n = 42$) without inflammatory arthritis compared with autoantibody-negative controls ($n = 15$).³⁰ In an adult, Finnish population study in which the RF test was performed in 7214 subjects, women with significant AFL (FEV1/FEV

TABLE 3. Multivariable Analysis of RF as Predictor for a Decline in Pulmonary Function in Smoke-Naïve Subjects (n = 55,299)

Outcome	Model 1		Model 2		Model 3	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
FVC% predicted \leq 82%	1.245 (1.134–1.367)	<0.001	1.250 (1.132–1.380)	<0.001	1.251 (1.133–1.382)	<0.001
FEV1% predicted \leq 84%	1.274 (1.156–1.403)	<0.001	1.288 (1.162–1.427)	<0.001	1.289 (1.163–1.429)	<0.001

Logistic regression analyses were performed in 55,299 subjects who had no experience of smoking. Model 1 was adjusted for age and gender, and the resulting model was unsatisfactory to fit to the data based on the Hosmer–Lemeshow test ($P = 0.002$ for FVC% and $P = 0.045$ for FEV1%) and the ROC curve analysis (AUC = 0.543 for FVC% and AUC = 0.632 for FEV1%). Model 2 was adjusted as in model 1 plus CRP, and the resulting model was unsatisfactory to fit to the data based on the Hosmer–Lemeshow test ($P = 0.011$ for FVC% and $P = 0.100$ for FEV1%) and the ROC curve analysis (AUC = 0.543 for FVC% and AUC = 0.630 for FEV1%). Model 3 was adjusted as in model 2 plus comorbidities including hypertension, coronary artery disease, diabetes, and malignancy, and the resulting model was unsatisfactory to fit to the data based on the Hosmer–Lemeshow test ($P = 0.009$ for FVC% and $P = 0.041$ for FEV1%) and the ROC curve analysis (AUC = 0.547 for FVC% and AUC = 0.635 for FEV1%). Models include the categorized variables: age of ≤ 30 , 31–40, 41–50, 51–60, 61–70, or ≥ 71 y; gender of female or male; CRP < 0.60 or ≥ 0.60 mg/dL; with or without comorbidities.

AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, FEV1% predicted = percent predicted forced expiratory volume in 1 s, FVC% predicted = percent predicted forced vital capacity, OR = odds ratio, RF = rheumatoid factor, ROC = receiver operating characteristics.

< 70%) had a significantly increased occurrence of RF.⁹ In the present study, we studied a larger population (n = 94,438) and found a significant relationship between RF and pulmonary function as assessed by FVC and FEV1 but not FVC in smokers, supporting that serum positivity for RF is a risk for reduction of pulmonary function. Furthermore, as RF titer increased, both FVC (% predicted) and FEV1 (% predicted) decreased significantly. These results suggest that a higher RF titer might be a relevant marker for decreasing pulmonary function in the general population, as it appears to be associated with an increased risk of developing RA-related interstitial lung disease.³¹ However, we found no association between a decline of FVC and RF positivity in smokers. Smoking may have stronger impact than RF positivity in relation to a decline of FVC (% predicted) in this study. There was also no relationship between AFL and RF positivity. A possible explanation for this is that functional debility of the large airways might have gone undetected on PFT screening by spirometry for healthy subjects, because FEV1/FVC mainly reveals obstruction of middle-sized airways.⁹ Moreover, HRCT findings in RA-related autoantibody-positive subjects can reveal airway problems including

bronchial wall thickening, bronchiectasis, centrilobular opacities, and air trapping.^{30,32} Biopsy specimens from patients with established RA who had similar HRCT findings showed small airway inflammation.²⁶ Taken these together, we believe that asymptomatic subjects without clinically apparent lung disease could have small airway structural and/or function abnormalities related to the presence of RF in their serum. Furthermore, RF positivity was an independent risk factor for a decline in FVC (% predicted) and FEV1 (% predicted) irrespective of age, gender, BMI, heavy smoking, drinking habits, or comorbidities. This suggests that lung tissue may be an inception site of RA-related autoimmunity.

Potential limitations of the present study are its cross-sectional descriptive design and the questionnaire-based collection of medical history. Further longitudinal follow-up studies are therefore required to verify the cause-and-effect relationship between RF and pulmonary function. In addition to recall bias, there was the possibility of selection bias when recruiting participants, as the participants were mostly residents of an urban community and were enrolled in checkup programs at a single university hospital. Caution should be used when

TABLE 4. Multivariable Analysis of RF as Predictor for a Decline in Pulmonary Function in Smoke-Exposed Subjects (n = 38,688)

Outcome	Model 1		Model 2		Model 3	
	OR (95% CI)	P Value	OR (95% CI)	P Value	OR (95% CI)	P Value
FVC% predicted \leq 82%	1.036 (0.914–1.173)	0.584	1.020 (0.896–1.161)	0.762	0.996 (0.874–1.135)	0.952
FEV1% predicted \leq 84%	1.173 (1.042–1.320)	0.008	1.160 (1.025–1.313)	0.018	1.138 (1.004–1.289)	0.043

Logistic regression analyses were performed in 38,688 subjects who had smoking experience in past or currently. Model 1 was adjusted for age and gender, and the resulting model was a good fit to the data based on the Hosmer–Lemeshow test ($P = 0.759$ for FVC% and $P = 0.530$ for FEV1%) and the ROC curve analysis (AUC = 0.577 for FVC% and AUC = 0.572 for FEV1%). Model 2 was adjusted as in model 1 plus CRP and smoking of 19 pack-y or more, and the resulting model was a good fit to the data based on the Hosmer–Lemeshow test ($P = 0.417$ for FVC% and $P = 0.968$ for FEV1%) and the ROC curve analysis (AUC = 0.587 for FVC% and AUC = 0.582 for FEV1%). Model 3 was adjusted as in model 2 plus comorbidities including hypertension, coronary artery disease, diabetes, and malignancy, and the resulting model was a good fit to the data based on the Hosmer–Lemeshow test ($P = 0.596$ for FVC% and $P = 0.857$ for FEV1%) and the ROC curve analysis (AUC = 0.606 for FVC% and AUC = 0.596 for FEV1%). Models include the categorized variables: age of ≤ 30 , 31–40, 41–50, 51–60, 61–70, or ≥ 71 y; gender of female or male; CRP < 0.60 or ≥ 0.60 mg/dL; smoking of < 20 or ≥ 20 pack-y; with or without comorbidities.

AUC = area under the curve, CI = confidence interval, CRP = C-reactive protein, FEV1% predicted = percent predicted forced expiratory volume in 1 s, FVC% predicted = percent predicted forced vital capacity, OR = odds ratio, RF = rheumatoid factor, ROC = receiver operating characteristics.

generalizing our data to other populations or races. The true incidence of lung disease or inflammatory arthritis could have been underestimated because we did not perform a standardized joint examination or test ACPA, and imaging studies such as HRCT were not conducted together with radiographs, as these were not part of the health-checkup program.

In conclusion, RF positivity in the Korean general population was significantly associated with increased risk of decreased pulmonary function as assessed by FVC (% predicted) and FEV1 (% predicted), especially in nonsmokers. This suggests that the lung might be an initiation site of RA-related autoimmunity, and that RF positivity might be a potent biomarker for pulmonary dysfunction in the general population. These findings highlight the need for additional studies, including serial assessments of the progression of pulmonary abnormalities and serum markers of autoimmunity in relation to the development of lung disease and inflammatory arthritis.

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