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Correlations of interleukin-17 and regulatory T cells with the severity of chronic obstructive pulmonary disease and pulmonary function.

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Keywords: Pulmonary Disease, Chronic Obstructive; Correlation Measures; Interleukins; Respiratory Function Tests; T-Lymphocytes, Regulatory; Disease Severity.

Abstract. We aimed to explore the correlation of interleukin-17 (IL-17) and regulatory T (Treg) cells with the severity of chronic obstructive pulmonary disease (COPD) and pulmonary function. A total of 90 COPD patients, all with a confirmed diagnosis of COPD and without any history of asthma, were included to ensure that the findings are specific to COPD. In addition, a smoking group (healthy smokers, n=90) and a healthy group (healthy non-smokers, n=90) were studied. The COPD group had the highest IL-17 level and the lowest cluster of differentiation 4 (CD4) + Treg cell count, CD25+Treg cell count, and CD4+CD25+Treg cell count in peripheral blood, followed by the smoking and healthy groups ($p<0.05$). The $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, $CD4^+CD25^+$ Treg cell count, forced vital capacity (FVC), forced expiratory volume in one second (FEV_1), and FEV_1/FVC were found to be the highest in the mild group, followed by those of moderate and severe groups ($p<0.05$). The $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count displayed positive correlations with FEV_1, FVC, and FEV_1/FVC ($r>0$, $p<0.05$) and negative correlations with the IL-17 level ($r<0$, $p<0.05$). The IL-17 level was negatively correlated with FEV_1, FVC, and FEV_1/FVC ($r<0$, $p<0.05$). Importantly, this study highlights the combined analysis of IL-17 and Treg subsets, which provides additional insights into their joint association with COPD severity beyond IL-17 alone.

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Correlación de la interleucina-17 y las células T reguladoras con la gravedad de la enfermedad pulmonar obstructiva crónica y la función pulmonar.

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Palabras clave: Enfermedad Pulmonar Obstructiva Crónica; Medidas de Correlación; Interleucinas; Pruebas de Función Respiratoria; Linfocitos T Reguladores; Gravedad de la Enfermedad.

Resumen. Nuestro objetivo fue explorar las correlaciones entre la interleucina-17 (IL-17) y las células T reguladoras (Treg), así como entre la gravedad de la enfermedad pulmonar obstructiva crónica (EPOC) y la función pulmonar. Se compararon los datos de un grupo con EPOC (pacientes con EPOC tratados entre junio de 2020 y septiembre de 2023, n=90), un grupo de fumadores (fumadores sanos, n=90) y un grupo control (no fumadores sanos, n=90). El grupo de EPOC presentó el nivel más alto de IL-17 y el recuento más bajo de células Treg CD4+, CD25+ y CD4+CD25+ en la sangre periférica, seguido por los grupos de fumadores y de control ($p<0,05$). El recuento de células Treg $CD4^+$, células Treg $CD25^+$, células Treg CD4+CD25+, la capacidad vital forzada (FVC), el volumen espiratorio forzado en el primer segundo (FEV_1) y la relación FEV1/FVC fueron más altos en el grupo leve de EPOC, seguido por los grupos moderado y severo ($p<0,05$). El recuento de células Treg $CD4^+$, células Treg $CD25^+$ y células Treg $CD4^+CD25^+$ mostró correlaciones positivas con FEV1, FVC y FEV_1/FVC ($r>0$, $p<0,05$) y correlaciones negativas con el nivel de IL-17 ($r<0$, $p<0,05$). El nivel de IL-17 se correlacionó negativamente con FEV_1, FVC y FEV_1/FVC ($r<0$, $p<0,05$). La detección combinada de IL-17 y de subconjuntos de Treg es útil para aumentar el valor predictivo de estos en la aparición de EPOC.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD), a chronic inflammatory disease, is pathologically characterized by airflow obstruction of the respiratory tract, and COPD patients usually develop fatigue, shortness of breath, cough, and other typical respiratory symptoms [1,2]. In China, the incidence rate of COPD is 13.6% in people aged over 40 years old and as high as 24.8% in the elderly [3]. The specific pathogenesis of COPD has not been fully elucidated. Still, it is mainly believed to involve mechanisms such as oxidative/antioxidative imbalance, chronic inflammatory responses in the airways and pulmonary parenchyma, and protein/anti-protein imbalance [4]. A study reported that T lymphocytes act as vital players in modulating airway inflammation in COPD, in which helper T (Th) cells are the major players [5]. Cluster of differentiation 4 $(CD4)^+$ T lymphocytes belong to Th lymphocytes, and activated $CD4^+$ T lymphocytes can be classified into Th17 cells and regulatory T (Treg) cells. Th17 and Treg cells repress and antagonize each oth-

er during differentiation, and their balance can confer immune tolerance, whereas an imbalance can induce various autoimmune and infectious diseases [6]. Th17 triggers and progressively amplifies immune responses primarily through the generation of interleukin-17 (IL-17), and a sustained increase in IL-17 content will induce neutrophilic chronic inflammation. As a result, airway inflammation and progressive airway obstruction emerge [7].

Based on this, in the present study, the levels of IL-17 and Treg subsets in the peripheral blood of COPD patients were measured, and their correlations with COPD occurrence and pulmonary function were investigated, aiming to identify targets for the prevention and treatment of COPD.

MATERIALS AND METHODS

Subjects

COPD patients visiting our hospital from June 2020 to September 2023 (a COPD group, n=90), healthy smokers (a smoking group, n=90), and healthy non-smokers (a healthy group, n=90) were enrolled as subjects. The COPD group was composed of 53 males and 37 females aged 49-83 years old, with an average age of (58.52 ± 4.87) years old. The body mass index (BMI) was (22.08 ± 1.87) kg/m^2, the number of cigarettes smoked was (400.36 ± 78.98) cigarettes/year, and the course of disease was (5.64 ± 1.75) years. As to the severity [according to the 2019 Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria] [8], there were 30 mild cases, 42 moderate cases, and 28 severe cases. The smoking group consisted of 51 males and 39 females aged 45-81 years old, with a mean of (59.48 ± 5.26) years old. BMI was (21.98 ± 1.58) kg/m^2, and the number of cigarettes smoked was (409.54 ± 82.59) cigarettes/year. In the healthy group composed of 55 males and 35 females, the age was 45-80 years old, with an average of (59.11 ± 5.59) years old, and MI was (22.19 ± 1.67) kg/m^2. The age, gender, and BMI were comparable among the three groups ($p>0.05$).

Inclusion and exclusion criteria

The following inclusion criteria were employed: 1) COPD patients meeting the diagnostic criteria for COPD and without a history of acute exacerbation in the past six months [8], 2) smokers with expected results in the pulmonary function test and number of cigarettes smoked ≥200 cigarettes/year, and non-smokers with expected results in the pulmonary function test and no smoking history, and 3) subjects who voluntarily signed the informed consent form.

The exclusion criteria involved: 1) subjects requiring mechanical ventilation due to severe condition, 2) those with rheumatic system diseases, allergic diseases or immune deficiencies, 3) those with acute pulmonary embolism, tuberculosis, bronchiectasis, asthma, cystic fibrosis, and other respiratory diseases, 4) those with coagulation dysfunction, 5) those with severe dysfunction of multiple organs, 6) those with a previous history of pulmonary surgery or lung tumors, 7) those with severe arrhythmia, acute myocardial infarction or myocardial ischemia, or 8) those taking immunosuppressants or glucocorticoids within 4 weeks before enrollment.

Detection of indicators in the peripheral blood

Peripheral venous blood (6 mL, evenly split into two portions) was collected before treatment in the COPD group and on the day of physical examination in the smoking and healthy groups. One portion was subjected to heparin anticoagulation, followed by 10 min of centrifugation (centrifugation radius: 6.5 cm, and centrifugation rate: 3500 rpm). Next, the supernatant was harvested for an enzyme-linked immunosorbent assay (Cat. No. DLR-IL17-Hu, Wuxi Donglin Sci & Tech Development Co., Ltd., China) to measure IL-17 levels. The other portion was subjected to Ficoll density gradient centrifugation using the

relevant kit (Cat. No. 17-1140-02, GE Healthcare Life Sciences, USA) to isolate peripheral blood mononuclear cells (PBMCs). Then, the resulting cell suspension was incubated with monoclonal antibodies against CD4-CD4-fluorescein isothiocyanate (FITC) and CD25-CD25-phycoerythrin (PE) (BD, USA), with immunoglobulin G (IgG)-FITC and IgG-PE as controls. Afterwards, the FAS-Calibur flow cytometer (BD, USA) was employed to detect CD4+ Treg cell count, CD25+ Treg cell count, and $CD4^+CD25^+$ Treg cell count.

Pulmonary function test

The forced expiratory volume in one second (FEV_1) and forced vital capacity (FVC) were determined with the HI-801 pulmonary function tester (CHEST, Japan) on the day of physical examination in the smoking group and the healthy group and before treatment in the COPD group, based on which the FEV_1/FVC value was calculated.

Statistical analysis

Statistical analysis was performed using the SPSS 26.0 software. Measurement data were expressed as mean ± standard deviation ($\bar{x} \pm s$) and subjected to the *t*-test for comparison between two groups and one-way analysis of variance for comparison among multiple groups. Count data were described as [n (%)] and examined by the χ^2 test. Spearman's rank correlation analysis was conducted to explore the correlations between levels of IL-17 and Treg subsets and pulmonary function. Receiver operating characteristic (ROC) curves were plotted, based on which the association between IL-17 levels and Treg subsets and the occurrence of COPD was assessed. $p<0.05$ indicated that the difference was statistically significant.

RESULTS

Levels of IL-17 and Treg subsets in the peripheral blood

The COPD group showed the highest IL-17 levels and the lowest CD4+ Treg cell count, CD25+ Treg cell count, and CD4+CD25+ Treg cell count in peripheral blood, followed by the smoking group and the healthy group ($p<0.05$) (Table 1).

Values of IL-17 and Treg subset levels in the peripheral blood for association with COPD occurrence

The areas under the ROC curves [AUCs, 95% confidence interval (95% CI)) of IL-17 level, $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count in the peripheral blood and their combination for associating with the occurrence of COPD were 0.866 (0.813-0.920), 0.885 (0.833-0.936), 0.799 (0.735-0.863), 0.773 (0.705-0.840), 0.949 (0.919-0.979), respectively (Table 2 and Fig. 1).

Table 1. Levels of IL-17 and Treg subsets in the peripheral blood.

Group	n	IL-17 level (ng/L)	$CD4^+$ Treg cell count (%)	$CD25^+$ Treg cell count (%)	$CD4^+CD25^+$ Treg cell count (%)
Healthy	90	13.26±3.84	31.57±4.52	4.53±0.85	3.68±0.75
Smoking	90	28.48±5.65[a]	25.15±5.68[a]	3.21±0.79[a]	3.05±0.64[a]
COPD	90	38.12±6.87[ab]	16.58±4.74[ab]	2.34±0.67[ab]	2.34±0.71[ab]
F		451.893	203.182	182.842	82.202
p		<0.001	<0.001	<0.001	<0.001

[a]$p<0.05$ *vs.* the healthy group, [b]$p<0.05$ *vs.* the smoking group.
Data is expressed as mean ± standard deviation. One-way analysis of variance was used to compare multiple groups. Chronic obstructive pulmonary disease (COPD).

Table 2. Values of IL-17 and Treg subset levels in the peripheral blood for predicting COPD occurrence.

Indicator	Area under the curve	Standard error	Optimal cut-off value	p	95% confidence interval
IL-17	0.866	0.027	32.584ng/L	<0.001	0.813-0.920
$CD4^+$Treg	0.885	0.026	20.025%	<0.001	0.833-0.936
$CD25^+$Treg	0.799	0.033	2.684%	<0.001	0.735-0.863
$CD4^+CD25^+$Treg	0.773	0.034	2.641%	<0.001	0.705-0.840
Combination	0.949	0.015	-	<0.001	0.919-0.979

Chronic obstructive pulmonary disease (COPD).

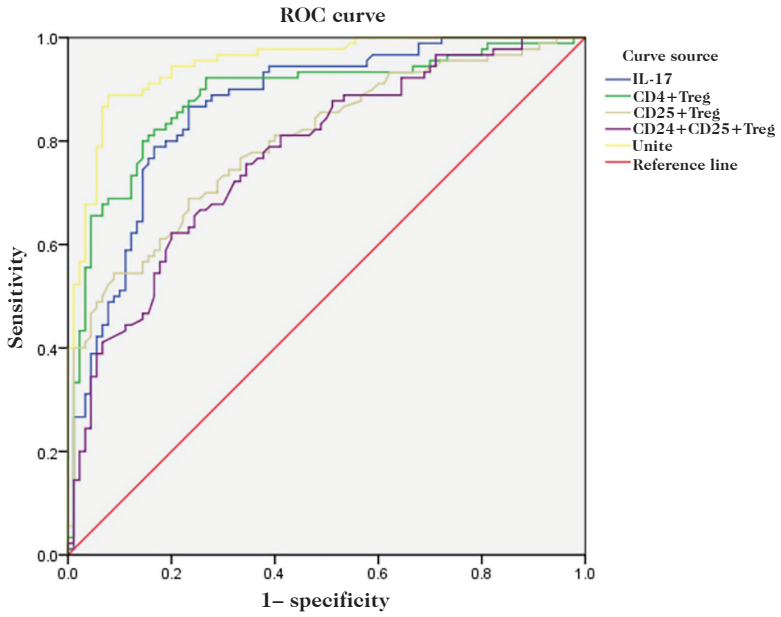

Fig. 1. ROC curves of IL-17 and Treg subset levels in the peripheral blood for predicting Chronic obstructive pulmonary disease (COPD) occurrence.

Levels of IL-17 and Treg subsets in the peripheral blood of COPD patients with different severities

The IL-17 level in the peripheral blood was the highest in the severe group, followed by the moderate group and the mild group, while the $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count were the highest in the mild group, followed by the moderate group and the severe group ($p<0.05$) (Table 3).

Pulmonary function in COPD patients with different severities

The FEV_1, FVC, and FEV_1/FVC were the highest in the mild group, moderate in the moderate group, and the lowest in the severe group ($p<0.05$) (Table 4).

Correlations of IL-17 and Treg subset levels in the peripheral blood with pulmonary function

The results of the Spearman's rank correlation analysis showed that the IL-17 level was negatively correlated with FEV_1, FVC, and FEV_1/FVC ($r<0$, $p<0.05$).

Table 3. Levels of IL-17 and Treg subsets in the peripheral blood of COPD patients with different severities.

Group	n	IL-17 level (ng/L)	$CD4^+$ Treg cell count (%)	$CD25^+$ Treg cell count (%)	$CD4^+CD25^+$ Treg cell count (%)
Mild	30	31.25±5.58	20.35±4.65	3.02±0.68	2.89±0.52
Moderate	42	37.85±6.85[a]	14.25±4.58[a]	2.03±0.59[a]	2.11±0.47[a]
Severe	28	45.10±5.87[ab]	10.11±3.68[ab]	1.24±0.49[ab]	1.26±0.57[ab]
F		35.865	40.607	65.732	72.701
p		<0.001	<0.001	<0.001	<0.001

[a]p<0.05 *vs.* the mild group, [b]p<0.05 *vs.* the moderate group. Chronic obstructive pulmonary disease (COPD). Data is expressed as mean ± standard deviation. One-way analysis of variance was used to compare multiple groups.

Table 4. Pulmonary function in COPD patients with different severities.

Group	n	FEV_1 (L)	FVC (L)	FEV_1/FVC (%)
Mild	30	1.89±0.56	3.58±0.71	63.25±6.58
Moderate	42	1.49±0.62[a]	2.95±0.68[a]	57.48±5.59[a]
Severe	28	1.15±0.49[ab]	2.32±0.65[ab]	51.74±6.68[ab]
F		12.343	24.802	24.885
p		<0.001	<0.001	<0.001

[a]p<0.05 *vs.* the mild group, [b]p<0.05 *vs.* the moderate group. Data is expressed as mean ± standard deviation. One-way analysis of variance was used to compare multiple groups. Forced vital capacity (FVC), Forced expiratory volume in one second (FEV_1), Chronic obstructive pulmonary disease (COPD).

In contrast, the $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count were positively correlated with FEV_1, FVC, and FEV_1/FVC ($r>0$, $p<0.05$) and negatively correlated with IL-17 level ($r<0$, $p<0.05$) (Table 5).

DISCUSSION

COPD is characterized by airway wall thickening, accumulation of inflammatory mucus, and infiltration of adaptive and innate immune cells. Among them, $CD4^+$ T lymphocytes play a critical role in the pathogenesis of COPD [9,10]. Under normal conditions, the balance of Th subsets helps maintain immune homeostasis, but in COPD, this balance is disturbed, with overactivation of Th17 cells and reduction of Treg cells [11].

Th17 cells secrete IL-17 and IL-22, which recruit neutrophils and other inflammatory cells, thus amplifying airway inflammation. IL-17 also stimulates macrophages, dendritic cells, and fibroblasts to release chemokines, pro-inflammatory cytokines, and proteolytic enzymes, all of which contribute to tissue damage and a decline in pulmonary function [12-14]. Elevated IL-17 further promotes neutrophil and macrophage infiltration, exacerbating airway injury [15]. Smoking additionally aggravates airway obstruction by inducing epithelial damage, mucosal gland hypertrophy, and ciliary dysfunction, and it promotes Th17 proliferation and IL-17 release [16].

In contrast, Treg cells play a protective role by suppressing autoreactive T cells and excessive immune activation [17]. $CD4^+CD25^+$

Table 5. Correlations of IL-17 and Treg subset levels in the peripheral blood with pulmonary function.

Indicator	Coefficient	IL-17	FEV_1	FVC	FEV_1/FVC
IL-17	*r*	-	-0.415	-0.535	-0.552
	p	-	<0.001	<0.001	<0.001
$CD4^+$Treg	*r*	-0.536	0.428	0.585	0.597
	p	<0.001	<0.001	<0.001	<0.001
$CD25^+$Treg	*r*	-0.589	0.448	0.597	0.603
	p	<0.001	<0.001	<0.001	<0.001
$CD4^+CD25^+$Treg	*r*	-0.645	0.487	0.615	0.637
	p	<0.001	<0.001	<0.001	<0.001

Forced vital capacity (FVC), Forced expiratory volume in one second (FEV_1).

Treg cells inhibit effector T-cell proliferation through IL-2 and IFN-γ suppression and TGF-β–mediated pathways [18]. In the present study, comparisons were carried out on the $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count among the three groups. The results showed that the CD4+ Treg cell count, CD25+ Treg cell count, and CD4+CD25+ Treg cell count were lowest in the COPD group, moderate in the smoking group, and highest in the healthy group, suggesting immunomodulatory dysfunction in COPD patients and smokers, especially in the former. The $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count were the lowest in the severe group, moderate in the moderate group, and the highest in the mild group. According to the Spearman's rank correlation analysis, the $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count were positively correlated with FEV_1, FVC and FEV_1/FVC, demonstrating that the level of Treg subsets can reflect the condition of COPD patients to a certain extent, and that patients with a high expression of Treg subsets often have good pulmonary function. This is because CD4+ Treg cells, CD25+ Treg cells, and CD4+CD25+ Treg cells can impede the production of Th1 and Th17 cells via the autocrine transforming growth factor-β (TGF-β) pathway. However, in cases of low Treg expression, they cannot suppress inflammatory cytokines, leading to an imbalance between Th1 and Th2 cell counts. Accordingly, IL-4 expression will be further suppressed, and IL-17 and IFN-γ levels will be increased, resulting in persistently high immune responses, damaging lung and airway tissues, weakening pulmonary function, and thereby inducing COPD [19,20].

Furthermore, the results of the present study also showed that the $CD4^+$ Treg cell count, $CD25^+$ Treg cell count, and $CD4^+CD25^+$ Treg cell count displayed negative correlations with IL-17 level, signifying that the down-regulation of Treg subsets and the high expression of IL-17 (a characteristic inflammatory factor of Th17 cells) will disrupt the balance between Th17 cell count and Treg cell count, increase airway secretions and airway inflammatory responses, affect lung ventilation function, and further damage pulmonary function and lung tissues. The balance between Th17 cell count and Treg cell count should be maintained by taking appropriate measures, thus preventing COPD or its exacerbation [21].

Our study provides novel insights into several aspects. First, our cohort included exclusively COPD patients without asthma, ensuring disease specificity. Second, we simultaneously evaluated IL-17 and Treg subsets, and demonstrated that their combined

imbalance (increased IL-17 and decreased Treg levels) was more strongly associated with COPD severity than IL-17 alone. Third, by stratifying patients by GOLD grade, we revealed dynamic changes in these immune markers across disease progression. Collectively, these findings highlight the importance of the IL-17/Treg axis in COPD immunopathogenesis.

However, several limitations should be recognized. One limitation is that detailed information on inhaled corticosteroid (ICS) use was not systematically collected for all COPD patients. Since ICS therapy may influence cytokine profiles, such as reducing IL-17 levels or affecting Treg responses, its impact on our findings cannot be ruled out. Future studies with more complete treatment records and subgroup analyses are needed to address this. Another limitation is that we did not measure eosinophil and neutrophil counts or their relationship with IL-17 levels. Because these cells are key players in airway inflammation, future research should include them to better understand the connection between IL-17 and innate immune responses in COPD.

In conclusion, IL-17 is upregulated, and Treg subsets are downregulated in COPD, with their imbalance closely linked to impaired lung function and disease severity. The combined detection of IL-17 and Treg subsets may thus offer more informative biomarkers for evaluating COPD progression.

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Conflict of interest

The authors confirm that the content of this article has no conflict of interest.

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Contributions of each author

JC and ZZ designed this study and prepared the manuscript; TZ and YG conducted this study and analyzed the data. All authors have approved the submission and publication of this paper.

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