ORIGINAL ARTICLE

Correlation of Sputum Eosinophils and total serum IgE with FEV_1/FVC ratio in asthma-COPD overlap

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ABSTRACT

Background: Asthma – Chronic Obstructive Pulmonary Disease (COPD) overlap (ACO) is a heterogeneous disorder characterized by persistent airway obstruction. Eosinophilic airway inflammation is associated with lung function disorders.
Aim: To show the correlation of sputum eosinophil levels, total serum IgE and the post-bronchodilatorFEV_1/FVC.
Methods: A cross-sectional study was conducted on outpatients in the asthma-COPD clinic. Diagnosis of ACO was based on 2 major criteria or 1 major and 2 minor criteria. We performed the following inflammatory biomarker examinations: sputum eosinophil levels, total serum IgE from peripheral blood, and pre- and post-bronchodilator spirometry examination. The association of sputum eosinophil level, total serum IgE and post-bronchodilator FEV_1/FVC ratio was analyzed.
Results: Of 80 outpatients registered from November 2017-June 2018, 26 patients met the inclusion criteria, and only 19 patients had complete data. The average age was approximately 58.3 years, the sputum eosinophil level (%) was 17.68 ± 10.58, serum IgE (IU/ml) was 161.1±161.2, post-bronchodilator FEV_1(%) was 64.89±14.51, post-bronchodilator FVC (%) was 76.53 ± 13.05, and post-bronchodilator FEV_1/FVC (%) was 60.74 ± 7.95. The sputum eosinophil level was >3%, but there was no correlation with FEV_1 (r 0.345, p=0.1480) or the FEV_1/FVC ratio (r 0.381, p = 0.108). High total serum IgE did not correlate with FEV_1 (r -0.247, p = 0.309) but was negatively correlated with FEV_1/FVC (r -0.486, p <0.050) with moderate strength.
Conclusion: ACO patients had eosinophilic airway inflammation, and total serum IgE correlated with persistent airway obstruction.
Keywords: Eosinophils; Inflammation; Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome; Airway obstruction

INTRODUCTION

Asthma and COPD are described as two different diseases that often overlap[1]. There is a group of patients who are not in the category of asthma and COPD but have mixed features of asthma and COPD. The experts refer to this overlap as asthma-COPD (ACO). ACO is one of the most important problems in the field of pulmonology because it often leads to exacerbation, thus resulting in high healthcare costs[2].

ACO is characterized by persistent airway obstruction accompanied by several features of asthma and COPD[3,4]. Asthma is based on eosinophilic inflammation, which is Th2dominant[5], while COPD involves neutrophils, macrophages and CD8+ cells[6]. In ACO there are shared features of asthma and COPD, so there is a mixed expression of inflammatory patterns of Th1 (characteristic of COPD) and Th2 (characteristic of asthma)[7]. A study reported the activation of the Th2 immune response in ACO[8].

There is a correlation between eosinophilic airway inflammation and poor lung function in adult asthma.[9] High blood eosinophil counts are known to be associated with airflow obstruction[10]. Blood eosinophils do not predict an increase in FEV_1 decline in adult asthmatic patients[9,11], but a greater decline in FEV_1 is found in patients with COPD with high blood eosinophils who do not receive inhaled corticosteroid therapy[12]. The aim of this study was to showthat sputum eosinophil levels and total serum IgE are associated with persistent airflow limitation in patients with ACO.

MATERIALS AND METHODS

This study was an analytical cross-sectional study in outpatientsasthma-COPD clinic at a tertiary hospital. All patients gave informed consent, and this study received ethical approval from the Health Research Ethics Committee of Dr Soetomo Hospital in Surabaya, Indonesia, no. 727/Panke.KKE/XII/2017.
Population and sample: The population was asthma-COPD patients who were treated at the asthma- COPD clinic of Dr Soetomo Hospital in Surabaya and who fulfilled inclusion criteria from November 2017 to June 2018. Of 80 patients selected, 26 patients met the inclusion criteria. Seven patients were unable to undergo sputum induction or had unreadable specimens, so only 19 patients, consisting of 9 males and 10 females, were available.
ACO criteria: Asthma-COPDoverlapcriteriabasedon: patients asthmawi than onset> 40 year, FEV_1/FVC<0.7 postbronchodilatorwithorwithoutsmokinghistory[13,14]. atients who participated in this study had a history of allergies based on a physician's diagnosis, such as allergic rhinitis, eczema, and asthma. The patients were excluded from the study if they had active pulmonary TB or lung cancer or experienced acute exacerbations within 4 weeks before the study began.
Examination of sputum eosinophil levels: Sputum induction was examined in accordance with Pin et al[15]. Before induction FEV_1 was examined. The patients inhaled 2.5 mg salbutamol and 7 ml 3% saline for 15-20 minutes using an Omron NE-C28 nebulizer jet at a speed of 0.25-0.75ml/minute. After induction, the patients gargled and

expectorated the sputum. The sputum was stored in sterile pots. The sputum was regarded as adequate if at least 3 ml was collected. A differential count of inflammatory cells from sputum induction specimens was carried out by counting total cells with a hemocytometer, and the determination of the differential count was performed with Cyto Diff differential calculation using flowcytometry (FC500; Beckman Coulter) with CytoDiff reagents and analysis software (CytoDiffCXP 2.0; Beckman Coulter, Miami, FL, USA). The differential count of sputum cells included eosinophils, basophils, neutrophils, lymphocytes, and monocytes.

IgE examination: Total blood immunoglobulin E was examined by chemiluminescent microparticle immunoassay (ADVIA Centaur XPT, Siemens, Tarrytown, NY, USA) from peripheral blood samples. Total serum IgE was regarded as increasing if serum total IgE was >100 IU/ml[16].

FEV_1 and FVC examination: Spirometry examination was carried out by experienced technicians when the patients did not have exacerbations or an infection. Spirometry (AUTOSPIROAS 500, Minato, Osaka, Japan) was used to evaluate pulmonary function and bronchodilator tests. FEV_1 and post-bronchodilator FEV_1/FVC was measured 15 minutes after the administration of 400 mcg Salbutamol.

Statistical analysis: Data were presented in mean ± standard deviation format. A normal distribution test was performed using the Shapiro-Wilk test, revealing that total IgE and FEV_1data had abnormal distributions. Correlation between IgE and FEV_1 and the FEV_1/FVC ratio was tested by means of the Spearman correlation test. A value of p <0.05 was regarded as a statistically significant difference.

RESULTS

The mean serum IgE level was 161.19±161.24 IU/ml (range: 71.31-724.57 IU/ml). The total IgE level was high in these patients with ACO. According to Kobayashi et al[17] the best diagnostic cut-off value of the total serum IgE level was 434 IU/L for ACO. The sputum eosinophil level was 17.68±10.58 (range 1.09-34.38). The sputum eosinophil level was high if ≥3%[16]. Table 2 depicts the correlation between sputum eosinophil level, serum IgE and FEV_1 and FEV_1/FVC. No correlation was observed between sputum eosinophil level and FEV_1 and the FEV_1/FVC ratio. No correlation was observed between serum IgE and FEV_1. However, there was a negative correlation between serum IgE and the FEV_1/FVC ratio (r=-0.486, p=0.035), and the correlation was moderate.

Table 1: ACO patient characteristics

Characteristics	**Results**
Age (years)	60.54 ± 8.64
Gender	
Male	10 (52.6%)
Female	9 (47.4%)
Smoking (current and ex-smoker)	9 (47.3%)
Asthma history	12 (63.1%)
Sputum eosinophil (%)	17.68±10.58
Sputum eosinophil >3%	16/19 (84.2%)
Serum IgE (IU/ml)	161.19±161.24
Total IgE>100 IU/ml	12/19 (63.1%)
FEV_1post-BD (ml) FEV_1postBD (% pred)	1634.21± 697.06 64.89±14.51
FVC post-BD (ml) FVCpostBD (% pred)	2699.47±1131.76 76.53±13.05
FEV_1/FVC post-BD (%)	60.74±7.95
Pharmacotherapy	
LAMA+LABA/ICS	3 (15.7%)
LABA/ICS	15 78.9%)
Atopy	12 (63.1%)

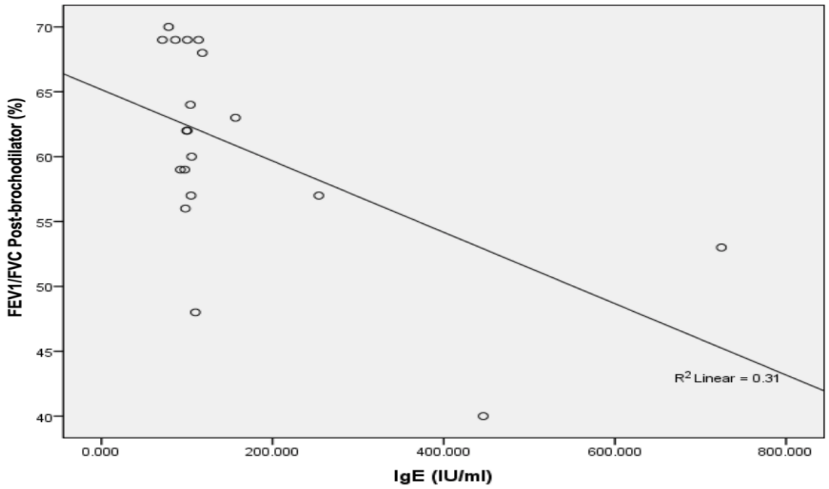
LAMA, Long acting muscarinic agent; LABA, Long acting β2 agonist; ICS, Inhaled corticosteroid; BD, Bronchodilator

Table 2: Correlation between serum IgE, sputum eosinophil level and spirometry in ACO

		ACO	
		r	**P**
IgE	vs FEV_1/FVC	-0.486	0.035
IgE	vs FEV_1	--0.247	0.309
Sputum eosinophil	vs FEV_1/FVC	0.381	0.108
Sputum eosinophil	vs FEV_1	0.345	0.148
Sputum eosinophil	vs IgE total	-0.311	0.195

IgE: Immunoglobulin E; ACO: Asthma-COPD overlap; FEV_1: Forced expiratory volume in one second; FVC: Forced vital capacity

Fig 1. Correlation between IgE and the FEV_1/FVC ratio. The correlation coefficients (r) and significance (p) are r=-0.486 and p=0.035, respectively.



DISCUSSION

ACO is a heterogeneous disorder. The shared clinical characteristics of asthma and COPD are based on inflammation and airway obstruction.[7] Because both asthma and COPD are inflammatory airway diseases, the overlap of both diseases should show evidence of Th1 inflammation (neutrophilic inflammation) and Th2 inflammation (eosinophilic inflammation)[7]. This statement is supported by Tommola et al., who reported ACO patients with a neutrophil predominant inflammatory pattern[18], whereas Kalinina et al. reported Th2 immune response activity[8].

There are several clinical criteria for identification of ACO[7]. In addition, inflammatory biomarkers can be used to support the diagnosis of ACO.[17] Sputum eosinophil count and total IgE level significantly increased in ACO[17,19]. According to Kobayashi et al., the best diagnostic cut-off values of blood eosinophil count and total serum IgE levels are 156.2/mm^3 and 434 IU/ml, respectively. Another study reported a cut-off of sputum eosinophil level of 2.5% for ACO detection with a sensitivity and specificity of 82.4% and 84.8%, respectively.[19] Studies of ACO patients reported that the serum IgE level was 161.16 IU/ml and sputum eosinophil level was 17.6%. These high serum total IgE and sputum eosinophil levels can be used to support the diagnosis of ACO.

The correlation of eosinophilic inflammation with ACO was recognized after a report of an increase in serum IgE and sputum eosinophil level in patients with ACO[19]. In addition, there are reports of the association between increased eosinophil, IgE and low lung function in ACO[16]. Eosinophil, FeNO, and periostin are biomarkers that can be used to detect eosinophilic airway inflammation[7,20]. Sputum cytology for exploration of airway inflammation has long been used. [20] An amount of sputum eosinophils as much as 3% has been categorized as a high sputum eosinophil level.[16] In this study, we used sputum eosinophils and total serum IgE as markers of airway eosinophilic inflammation. In this study, the mean value of sputum eosinophils was 17.6%. Kitaguchi reported an average of sputum eosinophils of 12.3%[19].

Persistent eosinophilic inflammation is a risk factor for airflow obstruction[10]. The correlation between eosinophilic inflammation and airflow obstruction is weak[20]. A study reported that patients with eosinophilic airway inflammation with cough do not show variable airflow obstruction[21]. Another study reported a correlation between eosinophilic bronchitis without asthma and irreversible airflow obstruction.[22]A longitudinal exploration on the association between blood eosinophil levels and lung function in the general population revealed that higher eosinophil level correlated with lower FEV_1/FVC and lower predicted FEV_1, both pre- and post-bronchodilator, independent of asthma and smoking.[10] In this cross-sectional study we found that there was no correlation between sputum eosinophil level either with FEV_1 or the FEV_1/FVC ratio (Table 2).

There is some evidence that an increase in serum IgE plays a role in the occurrence of chronic airflow limitation.[23] High total IgE can be found in allergic conditions[24] and smoking.[23,25] Cigarette smoke is widely known as a risk factor for allergies and respiratory diseases. Tobacco smoke has several detrimental effects on the immune system, including humoral and cellular. Cigarette smoke can initiate eosinophilic inflammation in the pathogenesis of allergic diseases. [25]Studies in patients with ACO reported that an increase in IgE was associated with an increase in B cells[8], higher level of IgEwas seen in smokers compared to non-smokers,the presence of an association between increased serum IgE levels and a decrease in FEV_1 in smokers cross-sectionally[23]. A study reported that COPD patients had higher serum IgE levels than healthy controls and that the IgE levels negatively correlated with FVC ($r = -0.477$, $p=0.034$) but did not correlate with FEV_1/FVC[25]. In this study, ACO patients had high serum IgE levels which correlated with the FEV_1/FVC ratio.

One of the criteria for ACO is persistent airflow limitation (post-bronchodilator FEV_1/FVC of <0.7)[14]. There is a correlation between high serum IgE (>400 IU/ml) and airflow limitation in asthmatics[27]. In asthma and COPD there are several pathological characteristics that are mutually shared[28]. We suspect that an increase in sputum eosinophil and total serum IgE levels can promote the occurrence of airway inflammation and remodeling and eventually deteriorate lung function. The limitation of this study was that this study was conducted in a tertiary hospital, so only severe patients were included. We did not examine fecal parasites.

CONCLUSION

Sputum eosinophil and total serum IgE levels in ACO patients increased. In patients with ACO, total serum IgE correlated with irreversible airway obstruction, and sputum eosinophil level was not associated with persistent airflow obstruction.

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