Difference in systemic inflammation and predictors of acute exacerbation between smoking-associated COPD and tuberculosis-associated COPD

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Purpose: Tuberculosis-associated COPD (T-COPD) has clinical characteristics similar to those of smoking-associated COPD (S-COPD), such as dyspnea, sputum production, and acute exacerbation (AE). However, the degree of systemic inflammation and prognosis might be different because of difference in the pathophysiology. The aim of this study was to compare the lung function, systemic inflammatory markers, and their impacts on AE in patients with S-COPD and T-COPD.

Patients and methods: We performed a multicenter cross-sectional cohort study. We evaluated clinical characteristics, pulmonary function tests, levels of inflammatory markers, including C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and IL-6, and the association of these markers with AE in patients with S-COPD and T-COPD.

Results: Patients with T-COPD included more women and had lesser smoking history and higher St George Respiratory Questionnaire score than did patients with S-COPD. Although the FEV1 of both groups was similar, FVC, vital capacity, total lung capacity, and functional residual capacity were lower in patients with T-COPD than in those with S-COPD. CRP, ESR, and IL-6 levels were significantly higher in patients with T-COPD compared to patients with S-COPD. According to a multivariate logistic regression analysis, FEV1 was a significant factor predicting AE in S-COPD, and IL-6 was a significant factor predicting AE in T-COPD. IL-6 level greater than 2.04 pg/mL was a cutoff for predicting exacerbation of T-COPD (sensitivity 84.8%, specificity 59.3%, P<0.001).

Conclusion: Patients with T-COPD have higher levels of inflammatory markers, and IL-6 has a predictive value for AE in T-COPD.

Keywords: COPD, tobacco smoke, tuberculosis, biomarker, inflammation, exacerbation

Introduction

COPD is a progressive disease with persistent airflow obstruction and chronic systemic inflammation caused by noxious particles and gases. The accumulation of inflammatory cells in the airway caused by chronic irritants present in tobacco smoke may induce respiratory histopathologic changes. These include elastolytic destruction of the alveolar wall, loss of elastic recoil, hypertrophy of bronchiolar wall muscles, fibrosis of small airways, and hyperplasia of the goblet cells, which may lead to irreversible obstruction. Moreover, activated inflammatory cells and proinflammatory cytokines lead to systemic inflammation, which is associated with extra-respiratory manifestations of COPD, such as atherosclerosis, osteoporosis, and cardiovascular diseases.
of systemic inflammatory markers such as C-reactive protein (CRP) and IL-6 are increased in patients with COPD.\textsuperscript{4,6}

Tobacco smoking is a well-known causative agent implicated in the pathogenesis of COPD; however, it is not the sole risk factor. Positive history of pulmonary tuberculosis has recently emerged as a risk factor in the development of COPD.\textsuperscript{7} Tuberculosis-associated COPD (T-COPD)\textsuperscript{8} is a condition in which pulmonary tuberculosis has caused destructive changes in the pulmonary parenchyma over the years, leading to chronic respiratory obstruction.\textsuperscript{9} The probable pathophysiological mechanisms include parenchymal destruction by bronchiectasis, emphysema, bronchiolitis, and persistent inflammation caused by sequelae of tuberculosis. Although the causative agents may be different, T-COPD shares pathogenic manifestations such as chronic respiratory obstruction due to emphysema and bronchiolitis with smoking-associated COPD (S-COPD). Moreover, patients with T-COPD have clinical characteristics similar to those of patients with S-COPD, such as dyspnea, sputum, and acute exacerbation (AE).\textsuperscript{10,11} T-COPD may be associated with systemic inflammation and could be described as a distinct phenotype among the other forms of COPD. However, there is limited knowledge about systemic inflammatory markers and risk factors for AE in T-COPD, which are key factors in understanding the pathogenesis and treatment planning of COPD. Therefore, this study aimed to compare the systemic inflammatory markers and their impacts on AE in patients with S-COPD and T-COPD.

Materials and methods

Study design

The present cross-sectional cohort study was undertaken to develop clinically useful biologic markers for diagnosis and assessment of response to treatment in patients with chronic airway disease. This multicenter study was conducted at three hospitals: Korea University Guro Hospital, Seoul St Mary’s Hospital, and Chonbuk National University Hospital. Patients who consented to participate in the study were consecutively enrolled from June 2015 to May 2016 using the airway disease registry. The study protocol was approved by the institutional review boards (Korea University Guro Hospital: KUGH 13246; Seoul St Mary’s Hospital: KC15OIM0553; and Chonbuk National University Hospital: 2015-01-018-005). The present study fulfilled the tenets of the Declaration of Helsinki and the patients provided written informed consent. A diagnosis of T-COPD was made on the basis of the following enrollment criteria: 1) patients with a history of tuberculosis and no change in chest imaging over the past 1 year; 2) patients with at least one finding of destructed pulmonary parenchyma on the chest image (lung volume loss, bronchovascular distortion, fibrosis, or secondary bronchiectasis) and the sum of volume of all lesions equivalent to over one-third of one lung confirmed by a radiologist or pulmonology specialist; 3) patients with airflow limitation (post-bronchodilator spirometry with FEV\textsubscript{1}/FVC <70%) and without any history of asthma or COPD before the diagnosis of tuberculosis; and 4) patients without respiratory infection within the previous 6 weeks.\textsuperscript{12}

A diagnosis of S-COPD was made according to the American Thoracic Society and Global Initiative for Chronic Obstructive Lung Disease guidelines. Patients with smoking history of over 10 packs per year were enrolled, and patients with bronchiectasis, sequela from prior tuberculosis infection, interstitial lung disease, and other diseases that could lead to airflow obstruction were excluded.

At baseline, the following variables were collected: smoking history and amount, past medical history, body mass index (BMI), symptom scores (modified Medical Research Council dyspnea score, St George Respiratory Questionnaire [SGRQ] score, COPD assessment test [CAT] score), pulmonary function tests (spirometry, lung volume, and diffusing capacity of the lung for carbon monoxide), and chest imaging.

Blood tests, including tests for CRP and erythrocyte sedimentation rate (ESR), were done routinely on the day of enrollment in the overnight-fasted and medication-free state. Peripheral whole-venous blood was collected into ethylenediaminetetraacetic acid tubes, and serum was prepared by centrifugation for 10–15 minutes at 4,500 rpm and stored at −80°C until it was analyzed. IL-6 level was measured using ELISA kits (IL-6: R&D Systems, Oxford, UK).

FEV\textsubscript{1} decline rate and AE history at 1 year from enrollment were determined. FEV\textsubscript{1} decline rate was calculated at stable status by change of FEV\textsubscript{1} after 1 year of enrollment from baseline. Exacerbation was defined as a sustained deterioration of acute respiratory symptoms, beyond stable state and day-to-day variations, which necessitated a change in regular medication and an unscheduled visit to the hospital.

Statistical analysis

Clinical data were presented as the median and IQR and was compared using Mann–Whitney U-test for continuous variables. For categorical variables, data were presented as percentage and number and were compared using Pearson’s chi-squared test or Fisher’s exact test. Correlations between variables were analyzed using Spearman’s correlation
analysis. For the risk factors of AE, a multivariate logistic regression analysis was carried out by adjusting factors that were significant (P<0.1) in the univariate model. Significance was defined as P<0.05. All statistical analyses were performed using SPSS Statistics for Windows, Ver 20.0 (IBM Corp., Armonk, NY, USA).

**Results**

**Characteristics of patients with S-COPD and T-COPD**

A total of 170 patients were enrolled (T-COPD, n=92; S-COPD, n=78). Their baseline characteristics are described in Table 1. Patients with S-COPD included more men than women. Patients with S-COPD had a greater smoking history than did patients with T-COPD (P<0.002). Comorbidities were similar in both groups. No significant difference was observed between the previous treatment modalities of S-COPD and T-COPD.

**Pulmonary function tests and outcomes of patients with S-COPD and T-COPD**

Although FEV₁ was similar, FVC, total lung capacity (TLC), functional residual capacity, and vital capacity were significantly lower in the T-COPD group than in the S-COPD group (Table 2). Patient-reported scores of symptom and quality of life were similar in both groups, except for SGRQ, which was higher in the T-COPD group.

| Table 1 Baseline characteristics of patients with S-COPD and T-COPD |
|-----------------|-----------------|-----------------|
| **S-COPD (N=78)** | **T-COPD (N=92)** | **P-value** |
| Age, years   | 66.0 (59.0–72.5) | 67.0 (63.0–71.8) | 0.261 |
| Sex, male    | 72 (92.3)       | 61 (66.3)       | <0.001 |
| BMI, kg/m²   | 23.6 (21.1–26.0) | 23.5 (21.6–25.5) | 0.605 |
| Smoking status |                |                | <0.001 |
| Never        | 9 (11.5)        | 43 (46.7)       |       |
| Former       | 35 (44.9)       | 35 (38.0)       |       |
| Current      | 34 (43.6)       | 14 (15.2)       |       |
| Smoking amount (pack-year) | 40.0 (20.0–45.3) | 0.0 (0.0–30.0) | <0.001 |
| Comorbidities |                |                |       |
| DM           | 3 (3.8)         | 9 (9.8)         | 0.132 |
| CVD          | 9 (11.5)        | 8 (8.7)         | 0.538 |
| Heart disease | 31 (39.7)       | 34 (37.0)       | 0.709 |
| GERD         | 6 (7.7)         | 4 (4.3)         | 0.356 |
| Depression   | 2 (2.6)         | 4 (4.3)         | 0.530 |

**Note:** Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables.

**Abbreviations:** BMI, body mass index; CVD, cerebrovascular disease; DM, diabetes mellitus; GERD, gastroesophageal reflux disease; S-COPD, smoking-associated COPD; TOPD, tuberculosis-associated COPD.

The FEV₁ decline rates and percentage of AE did not show significant differences.

**Comparison of systemic inflammatory markers in S-COPD and T-COPD**

CRP, ESR, and IL-6 levels were significantly higher in patients with T-COPD than in those with S-COPD (CRP: 1.25 [0.62–2.50] mg/dL in S-COPD, 2.92 [0.99–5.52] mg/dL in T-COPD, P<0.001; ESR: 10.50 [6.00–17.00] mm/h in S-COPD, 16.0 [8.25–22.0] mm/h in T-COPD, P=0.002; IL-6: 1.45 [0.43–2.35] pg/mL in S-COPD, 2.17 [1.11–5.86] pg/mL in T-COPD, P<0.001; Figure 1).

**Multivariate logistic analysis for risk factors of AE in S-COPD and T-COPD**

Multivariate logistic analysis was done to compare the factors affecting AE in patients with S-COPD (Table 3) and T-COPD (Table 4). In S-COPD, FEV₁, SGRQ, and IL-6 were the factors associated with AE in univariate analysis. After adjusting factors significant in univariate models, only FEV₁ was significantly associated with AE (adjusted odds ratio [aOR] 0.941 [0.901–0.983], P=0.006). In T-COPD, FEV₁, CAT, SGRQ, CRP, and IL-6 were the factors associated with AE in univariate analysis (P<0.1). After adjusting factors significant in univariate models, only IL-6 was significantly associated with AE (aOR 1.109 [1.004–1.225], P=0.023).

**Correlations between IL-6 and parameters in S-COPD and T-COPD**

The level of IL-6 was positively correlated with residual volume (R=0.326, P=0.004) and the number of exacerbations (R=0.397, P<0.001) and negatively correlated with BMI (R=–0.390, P=0.001) and FEV₁ (R=–0.308, P=0.006) in S-COPD. However, there was no correlation with IL-6 level and lung function in patients with T-COPD. Only the number of exacerbations was positively correlated with IL-6 level in patients with T-COPD (R=0.412, P<0.001).

**ROC curve of IL-6 as a predictor of AE in T-COPD**

IL-6 level >2.04 pg/mL was a cutoff for predicting exacerbation of T-COPD (sensitivity 84.8%, specificity 59.3%, P<0.001; Figure 2).

**Discussion**

In this study, we found that patients with T-COPD have higher levels of systemic inflammatory markers than do those with S-COPD. Moreover, unlike S-COPD, IL-6 level was
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not correlated with lung function, and AE was associated with IL-6 level rather than lung function in T-COPD. IL-6 level >2.04 pg/mL was a cutoff for predicting exacerbation of TOPD.

This study revealed that T-COPD was associated with higher levels of inflammatory markers compared to S-COPD, and T-COPD may be a dynamic inflammatory disease like S-COPD. A previous study also reported that the concentrations of soluble IL-2 receptor, IL-6, tumor necrosis factor-α, and interferon-γ in T-COPD patients were significantly higher than those in S-COPD patients. Systemic inflammation is associated with mortality and comorbidities of S-COPD such as cardiovascular disease. Patients with T-COPD have high levels of systemic inflammatory biomarkers; this implies that these patients are at high risk of systemic morbidities. The T-COPD group had a similar prevalence of comorbidities,

Table 2 Pulmonary function tests, symptom scores, and outcomes of patients with COPD and TOPD

| Pulmonary function tests | S-COPD (N=78) | T-COPD (N=92) | P-value |
|-------------------------|---------------|---------------|---------|
| FEV 1 %                 | 64.5 (46.8–71.0) | 57.5 (45.0–72.5) | 0.717   |
| FVC %                   | 84.5 (74.8–93.3) | 77.0 (64.3–88.0) | 0.003   |
| FEV /FVC %              | 55.0 (41.0–62.0) | 56.5 (45.3–66.0) | 0.080   |
| FEF 25–75%              | 23.5 (16.0–34.5) | 23.0 (16.0–37.8) | 0.999   |
| VC %                    | 93.0 (82.0–103.0) | 86.0 (72.0–99.5) | 0.007   |
| TLC %                   | 107.5 (102.8–116.0) | 103.5 (91.3–112.8) | 0.005   |
| IC %                    | 74.5 (58.8–93.3) | 65.5 (53.0–86.0) | 0.066   |
| FRC %                   | 140.0 (123.8–160.5) | 130.5 (109.3–148.5) | 0.011   |
| RV %                    | 142.0 (130.0–155.5) | 143.5 (118.8–154.0) | 0.547   |
| DL CO %                 | 80.5 (65.8–95.3) | 75.5 (62.0–89.0) | 0.187   |

| Symptom scores          | S-COPD (N=78) | T-COPD (N=92) | P-value |
|-------------------------|---------------|---------------|---------|
| mMRC                    | 1.0 (0.0–1.0) | 1.0 (0.0–1.0) | 0.216   |
| CAT                     | 14.0 (10.0–19.0) | 16.0 (10.0–21.0) | 0.116   |
| SGRQ                    | 17.5 (9.3–29.7) | 22.5 (14.5–33.0) | 0.029   |
| FEV, decline mL/year    | 10.5 (--48.5 to −170.0) | 50.0 (−17.5 to −140.0) | 0.323   |
| AE                      | 26 (33.3) | 33 (35.9) | 0.729   |

Note: Data are presented as median (IQR) for continuous variables and number (percentage) for categorical variables.

Abbreviations: AE, acute exacerbation; CAT, COPD assessment test; DL CO, diffusing capacity of the lung for carbon monoxide; FEF FRC, functional residual capacity; FEV, forced expiratory volume; FVC, forced vital capacity; mMRC, modified Medical Research Council; RV, residual volume; S-COPD, smoking-associated COPD; SGRQ, St George Respiratory Questionnaire; TLC, total lung capacity; TOPD, tuberculosis-associated chronic obstructive disease; VC, vital capacity.

Figure 1 Comparison of inflammatory biomarkers in patients with S-COPD and T-COPD.

Notes: (A) C-reactive protein in patients with S-COPD and T-COPD (P<0.001). (B) Erythrocyte sedimentation rate in patients with S-COPD and T-COPD (P=0.002). (C) IL-6 in patients with S-COPD and T-COPD (P<0.001).

Abbreviations: CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; S-COPD, smoking-associated COPD; T-COPD, tuberculosis-associated COPD.
Table 3 Parameters associated with acute exacerbation in patients with S-COPD

| Characteristics | Univariate analysis | Multivariate analysis* |
|-----------------|---------------------|------------------------|
|                 | OR (95% CI)         | P-value                | OR (95% CI)         | P-value |
| Age             | 0.998 (0.948–1.051) | 0.947                  | –                     | –       |
| Gender (male)   | 0.469 (0.088–2.507) | 0.376                  | –                     | –       |
| BMI             | 0.945 (0.831–1.075) | 0.392                  | –                     | –       |
| Smoking amount  | 1.003 (0.984–1.023) | 0.762                  | –                     | –       |
| FEV₁            | 0.930 (0.897–0.964) | <0.001                 | 0.941 (0.901–0.983)   | 0.006   |
| CAT             | 1.040 (0.967–1.118) | 0.294                  | –                     | –       |
| SGRQ            | 1.046 (1.011–1.082) | 0.010                  | 1.026 (0.987–1.065)   | 0.194   |
| CRP             | 1.016 (0.950–1.087) | 0.634                  | –                     | –       |
| IL-6            | 1.595 (1.137–2.239) | 0.007                  | 1.407 (0.950–2.083)   | 0.088   |

Note: *Variables with a P-value < 0.1 on univariate analysis were analyzed using multivariate logistic regression analysis.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CRP, C-reactive protein; S-COPD, smoking-associated COPD; SGRQ, St George Respiratory Questionnaire.

Table 4 Parameters associated with acute exacerbation in patients with T-COPD

| Characteristics | Univariate analysis | Multivariate analysis* |
|-----------------|---------------------|------------------------|
|                 | OR (95% CI)         | P-value                | OR (95% CI)         | P-value |
| Age             | 0.999 (0.948–1.051) | 0.947                  | –                     | –       |
| Gender (male)   | 0.469 (0.088–2.507) | 0.376                  | –                     | –       |
| BMI             | 0.945 (0.831–1.075) | 0.392                  | –                     | –       |
| Smoking amount  | 1.003 (0.984–1.023) | 0.762                  | –                     | –       |
| FEV₁            | 0.930 (0.897–0.964) | <0.001                 | 0.941 (0.901–0.983)   | 0.006   |
| CAT             | 1.040 (0.967–1.118) | 0.294                  | –                     | –       |
| SGRQ            | 1.046 (1.011–1.082) | 0.010                  | 1.026 (0.987–1.065)   | 0.194   |
| CRP             | 1.016 (0.950–1.087) | 0.634                  | –                     | –       |
| IL-6            | 1.595 (1.137–2.239) | 0.007                  | 1.407 (0.950–2.083)   | 0.088   |

Note: *Variables with a P-value < 0.1 on univariate analysis were analyzed using multivariate logistic regression analysis.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CRP, C-reactive protein; SGRQ, St George Respiratory Questionnaire; T-COPD, tuberculosis-associated COPD.

lungs function decline rate, and AE as the S-COPD group, which suggests that T-COPD might be a progressive disease like S-COPD.

The development of T-COPD might be mediated by mechanisms of chronic inflammation. A recent study demonstrated development of new inflammatory lesions in tuberculosis patients after 1 year of completion of treatment. The levels of inflammatory cytokines remained high, and lung remodeling and chronic inflammatory response may persist after cure of tuberculosis. Immuneologic mechanisms may also be involved in subsequent systemic inflammation after treatment of tuberculosis and cause progressive respiratory symptoms. Moreover, secondary bronchiectasis and microbial colonization in T-COPD may cause repetitive infection and inflammation that may lead to frequent AE.

Therefore, we need to focus more on how to treat and control the systemic inflammatory response of T-COPD, and we may use inflammatory markers for predicting AE in T-COPD.

Prediction of AE, which is a key factor for disease progression, is important for controlling chronic inflammatory airway disease. In COPD studies, FEV₁ is a key biomarker of severity and predictor of prognosis. Moreover, reduced lung function is known to be associated with increased levels of systemic inflammatory markers in S-COPD. However, lung function did not reflect the severity of inflammation or future AE risk in T-COPD in the present study. Airflow obstruction in T-COPD is probably due to cavitation, bronchiectasis, and inflammation-induced narrowing of airways. However, lung function of T-COPD is usually accompanied by restrictive changes resulting from extensive fibrosis, pleural thickening, and stiffening of the lung parenchyma. In this study, patients with T-COPD showed more mixed restrictive pathology (reduced FVC and TLC) than those with S-COPD, which was consistent with previous studies. Mixed pathophysiology of remodeling of lung destruction leads to a mixed pattern of pulmonary function tests and makes FEV₁ unsuitable as a marker of T-COPD. This result is in line with previous study, which described that IL-6 was negatively correlated with FEV₁ in S-COPD but not in T-COPD.

Given that FEV₁ correlated poorly...
with symptoms, impaired quality of life, and exacerbations,\textsuperscript{13} other biomarkers should be validated to evaluate and predict outcomes for T-COPD.

IL-6 is a proinflammatory cytokine that plays an important role in the systemic inflammatory response in COPD.\textsuperscript{34} It has been reported that elevated serum IL-6 levels are associated with decreased lung function, a faster decline in lung function, dyspnea, muscle weakness, and AE in COPD.\textsuperscript{35,36} Similarly, IL-6 was negatively correlated with BMI and FEV1 in S-COPD in this study. In S-COPD patients, IL-6 was associated with AE in the univariate model, but after adjustment of significant parameters, only FEV1, which was a more important factor in S-COPD, was correlated with AE. In contrast, activated inflammatory responses might be a more important predictor of poor outcomes in T-COPD patients in whom FEV1 is not a reliable parameter.

Our study had some limitations. First, the study was not a randomized controlled trial, and the cross-sectional cohort design may be associated with selection bias. Therefore, adjustment for variable confounding factors was attempted. Second, comparison of markers of inflammation in a healthy control group was not possible. However, it is well known that patients with stable COPD have higher inflammatory markers compared to the control groups (in the ECLIPSE cohort study, which included comparison of cytokine levels in nonsmokers with COPD, median [IQR] level of IL-6 in 1,755 COPD subjects was 1.5 [0.8–3.1] pg/mL, which was similar to that in the present study, and the level was 0.4 [0.2–0.9] pg/mL in 202 nonsmoker controls).\textsuperscript{37} Thus, it could be inferred that patients with T-COPD have higher levels of inflammatory markers than control groups. Third, other inflammatory cytokines shown to be elevated in COPD such as IL-8, tumor necrosis factor-\textalpha, or fibrinogen were not evaluated in the present study. Fourth, details of diagnosis and treatment of tuberculosis were not described. No change in chest imaging of patients included in the study was observed over the past year, which signified healed lesions and inactive state of tuberculosis. Despite this limitation, this study has strength in that we compared the systemic inflammatory markers between T-COPD and S-COPD and evaluated inflammatory markers as predictors of AE in T-COPD. To overcome the limitation of selection bias, further randomized clinical trials should be conducted on larger cohorts to validate the results of the present study.

Conclusion

In T-COPD, levels of inflammatory markers were higher and AE was associated with IL-6 rather than lung function, when compared to S-COPD. T-COPD may be a systemic inflammatory disease, and patients with T-COPD should be treated and monitored for systemic inflammation to prevent AE.

Acknowledgment

We would like to thank SY Hwang for the statistical support.

Authors contribution

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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