MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2016; 22: 2800-2808
DOI: 10.12659/MSM.896458

Received: 2015.10.28
Accepted: 2015.12.23
Published: 2016.08.09

Plasma Inflammatory Cytokine IL-4, IL-8, IL-10, and TNF-α Levels Correlate with Pulmonary Function in Patients with Asthma-Chronic Obstructive Pulmonary Disease (COPD) Overlap Syndrome

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Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Source of support: Departmental sources

Background: The aim of this study was to investigate the plasma inflammatory cytokine levels and their correlations with pulmonary function in patients with asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS).

Material/Methods: Between January 2013 and December 2014, a total of 96 patients with asthma, acute exacerbation of chronic obstructive pulmonary disease (AECOPD), or ACOS were enrolled, and 35 healthy people were included as a control group. Fasting plasma interleukin (IL)-4, IL-8, IL-10, and tumor necrosis factor alpha (TNF-α) levels were detected using enzyme-linked immunosorbent assay (ELISA). Correlations between the plasma inflammatory cytokine levels and forced expiratory volume in 1 second (FEV1), FEV1/predicted value ratio (FEV1%pred), and FEV1/forced vital capacity (FVC) were analyzed.

Results: IL-4 and IL-8 levels showed statistically significant differences among the 3 groups of patients (both $P<0.001$); IL-4 level was significantly lower, while IL-8 level was significantly higher in the AECOPD group and ACOS group than those in the asthma group (all $P<0.05$). IL-10 level and TNF-α level were significantly different among the 3 patient groups (both $P<0.001$). IL-10 level was significantly different between each of the 2 groups (all $P<0.001$). TNF-α level in the asthma group was higher than in the AECOPD group and ACOS group (both $P<0.001$). IL-4 and IL-10 were positively and IL-8 and TNF-α were negatively related with FEV1, FEV1%pred, and FEV1/FVC.

Conclusions: Plasma levels of inflammatory cytokines IL-4, IL-8, IL-10, and TNF-α are related with severity of airway diseases and could be potential markers for the evaluation of asthma, COPD, and ACOS.

MeSH Keywords: **Lung Diseases • Mitogen-Activated Protein Kinase 14 • Pulmonary Medicine**

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Background

As a chronic inflammatory respiratory disease, asthma is characterized by episodic bronchoconstriction and airway hyperresponsiveness to a variety of stimuli, such as viral antigens, allergens, and environmental exposures, and may cause shortness of breath, chest tightness, coughing, and wheezing [1]. It has been reported that 25.9 million (8.5%) people in the United States had asthma in 2011, including 7.0 million children, with increasing prevalence rates [2]. Chronic obstructive pulmonary disease (COPD) is mainly characterized by progressive and irreversible development of persistent airway obstruction [3,4]. Acute exacerbations of COPD (AECOPD) are episodes of sustained worsening of symptoms and decline of lung function, which reflects an extensive inflammatory process at onset stage; it contributes to poor life quality and is a major cause of mortality and morbidity [5,6]. Asthma and COPD may coexist, or one condition may evolve into the other, creating a condition commonly known as Asthma and COPD Overlap Syndrome (ACOS), which has indistinct clinical and pathophysiological features of asthma or COPD [7,8]. Compared to other individuals with COPD, patients with ACOS have an increased reversibility of airflow obstruction and, more importantly, a higher degree of eosinophilic bronchial inflammation [9]. Since all these 3 diseases are related to inflammatory processes, it is of great importance to study the roles of inflammatory cytokine levels in the development of these diseases.

Interleukin (IL)-4, also known as B-cell-stimulating factor, is a pleiotropic cytokine. It mainly promotes the proliferation of T cells and induces antibody production by B cells, and can also stimulate proliferation, differentiation, and activation of fibroblasts, and endothelial and epithelial cells, and increases the recruitment of inflammatory cells [10,11]. As an essential pro-inflammatory mediator, IL-8 can be produced by monocytes/macrophages, epithelial cells, smooth muscle cells, and endothelial cells. It is involved in cancer development and acts as an angiogenic growth factor in the progression and metastasis of non-small cell lung cancer [12,13]. IL-10 is a major anti-inflammatory cytokine and is a necessary and beneficial host response directed at regulating excessive pro-inflammatory cytokines and chemokines from respiratory syncytial virus-activated immune cells [14]. It has been reported that IL-10 can suppress macrophage activity by inhibiting the production of interferon gamma, IL-2, IL-12, and IL-18 and that the modulation of the inflammatory response is essential to preserve immune system balance [15]. Tumor necrosis factor α (TNF-α) is a multifunctional and pro-inflammatory cytokine that can respond to inflammation, infection, and injury by mast cells, macrophages, eosinophils, epithelial cells, and neutrophils in asthma pathogenesis [16]. However, few studies have systematically investigated the inflammatory cytokine levels in patients with asthma, AECOPD, and ACOS.

Therefore, in this study, we detected and compared the plasma IL-4, IL-8, and IL-10, and TNF-α levels in patients with asthma, AECOPD, and ACOS and conducted correlation studies to analyze the correlations between the inflammatory cytokine levels and pulmonary function.

Material and Methods

Study participants

Between January 2013 and December 2014, a total of 96 patients with asthma, AECOPD, or ACOS were enrolled from the Department of Respiratory Medicine, South Campus, Shanghai Jiaotong University 6th Hospital. Using the "Bronchial Asthma Therapeutic Guidelines" formulated by the Branch of Chinese Medical Association for Respiratory Diseases [17], 36 patients with acute exacerbation of bronchial asthma were enrolled as the asthma group. According to the "Chronic Obstructive Pulmonary Disease Therapeutic Guidelines" (Branch of Chinese Medical Association for Respiratory Diseases) [18], 32 patients with AECOPD were enrolled as the AECOPD group. Based on the "Diagnostic Criteria Consensus of Chronic Obstructive Pulmonary Disease-Asthma Overlap Syndrome" published in 2012 [19], 28 patients with acute exacerbation of ACOS were recruited as the ACOS group. Exclusion criteria were: patients with other lung diseases (e.g., bronchiectasis, lung cancer, pulmonary embolism, interstitial lung disease, and tuberculosis), severe heart, liver, kidney, or systemic diseases; and worm parasites in stool samples. We enrolled 35 healthy subjects as the control group. The study complied with the medical ethics standards and was approved by the Ethics Committee of Shanghai Jiaotong University 6th Hospital. Signed informed consent was obtained from all study subjects or their families. Ethics approval for this study conformed to the standards of the Declaration of Helsinki [20].

Indicator assessment

Venous blood (5 ml) was taken from each participant. Whole blood was collected using ethylene diamine tetraacetic acid (EDTA) tubes and naturally coagulated for about 20 minutes at room temperature, and centrifuged at 2000 r/min for 10 minutes. The supernatant was collected carefully and stored at –70°C. Enzyme-linked immunosorbent assay (ELISA) was used to detect plasma IL-4, IL-6, IL-8, IL-10, and TNF-α levels; all the kits were provided by Shenzhen Jingmei Co., Ltd., Shenzhen, China, and all the plasma sample processing, measurement, and content calculation were done according to kit instructions.

A Microtest 1 analyzer (Alifax Company, Italy) was used to detected erythrocyte sedimentation rate (ESR). A Sysmex XE-2100D automated hematology analyzer (Sysmex, Japan) was

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Table 1. Clinical and laboratory characteristics in control, asthma, AECOPD and ACOS groups.

	Control group	Asthma group	AECOPD group	ACOS group	*P*
Age	55.7±10.3	56.1±14.3	60.2±10.1	53.4±10.7	0.146
Gender					
Male	19 (54.28)	14 (38.89)	21 (65.62)	19 (67.86)	0.052
Female	16 (45.72)	22 (61.11)	11 (34.38)	9 (32.14)	
BMI (kg/m^2)	25.98±5.31	25.01±5.64	26.02±3.21	27.68±4.02	0.171
Smoking status					
Never smoking	16 (45.71)	20 (55.56)	11 (34.38)	9 (32.14)	0.062
Used to smoke	12 (34.28)	5 (13.89)	15 (46.87)	14 (50.00)	
Still smoking	7 (20.01)	11 (30.55)	6 (18.75)	5 (17.86)	
Smoking index					
0	16 (45.71)	20 (55.56)	11 (34.38)	10 (35.72)	0.306
0–200	7 (20.01)	5 (13.89)	3 (9.37)	4 (14.28)	
>200	12 (34.28)	11 (30.55)	18 (56.25)	14 (50.00)	
Allergic history					
No	25 (71.43)	18 (50.00)	23 (71.88)	15 (53.57)	0.128
Yes	10 (28.57)	18 (50.00)	9 (28.12)	13 (46.43)	
α1-antitrypsin (mg/dL)	128.8±6.1	143.9±3.5*	147.2±8.4*	145.9±5.1*	<0.001
Serum total IgE (IU/ml)	103.0±49.6	382.8 ±412.0*	189.0±191.2	306.4±336.7*	0.001
ESR (mm/h)	12.5±3.1	16.4±10.1	18.9±11.9*	13.1±6.2	0.010
Peripheral blood eosinophil (10^9/L)	0.14±0.07	0.29±0.17*	0.22±0.12	0.28±0.22*	0.001

P – comparisons between control, asthma, AECOPD and ACOS. * Compared with the control group, *P*<0.05. AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ACOS – asthma-chronic obstructive pulmonary disease overlap syndrome; BMI – body mass index; IgE – immunoglobulin E; ESR – erythrocyte sedimentation rate.

used to detect peripheral blood eosinophil count. Plasma α1-antitrypsin was detected by a Roche automated clinical chemistry analyzer (Roche, Germany) and determined by immune nephelometry method; reagents were provided by the Roche Company and the procedures done were in accordance with kit instructions. Serum total protein immunoglobulin E (IgE) was measured by use of a BN-II special protein analyzer (Siemens, Germany) and determined by immune nephelometry method; the reagents were supplied by the Siemens Company and the procedures were done in accordance with kit instructions. A MedGraphics 1085 Series Plethysmography (MedGraphics CPX/D, St Paul, MN, USA) was used to conduct pulmonary function testing and bronchial dilation testing. We measured arterial partial pressure of oxygen (PaO_2), arterial partial pressure of carbon dioxide ($PaCO_2$) in blood, forced expiratory volume in 1 second percentage (FEV1%), forced vital capacity (FVC), FEV1/FVC, FEV1/predicted value ratio (FEV1%pred), total lung capacity (TLC), and residual volume (RV) of subjects in each group.

Statistical methods

SPSS 21.0 statistical software (SPSS Inc, Chicago, IL, USA) was used for statistical data processing. Count data are expressed as percentages or rates, and were compared using the chi-square test between groups; measurement data are presented as mean±standard deviation and were compared using the *t* test between 2 groups, and analysis of variance (ANOVA) was used among groups. Pearson correlation analysis was used for correlation analysis. All tests were 2-sided and *P*<0.05 indicated a significant difference.

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Table 2. Comparisons of pulmonary function indexes among control, asthma, AECOPD and ACOS groups.

	Control group	Asthma group	AECOPD group	ACOS group	*P*
PaO_2 (mmHg)	84.1±8.4	79.1±10.6	69.9±12.0*,#	76.2±12.8*	<0.001
$PaCO_2$ (mmHg)	42.1±7.8	38.8±10.4	44.9±10.1	41.6±12.1	0.107
FEV1 (L)	2.75±0.09	1.86±0.92*	1.60±0.64*	2.08±0.80*	<0.001
FEV1improved (L)		0.35±0.16	0.52±0.47	0.42±0.16	
FEV1%pred (%)	85.1±2.6	70.3±20.8*	65.1±12.6*	54.3±22.9*,#	<0.001
FVC (L)	2.87±0.94	3.58±0.98*	3.50±0.74*	4.07±1.18*	<0.001
FEV1/FVC (%)	76.2±1.1	51.0±2.8*	46.2±1.3*,#	48.6±1.8*,#	<0.001
TLC (L)	4.85±1.05	4.64±1.60	5.41±1.22	4.82±1.45	0.115
RV (L)	1.28±0.22	1.68±0.92	2.15±0.84*	1.84±0.56*	<0.001
RV/TLC	30.1±8.6	47.6±9.9*	56.4±10.5*,#	50.8±11.2*,#	<0.001

P – comparisons between control, asthma, AECOPD and ACOS. *Compared with the control group, $P<0.05$; # Compared with the asthma group, $P<0.05$. AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ACOS – asthma-chronic obstructive pulmonary disease overlap syndrome; PaO_2 – arterial partial pressure of oxygen; $PaCO_2$ – arterial partial pressure of carbon dioxide; FEV1 – forced expiratory volume in 1 second, FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity; TLC – total lung capacity; RV – residual volume.

Results

Clinical and laboratory characteristics

As shown in Table 1, no significant differences in age, sex, body mass index (BMI), smoking status, smoking index, or allergic history were found among the control group, the asthma group, AECOPD group, and ACOS group (all $P>0.05$); but obvious differences in α1-antitrypsin level, serum total IgE, ESR, and peripheral blood eosinophil were found among the 4 groups (all $P<0.05$). The α1-antitrypsin level in the control group was remarkably lower than in the 3 patient groups (all $P<0.05$); serum total IgE was significantly higher in the asthma and ACOS groups than that in the control group (both $P<0.05$). ESR was obviously different between the AECOPD group and the control group ($P<0.05$). Statistically significant differences in peripheral blood eosinophil counts were found between the control group and the asthma group, and between the control group and the ACOS group (both $P<0.05$).

No significant differences in age, BMI, smoking index, allergic history, α1-antitrypsin level, serum total IgE, ESR, or peripheral blood eosinophil were found among the asthma group, AECOPD group, and ACOS group (all $P>0.05$). A significant difference in sex was found among the 3 groups of patients ($P=0.029$). The line × column table was further divided based on sex, the test standard and free degree were corrected, and the threshold $\chi^2_{0.0167,1}$ was 5.73. Comparing the asthma group and the ACOS group, the $\chi^2=3.78 <\chi^2_{0.0167,1}$, comparing the AECOPD group and ACOS group, the $\chi^2=0.19 <\chi^2_{0.0167,1}$; and comparing the asthma group and AECOPD group, the $\chi^2=6.35 >\chi^2_{0.0167,1}$, which indicated that the proportion of males in the AECOPD group was higher than that in the asthma group ($P<0.05$), but was not significantly different compared to the ACOS group ($P>0.05$). Differences in smoking status was found among the 3 groups of patients ($P=0.019$). The table was further divided based on smoking status, and test standard and free degree were corrected, the threshold $\chi^2_{0.0167,1}$ was 5.73, the χ^2 was 9.84 comparing the asthma and ACOS group and was more than the threshold value; it was 8.88 comparing the asthma group and AECOPD group and was also more than the threshold value, and was 0.06 comparing the AECOPD group and ACOS group and was less than the threshold value, indicating the percentage of patients with smoking history was higher in the AECOPD group than that in the asthma group, but it was not significantly different compared to the ACOS group.

Comparisons of pulmonary function indexes

The PaO_2, FEV1, and FEV1%pred were higher, while the FVC, RV, and RV/TLC were lower, in the control group than in the asthma group, AECOPD group, and ACOS group (all $P<0.05$). No significant differences in $PaCO_2$ and TLC were found among the 4 groups (both $P>0.05$).

PaO_2 was lower in the AECOPD group than in the asthma group, with a statistically significant difference ($P<0.01$); while there were no significant difference in PaO_2 between the asthma group and the ACOS group, and the AECOPD group and ACOS group (both $P>0.05$). $PaCO_2$, FEV1, $FEV1_{improved}$, TLC, FVC, and RV (after inhalation of bronchodilators) were not significantly different among the 3 groups of patients (all $P>0.05$).

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Table 3. Comparisons of plasma inflammatory cytokine levels among control, asthma, AECOPD and ACOS groups.

	Control group	Asthma group	AECOPD group	ACOS group	*P*
IL-4 (ng/L)	55.08±9.86	205.12±72.58*	140.50±20.66*,#	167.31±32.42*,#	<0.001
IL-8 (ng/L)	29.10±5.02	46.59±4.72*	52.68±5.64*,#	56.25±6.61*,#	<0.001
IL-10 (ng/L)	57.86±8.09	12.72±2.47*	20.60±1.89*,#	16.72±2.11*,#,&	<0.001
TNF-α (ng/L)	32.54±9.68	132.18±40.62*	82.68±15.32*,#	97.40±16.83*,#	<0.001

P – comparisons between control, asthma, AECOPD and ACOS. * Compared with the control group, $P<0.05$; # Compared with the asthma group, $P<0.05$; & Compared with the AECOPD group, $P<0.05$. AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ACOS – asthma-chronic obstructive pulmonary disease overlap syndrome; IL-4 – interleukin 4; IL-8 – interleukin 8; IL-10 – interleukin 10; TNF-α – tumor necrosis factor alpha.

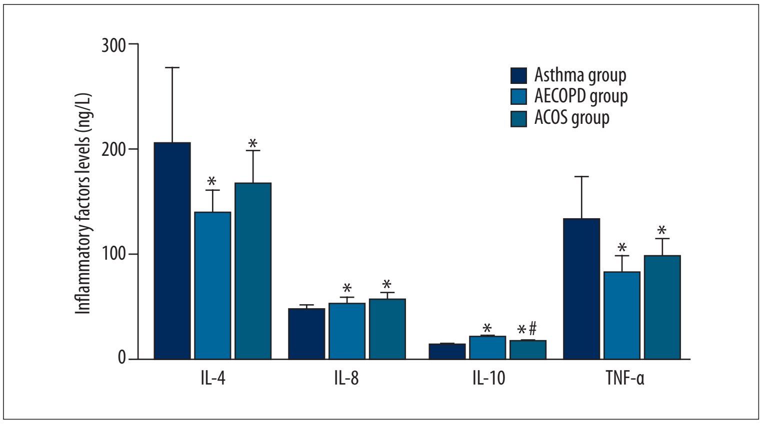

Figure 1. Comparisons of plasma inflammatory cytokine levels among control, asthma, AECOPD, and ACOS groups. * Compared with the asthma group, $P<0.05$; ** Compared with the AECOPD group, $P<0.05$; AECOPD – acute exacerbation of chronic obstructive pulmonary disease; ACOS – asthma-chronic obstructive pulmonary disease overlap syndrome; IL-4 – interleukin 4; IL-6 – interleukin 6; IL-8 – interleukin 8; IL-10 – interleukin 10; TNF-α – tumor necrosis factor alpha.

Table 4. Correlations between plasma inflammatory cytokine levels and pulmonary function indexes.

	FEV1		FEV1%pred		FEV1/FVC	
	r	*p*	r	*p*	r	*p*
IL-4	0.297	0.003	0.240	0.018	0.390	<0.001
IL-8	−0.580	<0.001	−0.641	<0.001	−0.455	<0.001
IL-10	0.535	<0.001	0.580	<0.001	0.477	<0.001
TNF-α	−0.494	<0.001	−0.491	<0.001	−0.452	<0.001

FEV1 – forced expiratory volume in 1 second; FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity; IL-4 – interleukin 4; IL-8 – interleukin 8; IL-10 – interleukin 10; TNF-α – tumor necrosis factor alpha.

The FEV1%pred was remarkably different between the asthma group and ACOS group ($P<0.05$); but was not significantly different between the asthma group and AECOPD group, and the AECOPD group and ACOS group (both $P>0.05$). The FEV1/FVC and the RV/TLC were significantly different among the 3 groups of patients ($P<0.01$; $P=0.003$) (Table 2).

Comparisons of plasma inflammatory cytokine levels

The IL-4, IL-8, IL-10, and TNF-α levels were significantly different among the control group, asthma group, AECOPD group, and ACOS group (all $P<0.05$) (Table 3). IL-4 and IL-8 levels showed statistically significant differences among the 3 groups of patients (F=14.78, $P<0.001$; F=20.43, $P<0.001$). The IL-4 level was significantly lower but the IL-8 level was significantly higher in the AECOPD group and ACOS group than those in the asthma group (all $P<0.05$). The IL-4 and IL-8 levels were not significantly different between the AECOPD group and ACOS group. IL-10 level and TNF-α level were significantly different among the 3 patient groups (both $P<0.001$). IL-10 level was significantly different between each of the 2 groups (all $P<0.001$). TNF-α level in the asthma group was higher than in the AECOPD group and ACOS group ($P<0.001$), but was not significantly different between the AECOPD group and the ACOS group (Figure 1).

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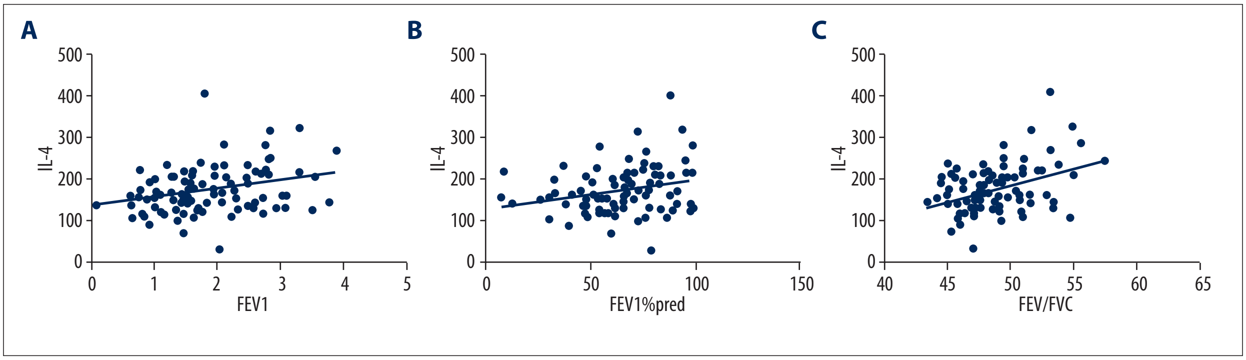

Figure 2. Correlations between IL-4 levels with (**A**) FEV1; (**B**) FEV1%pred, and (**C**) FEV1/FVC. IL-4 – interleukin 4; FEV1 – forced expiratory volume in 1 second; FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity.

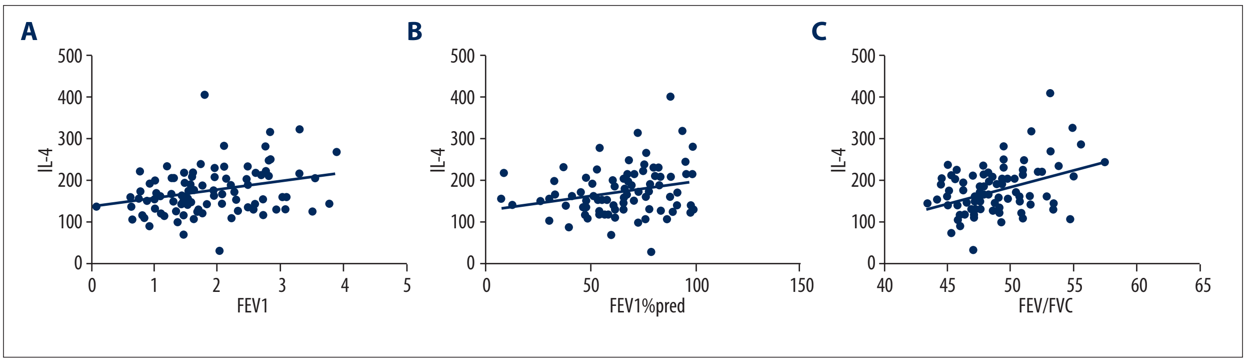

Figure 3. Correlations between IL-8 levels with (**A**) FEV1; (**B**) FEV1%pred and (**C**) FEV1/FVC. IL-8 – interleukin 8; FEV1 – forced expiratory volume in 1 second; FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity.

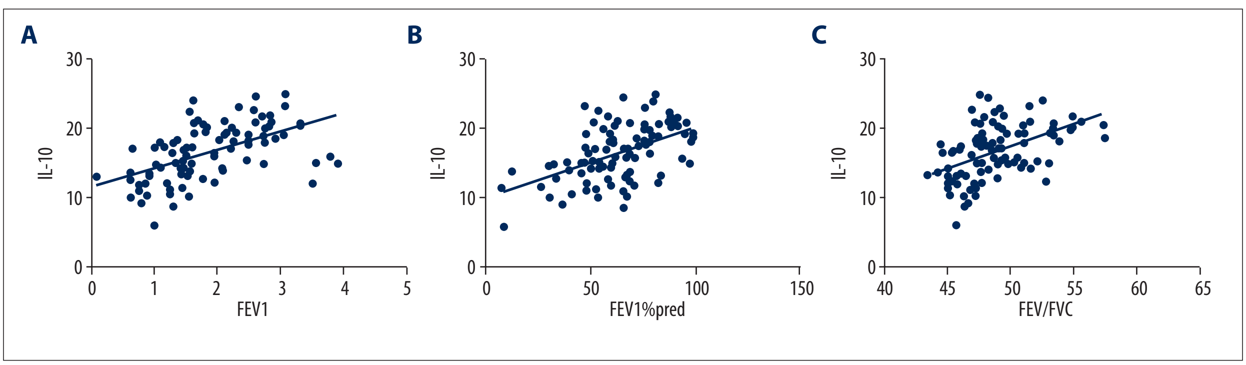

Figure 4. Correlations between IL-10 levels with (**A**) FEV1; (**B**) FEV1%pred and (**C**) FEV1/FVC. IL-10 – interleukin 10; FEV1 – forced expiratory volume in 1 second; FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity.

Correlations between plasma inflammatory cytokine levels and pulmonary function indexes

As shown in Table 4, the plasma level of IL-4 was positively correlated with FEV1, FEV1%pred, and FEV1/FVC (r=0.297, 0.240 and 0.390; all $P<0.05$) (Figure 2); the plasma level of IL-8 was negatively correlated with FEV1, FEV1%pred, and FEV1/FVC (r=–0.580, –0.641 and r=–0.455, all $P<0.05$) (Figure 3); the IL-10 plasma level was positively correlated with FEV1, FEV1%pred, and FEV1/FVC (r=0.535, 0.580 and 0.477; all $P<0.05$) (Figure 4); and the TNF-α plasma level was negatively correlated FEV1, FEV1%pred, and FEV1/FVC (r=–0.494, –0.491 and –0.452, all $P<0.05$) (Figure 5).

Discussion

Our study demonstrated that in the control group, PaO_2, FEV1, and FEV1%pred were higher and the FVC, RV, and RV/TLC were lower than that in the asthma group, AECOPD group, and ACOS group. Our results suggest that PaO_2 was significantly lower in the AECOPD group than in the asthma group; therefore, PaO_2

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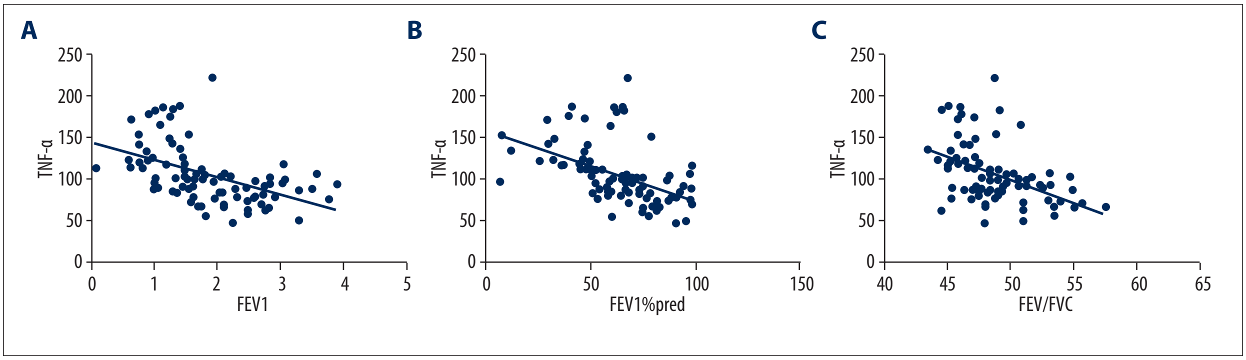

Figure 5. Correlations between TNF-α levels with (**A**) FEV1; (**B**) FEV1%pred; and (**C**) FEV1/FVC. TNF-α – tumor necrosis factor alpha; FEV1 – forced expiratory volume in 1 second; FEV1%pred – FEV1/predicted value ratio; FVC – forced vital capacity.

could be a valuable index to differentiate AECOPD and asthma. As a sensitive and objective measure of pulmonary function, PaO_2 is a very good predictor of the severity of lung lesions induced by virulent bovine respiratory syncytial virus [21]. PaO_2 less than 8.0 kPa (60 mmHg) is used to define hypoxemic respiratory failure; chronic hypoxemia is a serious complication of COPD and is related to increased mortality [22].

The FEV1%pred was remarkably different between the asthma group and the ACOS group; FEV1 measurement plays key roles in establishing the diagnosis of COPD, and decreasing FEV1 is correlated with increased respiratory mortality [23]. In addition, FEV1 was used to monitor a progressive decline in pulmonary function in patients with cystic fibrosis and greater rates of FEV1 decline was associated with poorer survival and the need for earlier lung transplantation [24]. Decreased FEV1%pred was associated with greater airway wall area and thickness and smaller airway luminal area, while higher FEV1%pred implies better airway condition and better ventilatory function [25]. FEV1%pred was significantly lower in the ACOS group than in the asthma group, further confirming that ACOS might be severe in disease condition and narrow in airway. Pathologically, structural changes in the small airways contribute to asthma-like features in ACOS and COPD patients, with a thicker reticular basement membrane than in COPD patients without these features [26].

FEV1/FVC and RV/TLC were significantly different among the 3 groups of patients. FVC has been a standard spirometric measure of pulmonary function in idiopathic pulmonary fibrosis. Longitudinal change in FVC is a widely accepted indication of disease progression [27]. The difference between vital capacity (VC) and FVC can be used as an index to measure the severity of airflow limitation and as a predictor in exercise performance of COPD patients [28]. Moreover, it has been demonstrated that RV/TLC is an independent risk factor for all-cause mortality in COPD [26]. As a parameter used to define the presence of airflow limitation, FEV1/FVC ratio has been recommended as an index to diagnose patients with COPD and those at risk, and a low FEV1/FVC ratio after bronchodilator use might indicate the need for corticosteroid therapy in mild asthma [29–31]. The differences in pulmonary function index in patients with asthma, AECOPD, and ACOS could help to diagnose these 3 diseases more quickly and accurately, which is of great clinical importance [32].

For plasma inflammatory cytokines, the result showed that the IL-4, IL-8, IL-10, and TNF-α levels were significantly different among the control group, asthma group, AECOPD, group and ACOS group. IL-4 level was significantly lower while IL-8 level was significantly higher in the AECOPD group and ACOS group than in the asthma group. As a pleiotropic cytokine, IL-4 plays a crucial role in type 2 T-helper responses and isotype class switching of B cells to IgE synthesis, and it has thus been suggested that IL-4 may have an important role in asthma pathogenesis [34,34]. IL-8 has chemotaxis of target cells to the site of inflammation during the inflammatory process and was observed to be released in greater quantities in patients who continue their smoking habit, and was more elevated in individuals with COPD than in smokers without flow obstruction [12,31]. The different expressions of IL-4 and IL-8 might be useful in differentiating AECOPD and ACOS from asthma. Systemic inflammation is commonly present in ACOS, and ACOS resembles COPD in terms of systemic inflammation [35].

IL-10 level was significantly different between each of the 2 groups. TNF-α level in the asthma group was higher than in the AECOPD group and the ACOS group. IL-10 has been shown to suppress all the pro-inflammatory cytokines, IL-10 activity is mediated by specific cell surface receptor complex, and lower IL-10 levels were reported to be associated with a higher frequency of bronchial asthma and COPD [14,36]. Persistently increased production of TNF-α in response to lipopolysaccharide-stimulated blood mononuclear cells at birth and at 3 months is a predictor for the development of childhood asthma [37].

Correlation studies showed that IL-4 and IL-10 were positively related, while IL-8 and TNF-α were negatively related with FEV1,

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FEV1%pred, and FEV1/FVC, which indicates that the roles of plasma inflammatory cytokine levels in the patients with asthma, AECOPD, and ACOS might be associated with their effects on pulmonary function indexes. However, the detailed mechanisms involved in determining plasma inflammatory cytokine levels and the pulmonary function indexes need further study.

Conclusions

Our study shows that plasma levels of inflammatory cytokines IL-4, IL-8, IL-10, and TNF-α were significantly different among control, asthma, AECOPD, and ACOS groups and might be useful indexes for use in assessing the development of these diseases. The inflammatory cytokines might be related with pulmonary function indexes, which might explain how inflammatory cytokines affect asthma, AECOPD, and ACOS, but the detailed mechanism still needs further investigation.

Acknowledgments

We give our sincere appreciation to the reviewers for their helpful comments on this article.

Competing interests

The authors have declared that no competing interests exist.

References:

1. Raje N, Vyhlidal CA, Dai H, Jones BL: Genetic variation within the histamine pathway among patients with asthma – a pilot study. J Asthma, 2015; 52: 353–62
2. Zahran HS, Bailey CM, Qin X, Moorman JE: Assessing asthma control and associated risk factors among persons with current asthma – findings from the child and adult Asthma Call-back Survey. J Asthma, 2015; 52: 318–26
3. Jia TG, Zhao JQ, Liu JH: Serum inflammatory factor and cytokines in AECOPD. Asian Pac J Trop Med, 2014; 7: 1005–8
4. do Amaral AF, Rodrigues-Junior AL, Terra Filho J et al: Effects of acute magnesium loading on pulmonary function of stable COPD patients. Med Sci Monit, 2008; 14: CR524–29
5. Kherad O, Bridevaux PO, Kaiser L et al: Is Acute exacerbation of COPD (AECOPD) related to viral infection associated with subsequent mortality or exacerbation rate? Open Respir Med J, 2014; 8: 18–21
6. Chang C, Guo Z, Shen N et al: Dynamics of inflammation resolution and symptom recovery during AECOPD treatment. Sci Rep, 2014; 4: 5516
7. Alshabanat A, Zafari Z, Albanyan O et al: Asthma and COPD Overlap Syndrome (ACOS): A systematic review and meta analysis. PLoS One, 2015; 10: e0136065
8. Papaiwannou A, Zarogoulidis P, Porpodis K et al: Asthma-chronic obstructive pulmonary disease overlap syndrome (ACOS): current literature review. J Thorac Dis, 2014; 6(Suppl.1): S146–51
9. Barrecheguren M, Roman-Rodriguez M, Miravitlles M: Is a previous diagnosis of asthma a reliable criterion for asthma-COPD overlap syndrome in a patient with COPD? Int J Chron Obstruct Pulmon Dis, 2015; 10: 1745–52
10. Shen H, Xia L, Lu J: Interleukin-4 in rheumatoid arthritis patients with interstitial lung disease: A pilot study. Indian J Med Res, 2013; 138: 919–21
11. Luzina IG, Lockatell V, Todd NW et al: Alternatively spliced variants of interleukin-4 promote inflammation differentially. J Leukoc Biol, 2011; 89: 763–70
12. Sunaga N, Kaira K, Tomizawa Y et al: Clinicopathological and prognostic significance of interleukin-8 expression and its relationship to KRAS mutation in lung adenocarcinoma. Br J Cancer, 2014; 110: 2047–53
13. Jundi K, Greene CM: Transcription of interleukin-8: How altered regulation can affect cystic fibrosis lung disease. Biomolecules, 2015; 5: 1386–98
14. Sun L, Cornell TT, LeVine A et al: Dual role of interleukin-10 in the regulation of respiratory syncitial virus (RSV)-induced lung inflammation. Clin Exp Immunol, 2013; 172: 263–79
15. Dolgachev VA, Yu B, Sun L et al: Interleukin 10 overexpression alters survival in the setting of gram-negative pneumonia following lung contusion. Shock, 2014; 41: 301–10
16. Despotovic M, Stoimenov TJ, Stankovic I et al: Gene polymorphisms of tumor necrosis factor alpha and antioxidant enzymes in bronchial asthma. Adv Clin Exp Med, 2015; 24: 251–56
17. Chiang LC, Wen TN, Tien CH, Huang JL: [Evidence-based management of acute asthma exacerbation in children]. Hu Li Za Zhi, 2012; 59: 16–23 [in Chinese]
18. Kruis AL, Boland MR, Assendelft WJ et al: Effectiveness of integrated disease management for primary care chronic obstructive pulmonary disease patients: results of cluster randomised trial. BMJ, 2014; 349: g5392
19. Soler-Cataluna JJ, Cosio B, Izquierdo JL et al: Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol, 2012; 48: 331–37
20. M PN: World Medical Association publishes the Revised Declaration of Helsinki. Natl Med J India, 2014; 27: 56
21. Ellis J, Waldner C, Gow S, Jackson M: Relationship of the extent of pulmonary lesions to the partial pressure of oxygen and the lactate concentration in arterial blood in calves experimentally infected with bovine respiratory syncytial virus. Can J Vet Res, 2013; 77: 205–10
22. Saure EW, Eagan TM, Jensen RL et al: Predictors for PaO2 and hypoxemic respiratory failure in COPD-A three-year follow-up. COPD, 2014; 11: 531–38
23. Wedzicha JA, Donaldson GC: Rapid FEV1 decline, early COPD, and angiotensin-converting enzymes? Chest, 2014; 145: 671–72
24. Sanders DB, Bittner RC, Rosenfeld M et al: Pulmonary exacerbations are associated with subsequent FEV1 decline in both adults and children with cystic fibrosis. Pediatr Pulmonol, 2011; 46: 393–400
25. Wang W, Ma D, Li T et al: People with older age and lower FEV1%pred tend to have a smaller FVC than VC in pre-bronchodilator spirometry. Respir Physiol Neurobiol, 2014; 194: 1–5
26. Tho NV, Park HY, Nakano Y: Asthma-COPD overlap syndrome (ACOS): A diagnostic challenge. Respirology, 2015 [Epub ahead of print]
27. du Bois RM, Weycker D, Albera C et al: Forced vital capacity in patients with idiopathic pulmonary fibrosis: test properties and minimal clinically important difference. Am J Respir Crit Care Med, 2011; 184: 1382–89
28. Yuan W, He X, Xu QF et al: Increased difference between slow and forced vital capacity is associated with reduced exercise tolerance in COPD patients. BMC Pulm Med, 2014; 14: 16
29. Perez-Padilla R, Wehrmeister FC, Celli BR et al: Reliability of FEV1/FEV6 to diagnose airflow obstruction compared with FEV1/FVC: the PLATINO longitudinal study. PLoS One, 2013; 8: e67960
30. van Dijk W, Tan W, Li P et al: Clinical relevance of fixed ratio *vs.* lower limit of normal of FEV1/FVC in COPD: Patient-reported outcomes from the CanCOLD cohort. Ann Fam Med, 2015; 13: 41–48
31. Chae EJ, Kim TB, Cho YS et al: Airway measurement for airway remodeling defined by post-bronchodilator FEV1/FVC in asthma: Investigation using inspiration-expiration computed tomography. Allergy Asthma Immunol Res, 2011; 3: 111–17
32. Shin TR, Oh YM, Park JH et al: The Prognostic value of residual volume/total lung capacity in patients with chronic obstructive pulmonary disease. J Korean Med Sci, 2015; 30: 1459–65
33. Luzina IG, Lockatell V, Lavania S et al: Natural production and functional effects of alternatively spliced interleukin-4 protein in asthma. Cytokine, 2012; 58: 20–26

Indexed in: [Current Contents/Clinical Medicine] [SCI Expanded] [ISI Alerting System] [ISI Journals Master List] [Index Medicus/MEDLINE] [EMBASE/Excerpta Medica] [Chemical Abstracts/CAS] [Index Copernicus]

34. Liu Y, Zhuo A, Liu W et al: The -33C/T polymorphism in the interleukin 4 gene is associated with asthma risk: a meta-analysis. J Investig Allergol Clin Immunol, 2014; 24: 114–21
35. Fu JJ, McDonald VM, Gibson PG, Simpson JL: Systemic inflammation in older adults with asthma-COPD overlap syndrome. Allergy Asthma Immunol Res, 2014; 6: 316–24
36. de Moraes MR, da Costa AC, Correa Kde S et al: Interleukin-6 and interleukin-8 blood levels' poor association with the severity and clinical profile of ex-smokers with COPD. Int J Chron Obstruct Pulmon Dis, 2014; 9: 735–43
37. Reyes-Gibby CC, Wang J, Spitz M et al: Genetic variations in interleukin-8 and interleukin-10 are associated with pain, depressed mood, and fatigue in lung cancer patients. J Pain Symptom Manage, 2013; 46: 161–72
38. Halonen M, Lohman IC, Stern DA et al: Perinatal tumor necrosis factor-alpha production, influenced by maternal pregnancy weight gain, predicts childhood asthma. Am J Respir Crit Care Med, 2013; 188: 35–41

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