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Changes in Th1/Th2-producing cytokines during acute exacerbation chronic obstructive pulmonary disease

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Abstract

Objective: This study aimed to explore cytokine serum levels and the ratio of type 1 T helper (Th1)/Th2 cells in patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methods: A total 245 patients diagnosed with AECOPD and 193 patients who progressed to stable COPD after the initiation of treatment in hospital were selected, while a further 50 healthy individuals served as controls. All patients with COPD were diagnosed using Global Initiative for Chronic Obstructive Lung Disease criteria. Serum concentrations of interleukin (IL)-2, interferon (IFN)-γ, IL-4, IL-10, IL-17, and immunoglobulin (Ig)E were measured using enzyme-linked immunosorbent assays.

Results: AECOPD patients had higher levels of IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE than those with stable COPD or controls. Intriguingly, the ratios of Th1/Th2 and IL-17/IgE were lower in AECOPD patients compared with the other two groups. These data suggest that AECOPD patients produce more IgE and have more differentiated Th2 cells than other groups.

Conclusion: Our findings suggest that an imbalance of circulating $CD4^+$ T cell subsets correlates with AECOPD, and that a shift of Th1/Th2 and IL-17/IgE ratios may be caused by increased Th2 cell production.

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Introduction

Patients with chronic obstructive pulmonary disease (COPD) who show a sudden deterioration in lung function are said to suffer from acute exacerbation COPD (AECOPD). This is characterized by rapidly worsening respiratory symptoms that can have a negative effect on their quality of life and which are associated with an increased risk of mortality.[1] Patients with AECOPD are prone to develop respiratory failure and progressive chronic disease characterized by irreversible airway obstruction.[2] Infections, tobacco, toxic particle inhalation, and air pollution have all been reported to induce immune system malfunction and the over-secretion of cytokines and chemotactic factors that can destroy immunologic tolerance.[3–5]

T lymphocytes, especially $CD4^+$ T lymphocytes, play a central role in immune protection through their capacity to assist B cells.[6] Previous studies showed that type 1 T helper (Th1) and Th2 cells were increased in COPD patients compared with healthy controls.[7,8] Th1 cells mainly secrete interleukin (IL)-2 and interferon (IFN)-γ which mediate cellular immunity, while Th2 cells secrete IL-4 and IL-10 that mediate humoral immunity. Moreover, only IFN-γ/IL-4 and IFN-γ/IL-2 ratios have been compared between AECOPD and stable COPD patients,[9] while the relevance of changes in the Th1/Th2 ratio in AECOPD remains unclear. Besides Th1 and Th2 lymphocytes, Th17 cells, which produce IL-17, have recently been identified as a subset of $CD4^+$ Th cells.[10] In animal experiments, Th-17 cells were shown to protect the host from respiratory infections by producing a variety of cytokines and chemokines.[11,12] Previous reports have shown that IL-17 levels are significantly increased in the bronchial submucosa of COPD patients.[13] However, the mechanism of action of IL-17 in AECOPD remains to be elucidated.

A number of studies reported that patients with smoking-induced COPD have high serum immunoglobulin E (IgE) levels. This in turn was confirmed to be associated with the development of COPD.[14] Additionally, IgE has the capacity to induce the production of Th2-type cytokines and the development of airway inflammation and hyper-responsiveness in mice.[15–18] However, the role of IgE in AECOPD is still unclear.

Therefore, the purpose of this study was to analyze levels of IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE in AECOPD and stable COPD patients to determine whether a correlation exists between Th1/Th2 and IL-17/IgE ratios in AECOPD.

Materials and methods

Study subjects

A total of 245 patients diagnosed with AECOPD, 193 patients who progressed to stable COPD after the initiation of treatment, and 50 healthy controls were enrolled in this investigation. All patients were evaluated according to 2015 diagnostic criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) as follows: 1) COPD: patients with difficulty in breathing, with a cough, sputum, and

pulmonary function testing showing a post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity ratio <70% and FEV1 <80%; 2) AECOPD: a sudden worsening of COPD symptoms (shortness of breath, quantity and color of phlegm) that typically last for several days; and 3) Controls: COPD-free individuals with normal pulmonary function. Airflow obstruction was determined by spirometry. Biological specimens and clinical datasets were obtained from patients with COPD and who were enrolled in the study.

Each patient was given a COPD assessment test (CAT)[19] and a questionnaire with eight questions concerning the presence of coughing, sputum, chest distress, asthma, and activity limitations caused by COPD at home and outdoors. For each question, a score of 0–5 was selected by the patients. The total score (0–10: slight effect; 11–20: median effect; 21–30: severe effect; 31–40: extreme severe effect) was then calculated to determine the effect of COPD on the daily activity level. A modified UK Medical Research Council (mMRC)[20] evaluation was used to assess dyspnea levels in COPD patients. An mMRC score of ≥ 2 was considered to be an indication of severe dyspnea. Patients using oral steroids, with apparent infections (urinary tract infections or pneumonia) or signs of sepsis, or who had chronic diseases such as diabetes, renal failure, cancer, or any other respiratory diseases were excluded from the study.

This study was approved by the human research ethics committee of Beijing Chaoyang Hospital affiliated with Capital Medical University (reference number: 2014-KE-124); consent forms were obtained from each patient upon admission to the emergency department.

Peripheral blood assays

Peripheral venous blood samples (5 ml) were collected from each patient when they were enrolled in the investigation. The blood was centrifuged at $724 \times g$ for 20 min to separate the serum, which was stored at $-80°C$ for subsequent analysis.

Cytokine enzyme-linked immunosorbent assay

Levels of IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE were determined by enzyme-linked immunosorbent assay according to the manufacturer's recommendations (Cloud-Clone Corp., Houston, TX).

Statistical analysis

SPSS software (SPSS Inc., Chicago, IL, USA) was used to analyze data. Normally distributed data were expressed as means $\pm$ standard deviation, while those with a non-normal distribution were expressed as median values (with upper and lower quartiles). Comparisons were made by a rank-sum test (Kruskal–Wallis test). P values < 0.05 were considered statistically significant.

Results

Patient findings

A summary of patient demographics and clinical characteristics is shown in Table 1. All AECOPD and COPD patients were treated with aminophylline, ambroxol hydrochloride, long-acting anticholinergic drugs, and long-acting β_2 receptor agonists. There was no significant difference in medicine dosage between the two groups. No significant difference in patient age was found between control and AECOPD groups. There were significantly more smokers in the AECOPD group compared with the control group (P=0.02; Table 1).

In AECOPD patients, pulmonary function deteriorated significantly compared with stable COPD patients (P<0.001;

Table 1. Patient demographic and clinical characteristics

Variable	Group			*P*-value
	AECOPD (n=245)	COPD (n=193)	Control (n=50)	
Age (years), mean ± SD	60.21±11.18		58.37±11.92	0.6321
Male/Female	175/70		28/22	0.0157
Smokers (%)	169 (68.98)		16 (32)	0.0219
Obesity (BMI > 25) (%)	39 (15.92)		12 (24)	0.3521
Ambroxol hydrochloride (mg/day)	44.45±2.82	44.32±3.11		0.3090
Aminophylline (g/day)	0.59±0.12	0.58±0.12		0.1023
Budesonide/Formoterol	60 μg/4.5 μg	60 μg/4.5 μg		
Tiotropium bromide, Spiriva Respimat®	1 daily dose	1 daily dose		

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; BMI, body mass index.

Table 2. Comparison of pulmonary function in AECOPD and stable COPD

Variable	AECOPD (n=245)		Stable COPD (n=193)		χ^2	*P*-value
	Subjects	Ratio (%)	Subjects	Ratio (%)		
GOLD (grade)					20.691	<0.001
1	4	1.64	5	5.66		
2	49	20.00	73	37.72		
3	182	74.28	114	55.91		
4	10	4.08	1	0.71		
CAT (score)					3.848	0.05
0–10	37	15.10	23	15.04		
11–20	58	23.67	70	34.69		
21–30	132	53.88	98	49.13		
31–40	18	7.35	2	1.14		
mMRC (score)					26.517	<0.001
0–1	83	33.88	113	54.29		
≥2	162	66.12	80	45.71		
Pulmonary function					74.728	<0.001
A	8	3.26	25	16.57		
B	62	25.71	109	52.22		
C	159	64.49	57	30.07		
D	16	6.53	2	1.14		

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; GOLD, Global Initiative for Chronic Obstructive Lung Disease; CAT, COPD assessment test; mMRC, modified Medical Research Council. A, B, C, and D rank the lung function in patients with COPD, see Table 3.

Table 2). Lung function in COPD patients was assessed using GOLD, CAT, and mMRC questionnaires. As shown in Figure 1, the higher the grade or score, the greater the deterioration in AECOPD patients.

IL-2, IFN-γ, IL-4, IL-10, IL-17 and IgE increase in COPD patients

The levels of cytokines IL-2, IL-4, IL-10, IL-17, IFN-γ, and IgE were significantly higher in AECOPD patients compared

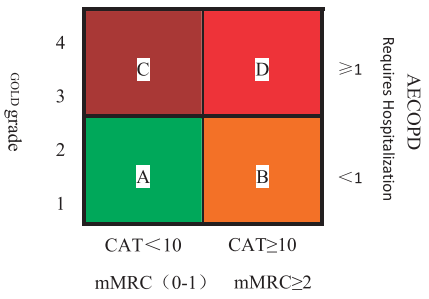

Figure 1. Comprehensive assessment of lung function in COPD patients.
A, fewer symptoms and low risk; B, more symptoms and low risk; C, fewer symptoms and high risk; D, more symptoms and high risk.

with stable COPD and control groups (all $P<0.001$; Table 3). Analysis of all data by rank sum test indicated that IgE increased obviously from A to D in the AECOPD group (Table 4). Gaussian distribution was used to show that the data were not normally distributed (Tables 5, and 6).

Th1/Th2 and IL-17/IgE ratios in COPD patients

The Th1/Th2 ratio was calculated to determine the skew of Th1/Th2 cell polarity. The ratios of IFN-γ/IL-10 and IL-2/IL-10 in AECOPD patients were significantly lower

Table 3. Comparison of cytokines between AECOPD, stable COPD and control groups

Variable	Group	Mean conc. (pg/mL)	Mean rank	χ^2	df	*P*-value
IL-2				95.17	2	<0.001
	Control	541.07	30.63			
	Stable COPD	906.35	97.33			
	AECOPD	1086.65	140.16			
IFN-γ				90.417	2	<0.001
	Control	570.47	29.05			
	Stable COPD	940.51	104.13			
	AECOPD	1067.38	137.20			
IL-4						
				97.264	2	<0.001
	Control	167.15	27.23			
	Stable COPD	310.09	105.17			
	AECOPD	354.24	135.82			
IL-10				35.782	2	<0.001
	Control	186.29	62.93			
	Stable COPD	236.94	97.06			
	AECOPD	272.42	128.82			
IL-17				30.017	2	<0.001
	Control	275.59	62.23			
	Stable COPD	338.24	106.33			
	AECOPD	361.75	124.98			
IgE				120.886	2	<0.001
	Control	189.79	23.93			
	Stable COPD	355.95	92.41			
	AECOPD	445.77	146.43			

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; Conc., concentration; df, degrees of freedom; IL, interleukin; IFN, interferon; Ig, immunoglobulin.

Table 4. Gaussian distribution for the concentration of cytokines between severities of AECOPD

	Central tendency and discrete tendency					
Variables	Std. dev	Median	Range	P_5–P_{95}	*Sk*	*Ku*
IL-2						
A	204.43	868.57	399.83	410.08 – 1425.73	1.023	
B	216.05	1023.90	834.03	934.40 – 1105.33	0.551	−0.373
C	212.37	1098.78	966.18	1070.77 – 1173.58	0.057	−0.518
D	67.87	1068.57	205.83	1008.75 – 1134.28	0.430	0.276
IFN-γ						
A	32.59	1020.24	64.9	935.79 – 1097.72	−0.475	
B	209.17	1074.43	823.34	970.17 – 1135.66	−0.008	−0.542
C	198.22	1101.46	957.94	1026.69 – 1121.92	−0.061	−0.258
D	285.66	1005.21	834.96	812.40 – 1340.80	0.617	0.146
IL-4						
A	61.23	382.00	119.83	244.49 – 548.72	1.01	
B	42.89	358.00	217.87	343.20 – 377.13	0.448	0.872
C	52.96	350.59	324.53	339.97 – 365.81	−0.476	2.007
D	24.51	330.18	74.67	303.51 – 348.86	−0.518	0.202
IL-10						
A	35.48	262.36	70.47	169.45 – 345.72	−0.595	
B	72.17	260.16	250.40	239.99 – 297.09	0.574	−0.643
C	62.12	279.66	305.19	263.85 – 293.69	0.094	0.042
D	75.80	224.67	204.53	160.97 – 301.17	0.291	−1.060
IL-17						
A	210.90	304.74	400.71	−143.12 – 904.70	1.412	
B	77.20	403.75	304.50	384.33 – 445.40	−0.332	−0.035
C	81.87	417.78	349.10	379.05 – 418.38	−0.274	−0.398
D	80.33	438.30	250.09	370.28 – 518.87	0.426	0.533
IgE						
A	18.65	301.92	34.89	247.96 – 340.64	−1.532	
B	20.74	346.23	70.47	333.80 – 350.20	0.082	−1.049
C	42.38	440.27	159.11	431.68 – 452.04	0.608	−0.309
D	20.43	545.92	56.53	536.35 – 574.14	1.716	2.988

A, less symptoms and low risk; B, more symptoms and low risk; C, less symptoms and high risk; D, more symptoms and high risk. (As shown in the figure 1).

than those in stable COPD patients and controls, while IFN-γ/IL-4 was lower than in controls. However, these ratios were not significantly different between stable COPD patients and controls. The IL-17/IgE ratio was significantly decreased ($P<0.001$) in AECOPD patients because of improved IgE levels (Tables 7, 8). Analysis of the correlation between cytokine ratios and clinical outcomes showed that AECOPD patients with IL-2/IL-10 ratios >4.18 and IL-17/IgE ratios <0.82 had more ICU admissions, longer hospital stays, higher mortality rates, and more readmissions in 30 and 90 days (Table 9).

Discussion

There are conflicting reports regarding changes in cytokines levels in COPD

Table 5. Gaussian distribution of cytokine concentrations in AECOPD, stable COPD, and control groups

		Central tendency and discrete tendency					
Variable	Group	SD	Median	Range	P_5–P_{95}	*Sk*	*Ku*
IL-2							
	AECOPD	211.22	1070.81	966.18	1045.78–1127.53	0.199	−0.511
	Stable COPD	211.17	897.50	948.96	854.44–958.26	0.609	0.150
	Control	203.80	540.57	725.67	475.89–606.25	0.195	−0.914
IFN-γ							
	AECOPD	202.80	1090.19	967.31	1028.32–1106.44	0.055	−0.274
	Stable COPD	239.74	969.88	1465.15	881.58–999.45	1.152	3.609
	Control	164.35	561.03	716.49	517.91–623.03	0.351	0.1080
IL-4							
	AECOPD	49.86	351.61	324.53	344.54–363.94	−0.068	2.363
	Stable COPD	84.40	311.72	375.04	289.36–330.36	−0.189	−0.267
	Control	59.46	159.62	255.28	148.14–185.18	0.525	−0.162
IL-10							
	AECOPD	65.51	275.18	305.19	259.80–285.03	0.199	−0.289
	Stable COPD	56.30	240.02	350.46	223.10–250.78	0.258	1.474
	Control	77.35	200.53	283.60	161.56–211.03	−0.189	−0.748
IL-17							
	AECOPD	78.85	358.37	369.99	346.71–376.79	0.087	−0.574
	Stable COPD	81.04	337.76	322.23	318.32–358.16	0.353	−0.820
	Control	58.94	285.70	277.66	256.74–294.44	−1.002	1.460
IgE							
	AECOPD	64.97	446.36	294.92	433.26–458.29	−0.068	−0.330
	Stable COPD	84.14	336.01	403.84	335.26–376.63	0.526	0.236
	Control	59.22	184.77	254.58	170.85–208.73	0.617	0.075

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; IL, interleukin; IFN, interferon; Ig, immunoglobulin; Sk, skewness; Ku, kurtosis.

patients. However, systemic and local changes may be an indicator of disease severity. The rapid deterioration in lung function associated with AECOPD is, for the most part, associated with bacterial infections. Systemic inflammation is considered one of the major pathophysiological causes of AECOPD. In this study, we compared levels of cytokines and ratios of Th1/Th2 and IL-17/IgE between patients with AECOPD and those with stable COPD. Our results demonstrated that cytokine and IgE secretion from Th1, Th2, and Th17 cells is correlated with disease severity, as shown by mortality rates and hospital admissions. The ratios of Th1/Th2 and IL-17/IgE can be considered Th indexes that indicate the severity of AECOPD according to clinical outcome. We found that patients with AECOPD have low Th1/Th2 and IL-17/IgE ratios even though Th1, Th2, and Th17 cells and IgE levels were all increased during AECOPD.

$CD4^+$ T cells can differentiate into either Th1 or Th2 cells, depending on the type of cytokines they produce. Th1 cells mainly secrete IL-2, IFN-γ, and tumor necrosis factor (TNF)-β.[21] A previous study revealed an increased number of IFN-γ-producing lymphocytes and a stronger IFN-γ signal in the lungs of COPD patients.[22] A significant increase in IL-2

Table 6. Comparison of cytokines between different grades of AECOPD

Variables	Concn. Mean (pg/mL)	Mean Rank	χ^2	df	*P-value*
IL-2			6.082	3	>0.05
A	917.91	30.67			
B	1019.86	43.43			
C	1122.18	57.93			
D	1071.52	51.57			
IFN-γ			0.764	3	>0.05
A	1016.76	41.33			
B	1052.92	51.41			
C	1074.30	54.97			
D	1076.60	52.29			
IL-4			5.768	3	>0.05
A	396.61	73.33			
B	360.16	55.11			
C	352.89	52.93			
D	326.19	29.36			
IL-10			3.288	3	>0.05
A	257.58	46.33			
B	268.54	50.06			
C	278.78	56.82			
D	231.07	37.14			
IL-17			2.390	3	>0.05
A	380.79	40.67			
B	414.86	57.41			
C	398.72	51.30			
D	444.57	65.57			
IgE			74.281	3	<0.001
A	294.30	2.00			
B	342.00	17.00			
C	441.86	65.00			
D	555.24	103.00			

A, less symptoms and low risk; B, more symptoms and low risk; C, less symptoms and high risk; D, more symptoms and high risk. (As shown in the figure 1).

and IFN-γ levels was also observed in COPD patients in another investigation.[23] In the present study, abundant levels of IL-2 and IFN-γ were induced in AECOPD patients, which were significantly higher than in control and stable COPD groups. Additionally, IL-2 levels in AECOPD without viral infections were previously shown to be higher than in the control group.[24] These data indicate that the number or function of Th1 cells may be enhanced during AECOPD progression.

Th2 cells mainly secrete IL-4, IL-10, and IL-6, which stimulate the proliferation of B lymphocytes to produce IgG and IgE, and mediate humoral immunization.[25] Additionally, high levels of IL-4 can aggravate COPD by activating invariant natural killer T cells.[26] IL-10 is a classical stimulator of B lymphocytes[27] that suppresses Th1 cells to produce TNF-α, IL-2, and IFN-γ by inhibiting the expression of nuclear factor-κB, which is a key inflammatory transcription factor. Our results showed that IL-4

Table 7. Gaussian distribution of Th1/Th2 ratio changes in AECOPD, stable COPD, and control groups

		Central tendency and discrete tendency					
Variable	Group	Std. dev	Median	Range	P5–P95	*Sk*	*Ku*
IFN-γ/IL-10							
	AECOPD	1.35	3.97	8.39	3.90–4.42	1.347	4.112
	Stable COPD	1.51	3.79	11.71	3.76–4.51	4.402	25.886
	Control	4.18	2.77	20.61	2.92–5.60	2.967	9.541
IFN-γ/IL-4							
	AECOPD	0.77	3.01	4.57	2.92–3.22	1.227	2.895
	Stable COPD	1.26	2.94	6.06	2.97–3.59	1.155	1.368
	Control	2.19	3.63	10.14	3.28–4.68	1.491	2.779
IL-2/IL-10							
	AECOPD	1.21	4.03	6.10	3.94–4.42	1.066	1.748
	Stable COPD	1.42	3.61	10.69	3.65–4.35	3.798	19.991
	Control	2.66	2.86	12.58	2.77–4.47	2.322	5.896
IL-2/IL-4							
	AECOPD	0.85	3.09	6.55	2.97–3.30	2.126	10.649
	Stable COPD	1.30	2.78	6.57	2.87–3.50	1.577	3.178
	Control	1.51	3.18	6.05	3.01–3.97	0.867	0.373
IL-17/IgE							
	AECOPD	0.17	0.82	0.79	0.78–0.85	0.085	−0.610
	Stable COPD	0.35	0.94	1.74	0.92–1.09	1.183	1.732
	Control	0.39	1.44	1.53	1.40–1.65	0.709	−0.076

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; IL, interleukin; IFN, interferon; Ig, immunoglobulin.

and IL-10 levels were significantly higher in the AECOPD group than in stable COPD and control groups, though levels did not increase in line with the severity of AECOPD. Additionally, IL-4 was found to be dramatically increased in *Mycoplasma pneumoniae*-induced airway diseases, including AECOPD.[28] Moreover, Hackett et al.[29] demonstrated that IL-10 increased between 24–48 h after lipopolysaccharide was injected in an AECOPD model. These data indicate that cytokines secreted by Th2 cells play an important role in reducing inflammation.

Previous studies reported increased IL-17 levels in AECOPD patients, which may lead to neutrophil recruitment and infiltration into inflammatory sites, finally aggravating AECOPD by stimulating lung microvascular endothelial cells to produce CXCL8 (IL-8), E-selectin, vascular cell adhesion molecule-1, and intercellular adhesion molecule-1. Thus, IL-17 is a key starter of neutrophilic inflammation.[30] In this study, we found that IL-17 was increased in AECOPD compared with stable COPD or control groups. These data suggested that IL-17 may induce acute inflammation, recruit Th17 cells, and activate Th1 cells to promote a cellular immune response, thus converting AECOPD to stable COPD.

Because asthma and COPD share the same pathological characteristics,[31] we speculate that elevated serum IgE levels might result in more serious symptoms and reduced lung function. Previous studies confirmed that Th cells and their associated cytokines play an important role in IgE

Table 8. Comparison of Th1/Th2 ratio changes in AECOPD, stable COPD, and control groups

Variables	Group	Mean	Mean rank	χ^2	df	*P*-value
IFN-γ/IL-10				11.621	2	0.003
	Control	4.26	76.93			
	Stable COPD	4.14	111.00			
	AECOPD	4.16	114.86			
IFN-γ/IL-4				4.336	2	0.114[a]
	Control	3.98	123.23			
	Stable COPD	3.28	103.45			
	AECOPD	3.07	99.98			
IL-2/IL-10				19.844	2	<0.001
	Control	3.62	70.68			
	Stable COPD	4.00	103.53			
	AECOPD	4.18	121.01			
IL-2/IL-4				1.450	2	0.484
	Control	3.49	113.00			
	Stable COPD	3.18	98.85			
	AECOPD	3.13	106.84			
IL-17/IgE				83.71	2	<0.001
	Control	1.52	180.95			
	Stable COPD	1.00	108.92			
	AECOPD	0.82	76.9			

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; df, degrees of freedom; IL, interleukin; IFN, interferon; Ig, immunoglobulin.
[a]$P<0.05$, AECOPD vs Control.

synthesis.[32] IL-4 increases the level of IgE, while IFN-γ inhibits it,[33] indicating that both Th1 and Th2 cells regulate the secretion of IgE. The balance of Th1/Th2 may therefore be the crucial factor in the regulation of IgE. In this study, we found that IgE, IL-4, and IL-10 increased in AECOPD, suggesting that the immune response in this case was predominantly caused by Th2 cells. Hyper-activated Th2 cells may secrete excess IL-4 and IL-10 cytokines, thus raising IgE levels[34] and leading to airway hyper-responsiveness. We also found that the levels of IL-17 and IgE increased and the IL-17/IgE ratio decreased in AECOPD patients, while IgE secretion remarkably increased from A to D in the AECOPD group; together these indicate that IgE is further induced in AECOPD.

Generally, the Th1/Th2 ratio is maintained in a dynamic balance, but it becomes skewed and the polarity shifts to one side when the body reacts to foreign antigens.[35] Our results suggest that IL-4 activates Th2 cells and inhibits Th1 proliferation. Hence, Th2 cells had a greater influence than Th1 cells in shifting the Th1/Th2 ratio polarity to the Th2 side. Similar results were also observed by Tsoumakidou et al.[36] A possible explanation for the Th1/Th2 shift could be microbial infection, which induces Th2 cell activation and proliferation.[37,38] Th2 cells then enhance IgE secretion by activating B lymphocytes. Furthermore, the Th1/Th2 shift results in an increased IgE production and low IL-17/IgE ratio; hence, the ratios of Th1/Th2 (especially IL-2/IL-10) and IL-17/IgE might be considered a Th index that represents the severity of

Table 9. Correlation of cytokine ratios and clinical outcomes in AECOPD

	AECOPD			
Clinical outcome	Total	IL-2/IL-10 < 4.18 + IL-17/IgE > 0.82	IL-2/IL-10 > 4.18 + IL-17/IgE < 0.82	*P*-value
ICU admission (%)	245	62 (25.31)	183 (74.69)	0.015
Length of stay in hospital (days)	15.4±3.8	7.8±1.1	17.5±3.5	0.028
Length of stay in ICU (days)	8.2±1.3	7.1±0.8	9.5±1.2	0.137
30-day mortality (%)	18 (7.35)	5 (27.78)	13 (72.22)	0.035
90-day mortality (%)	31 (12.65)	9 (29.03)	22 (70.97)	0.031
In hospital mortality	52 (21.22)	14 (26.92)	38 (73.08)	0.025
30-day readmission	34 (13.88)	11 (32.35)	23 (67.65)	0.037
90-day readmission	10 (4.08)	4 (40.00)	6 (60.00)	0.081

AECOPD, acute exacerbation of chronic obstructive pulmonary disease; ICU, intensive care unit; IL, interleukin; Ig, immunoglobulin.

AECOPD. Our clinical outcome data showed that lower ratios of IL-2/IL-10 and IL-17/IgE aggravate AECOPD despite increased levels of IgE and Th1, Th2, and Th17 cells. However, a larger sample size is needed to support the viewpoint that the Th index could be used to assess AECOPD severity.

Conclusion

In this study, we investigated cytokines secreted by Th1, Th2, and Th17 cells in COPD patients, and found that IL-2, IFN-γ, IL-4, IL-10, IL-17, and IgE were all increased in AECOPD patients compared with stable COPD and control groups. Moreover, a high IL-2/IL-10 ratio and low IL-17/IgE ratio were closely correlated with the severity of AECOPD.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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