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ORIGINAL ARTICLE

The prevalence of asthma-COPD overlap syndrome in women patients with biomass fuel utilizing

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Abstract

Asthma-chronic obstructive pulmonary disease overlap (ACO) indicates that its characteristics with pulmonary exaggerated reactivity and airflow limitation chronically. We aimed to investigate the differences among women non smoker participants who have asthma, chronic obstructive pulmonary disease (COPD) and ACO with biomass smoke exposure. Patients were examined at the outpatient clinic from September 2017 to March 2020. Non-smoker women patients aged ≥40 years, diagnosed with obstructive pulmonary disease were included in the study. pulmonary function tests (PFT), early reversibility testing (bronchodilator test), and sputum eosinophil analysis were performed to all patients. A total of 102 patients were included. The mean age was 46.95±9.50 years. In the differential diagnosis, 65 patients (63.7%) had asthma and 37 patients (36.3%) had COPD. Among COPD patients, 10 (27.0%) were diagnosed with ACO. The actual prevalence rates of COPD and ACO were 26.5% and 9.8%, respectively. Poisson regression analysis showed that COPD compared to asthma, while holding the others variable constant in the model, are expected to have 2.976 times greater rate for exacerbations. (IRR, 95% CI, 2.976 (0.687 to 1.494), 5.296 (1.203 to 2.130), P<0.001, Coef. 1.091, 1.667 respectively). Logistic Regression analysis demonstrated that, the count of sputum, blood eosinophil and total IgE results were correlated with the exacerbation times. Biomass smoke exposure in the women population is revealed as a significant factor for the diagnosis of ACO.

Keywords: *Chronic obstructive pulmonary disease, asthma, asthma-COPD overlap, biomass smoke*

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Introduction

Asthma and COPD are the most common lung diseases all over the World [1,2]. Chronic obstructive pulmonary disease (COPD) is characterized by permanent airflow obstruction the pulmonary parenchyma. Tobacco smoking is main cause of COPD, but increasing evidence suggests that 30% of COPD patients have never smoked. Exposure to high levels of indoor biomass smoke, and workplace exposure to dust and fumes are also known as independent risk factors for COPD. On the other hand, asthma may be a risk factor for the development of COPD [3-4].

Biomass is more frequently used for cooking and heating in rural areas of developing countries. Biomass-burning stoves emit significant quantities inhalable health-damaging pollutants. Exposure to biomass smoke has been shown to increase the risk for development of chronic bronchitis, COPD, and asthma [5-8].

Differential diagnosis of asthma and COPD is usually easy with age, symptoms, and spirometric examinations. However, it is not always possible to make a differential diagnosis of COPD with asthma, especially in the population above 40 years of age who is smoker or exposed to biomass smoke. On the other hand, there is a growing consensus that typical asthma and COPD manifestations can both exist simultaneously in a single patient. Therefore, the ACO is used at when the patient with asthma has COPD features or vice versa. [9,10] .

In this study, we aimed to determine the frequency of ACO and to make differential diagnosis of asthma and COPD in non-smoker women patients with long-term biomass smoke exposure

Materials and Methods

Participants

This study was planned prospectively. The study protocol was accepted by the Local Ethics Committee of University, and an informed consent was taken from all participants. Furthermore this study was performed according to the principles of the Declaration of Helsinki.

The patients were selected at the outpatient clinic of University Hospital from September 2017 to March 2020. Inclusion criteria were as follows: women patients aged 40 years diagnosed with asthma or COPD based on the medical records, non-smoker, biomass smoke exposure at least 20 years, and the use of inhaled drugs (bronchodilator and/or corticosteroid) for at least 12 months. Exclusion criteria were as follows: the presence of comorbid severe chronic respiratory disease (cystic bronchiectasis, pulmonary fibrosis, kyphoscoliosis, active neoplasm) and the inability to perform diagnostic spirometry.

Spirometric Tests

All spirometric examinations were carried out using a single pulmonary function testing system (Viasys Mastercope, Germany). A standard spirometric examination and early reversibility testing (bronchodilator test) were performed in all patients. Spirometry was performed 12 h after the use of long-acting bronchodilator and 24 h after. The patients inhaled 400 µg β2-agonist (salbutamol) aerosol (metered-dose inhaler) with a spacer and the test was repeated 20 min later to evaluate early reversibility.

Sputum collection and analysis

Sputum samples induced by the inhalation of 3% sterile saline solution with a nebulizer were collected as described previously. The nebulization with tidal breathing was continued for at least 10 min. The patient was asked to cough and expectorate at 5 min intervals during nebulization. The sputum samples were collected in sputum collection bottles and sent to the pathology laboratory. In the initial step of preparation, 5 cc alcohol-based solution was added to the sample for fixation and elimination of erythrocytes. After separation from supernatant by centrifugation, the sample was put into the BD PrepStain™ automatic staining machine and Papanicolaou's (PAP) stain was performed. The glasses were covered with a cover slip and subsequently examined under a light microscope. The eosinophil count was expressed in the ratio of eosinophils to total cell count. Therefore, at least 10 high-power fields were evaluated on each PAP-stained slide [11].

Diagnosis of asthma and COPD

The criteria used to diagnose asthma were as follows: (1) history of wheeze; (2) a positive early reversibility test; and (3) forced expiratory volüme in 1 second/ forced vital capacity (FEV1/FVC) >0.70 after 400 µg salbutamol inhalation. (12) The diagnosis of COPD was made in the patients with symptoms compatible with COPD and was not fully reversible airflow limitation (post-bronchodilator FEV1/FVC ratio 0.70).

Diagnosis of ACO

Major diagnostic criteria were as follows: (1) biomass smoke exposure for at least 20 years; (2) history of asthma before the age of 40; (3) an increase in the post-bronchodilator FEV1 400 mL and 15% of the baseline; (4) a sputum eosinophil ratio of 3%. Minor diagnostic criteria were as follows: (1) history of atopy or allergic rhinitis; (2) an increase in the post-bronchodilator FEV1 200 mL and 12% of the baseline; (3) peripheral eosinophilia (300 cells/μL); (4) increased total immunoglobulin E. The diagnosis of ACO was based on at least three major criteria and a minor criteria in patients with permanent airflow limitation (FEV1/ FVC 0.70).

Statistical Analysis

All statistical analysis enrolled with R Version 3.6.0 (www.r-project.org). Anderson Darling test and Levene test were used to check assumptions of normality and homogeneity of variances, respectively. Continuous variables were described as median (interquartile range), and analyzed with Kruskal Wallis test. After Kruskal Wallis test, post hoc analysis with Conover-Iman test was performed with a Bonferroni test with significance level set at $p<0.016$. Spearman's rho correlation analyses were applied to evaluate relationship between parameters. $p<0.05$ was considered statistically significant for general analyses. Box-plot with test and significance values was presented for the number of exacerbations within the last year according to patients groups. Scatter plot was presented to show for relationship between sputum eosinophil count and blood eosinophil count. The risk factor for the number of exacerbations within the last year was calculated in a model using Poisson regression, and it was expressed as an incidence rate ratio (IRR) with 95% confidence interval (CI). The independent variables in this model were patients groups, sputum and blood eosinophil counts, and Total IgE. Poisson regression is used to count variables. Due to the number of exacerbations within the last year had Poisson distribution, we used Poisson regression model to determine the risk factor of its.

Results

A total of 102 non-smoker women patients aged 40 years with a history of biomass smoke exposure for at least 20 years were included. Patients who were diagnosed as asthma in 63.7% (65/102) and COPD in 36.3% (37/102), Also ACO were diagnosed in 10 (27.0%) patients who were detected in COPD group (Figure 1).

The actual prevalence rates of COPD and ACO were 26.5% and 9.8%, respectively. Table 1 shows demographic, clinical and functional characteristics of patients.

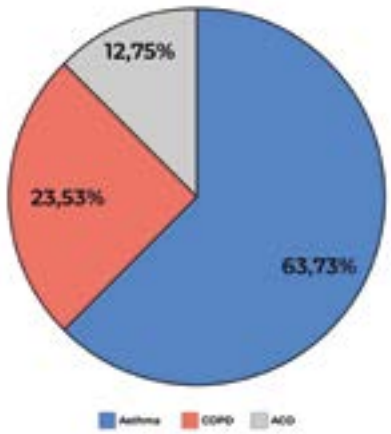

Figure 1. Distribution of patients according to diagnosis

Table 1. Demographic and clinical characteristics of patients

Characteristics	Asthma (n=65)	COPD (n=27)	ACO (n=10)	p-value
Age (year)	32 (24 – 39)a	51.5 (43 – 57.25)b	58 (45 – 64)	0.001
BMI	33 (28 – 37)	31 (28 – 35.25)	31 (28 – 36)	ns
Mean Exacerbations times (n, 12 months)	0 (0 – 1)a	2 (1 – 3)b	4 (3 – 5)c	<0.001
Survival of Exacerbations	1.7(1.1-2).3	2.5(1.5-3.1)	2.9/(2.3-3.7)	<0.001
FEV1 (%)	101.5 (84 – 11.25)a	56.5 (43.5 – 70.25)b	61 (46 – 75)b	<0.001
FVC (%)	100 (85.25 – 110.5)a	74 (60.5 – 85)b	84 (69 – 97)	<0.001
FEV1/FVC	82.5 (78 – 87.25)a	63.5 (56 – 68.85)b	60 (55 – 62)b	<0.001
Sputum eosinophil (%)	1 (0.20 – 2.50)a	0.50 (0.20 – 1.50)a	4.30 (3 – 5.20)b	<0.001
Blood eosinophil (cell/μL)	0.13 (0.07 – 0.30)a	0.04 (0.01 – 0.11)b	0.35 (0.19 – 0.40)c	<0.001
Total IgE (IU/mL)	18 (9 – 87)a	27.5 (8.75 – 72)a	134 (41 – 246)b	<0.001

p-value: Kruskal Wallis test, $p<0.001$was considered statistically significant, ns: not significant,Values were presented as median (interquartile range), Conover-Iman test with a Bonferroni correction was used to multiple comparisons, Different letters in rows indicated that statistically significant difference ,BMI: Body mass index, FEV1: Forced expiratory volûme in 1 second, FVC: Forced vital capacity.

The mean age of the study population was 36.95±2.50 (range, 24 to 64) years. There was a significant difference in the FEV1/FVC and FVC between asthma and COPD, between asthma and ACO patients, while no significant difference was found between COPD and ACO patients (Table 1). Also, there was a significant difference in the FEV1 between asthma and

COPD patients and between asthma and ACO patients (p=0.0001 and p=0.001, respectively), while there was no significant difference between COPD and ACO patients. Furthermore, we have found that there were significant differences in the reversibility of airflow limitation among patients groups. The reversibility of airflow limitation was the greatest in patients with ACO. The increase in post-bronchodilator FEV1 was significantly greater in the ACO group than COPD group and the asthma group (p<0.001). The increase in FEV1 was also significantly greater in the asthma group than in the COPD group (p<0.001). The number of the patients with a FEV1 of 200 mL and 12% in bronchodilator response was 18 (27.69%) in the asthma group, 4 (12.5%) in the COPD group and 8 (61.5%) in the ACO group. Kruskal Wallis test showed that there was a statistically significant difference in numbers of exacerbations within the last year according to patients groups. Post hoc analysis with Conover-Iman test was conducted with a Bonferroni correction applied, resulting in as significance level. The median (IQR) number of exacerbations for the asthma, COPD and ACO patients were 0 (IQR 0 – 1), 2 (IQR 1 – 3) and 4 (IQR 3 – 5), respectively. Also, the mean number of exacerbations within the last year for the asthma, COPD and ACO patients were 0.72 ± 0.91, 2.17 ± 1.55 and 3.77 ± 1.54, respectively (Figure 2). The number of exacerbations within the last year was statistically significant in the ACO group than in the asthma and COPD group. Also, the number of exacerbation within the last year was statistically significantly higher in the COPD group than in the asthma. Mean total IgE values were highest in ACO patients (p<0.001). Sputum hypereosinophilia was seen in 38.4%, 12.5%, 61.53% patients with asthma, COPD and ACO, respectively. There was a significant correlation between the blood and sputum eosinophil counts (Figure 3). However, no significant correlation between the post-bronchodilator FEV1 and blood and sputum eosinophil counts. There was also no significant correlation between the frequency of exacerbations and blood and sputum eosinophil counts. COPD compared to asthma, while holding the others variable constant in the model, are expected to have a rate 2.976 times greater for the number of exacerbations within the last one year. Furthermore ACO compared to asthma, while holding the others variable constant in the model, are expected to have a rate 5.296 times greater for the number of exacerbations within the last one year (Table 2). The assessment of sputum, blood eosinophil and total IgE count within the last year showed in Table 3. The effect of number of exacerbations within the last year was statistically significant in groups besides that, the count of sputum, blood eosinophil and total IgE results were correlated with the exacerbation times significantly per year. The survival of ACO patients was significantly better than of COPD patients (Figure 4). Predicted lung function was poor and worse in patient with COPD and Asthma groups but the prognosis was better in ACO patients with the improvement in FEV1 outcomes.

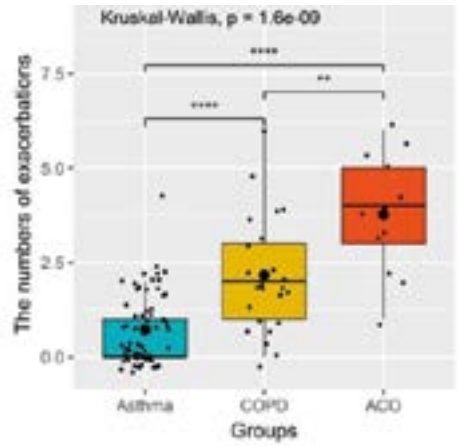

Figure 2. Exacerbations within the last year according to patients group

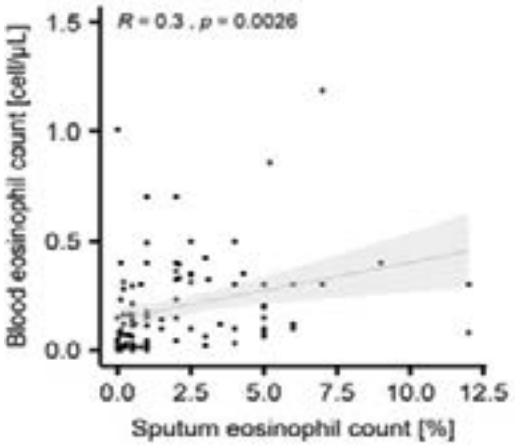

Figure 3. Correlation between blood and sputum eosinophil [%] count

Table 2. Poisson Regression for The Number of Exacerbations within the last one year

Parameters	Coef.	Std. Err.	IRR	95% Conf. Interval	p-value
Patients Groups					
Asthma	**Reference group**				
COPD	1.091	0.206	2.976	0.687 to 1.494	<0.001
ACO	1.667	0.237	5.296	1.203 to 2.130	<0.001

Coef.: Estimated Poisson regression coefficients, Std. Err.: Standard errors of the regression coefficients, z: Test statistics, 95% Conf. Interval: Confidence interval of poisson regression coefficients, IRR: Incidence rate ratio. p<0.001 was considered statistically significant, ACO: Asthma-chronic obstructive pulmonary disease overlap, COPD: chronic obstructive pulmonary disease

Table 3. Logistic Regression analysis of laboratory markers efficacy for evaluating the exacerbation time

Parameters	Coef.	Std. Err.	IRR	95% Conf. Interval	p-value
Sputum eosinophil count (%)	-0.018	0.043	0.981	-0.102 to 0.066	<0.001
Blood eosinophil count (cell/µL)	0.043	0.436	1.043	-0.812 to 0.897	<0.001
Total IgE (%)	0.001	0.001	1.001	-0.001 to 0.029	<0.001

Coef.: Estimated Poisson regression coefficients, Std. Err.: Standard errors of the regression coefficients, z: Test statistics, 95% Conf. Interval: Confidence interval of poisson regression coefficients, IRR: Incidence rate ratio. p<0.001 was considered statistically significant

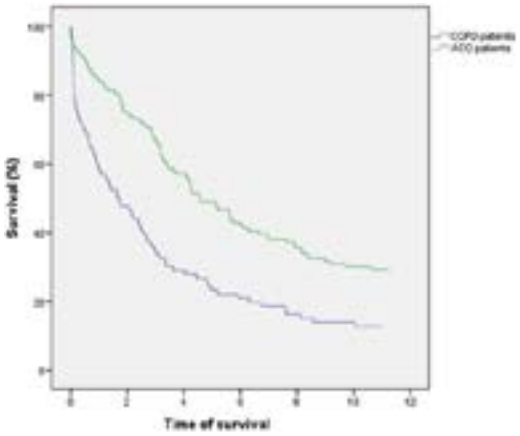

Figure 4. The survival of ACO patients was significantly better with median survival time, compared to COPD patients

Discussion

In developed countries, tobacco smoke is the common risk factor for COPD. On the other hand biomass smoke exposure is the most important factor in undeveloped countries, primarily. Biomass smoke exposure is estimated to effect 2 million women negatively every year [12-14].This study investigated the non-smoker women patients with asthma, COPD or ACO with biomass smoke exposure.

Data describing the pathophysiology of biomass smoke-related COPD emerges mainly from in vitro researchs. Acute exposure to biomass smoke lead to elevation in neutrophilic inflammatory reaction of pulmonary structure. Besides that eosinophilic and lymphocytic inflammation detected in Subchronic exposure. And also Chronic exposure is detected in experimental research characterized by increase in fibroblasts volume and collagen accumulation at bronchioles, and elevation in matrix metalloproteinases in the epithelial cells of lung. A research study demonstrated that smoke particules may lead to inflammatory response at lung structure. In an invitro study, it is revealed that plant smoke significantly evokes the expression of aryl hydrocarbon receptor (AHR) which lead to decline in anti-inflammatory way, also resulted to increasing in inflammation. Hence, pressive of AHR is a remedial destination for smoke-related exacerbation [15-18].

Patients who were over 40 years old, show with symptoms of chronic airways disease findings of asthma and COPD called as the asthma-COPD overlap syndrome (ACO); identified in the GOLD consensus as 'described by permanent limitation of air flow oftenly related with asthma and COPD features. Patients who were afflicted by ACO more prone to hyper-reactivity in pulmonary system than with COPD. Furthermore, patients with ACO tend to have more pulmonary exacerbations than s with COPD alone and asthma alone [19]. Solleiro-Villavicencio et al. found that Th2 inflammatory response which may cause to airway hyperresponsiveness, progressed mucus production evoked by the exposing of biomass smoke who have diagnosed of COPD. Various studies demonstrate a dose-response relationship between the biomass smoke exposure and the severity of airflow obstruction [20-24]. In evaluation of longutudinal meta-analysis showed that biomass-exposing has contributed to establishment of COPD than non-exposing situations. Furthermore, In an epidemiological research demonstrated that the rate of biomass smoke exposure was more than half among women population living in rural areas. Also this research suggested that the risk percentage of COPD was detected twice as much higher than cigarette smoking [25,26].

In this study, we have revealed that patients with ACO have better prognosis compared to COPD and asthmatic patients. Furthermore the overall survival of ACO patients hospitalised for exacerbation was poor than COPD and Asthma [27]. In a midterm research study, ACO was related with the decreasing in lung function than COPD or asthma alone [28]. The lung function of patients with ACO was worse than patients with COPD, however of obstruction of respiratory way and inflammation have better than patients with asthma. ACO patients with FEV1 under 50% of their predicted value had superior survival when compared to COPD patients with similar lung function. The variables (such as FEV1, FVC) used for evaluating the severity of illness and identify the risk of mortality, which can predict the prognosis of patients with

airflow limitation diseases like as COPD, ACO and Asthma [29] .

Kitaguchi et al. founded that only FEV1, FVC was significantly higher in the asthma group than in the ACO group. We have found that there were significant differences in spirometry parameters. There was also a significant difference detected in FEV1, FVC outcomes among the groups, while there was no significant difference detected between patients with COPD and ACO [30]. It is still unclear that whether sputum or blood eosinophil count is reliable and valid. Some studies have used sputum eosinophil in the diagnostic criteria of ACO. On the other hand, blood eosinophil count was considered as the main diagnostic marker of ACO. Both paremeters were used for diagnosis of ACO in present study. Furthermore It was suggested that peripheral blood eosinophil counts could be helpful for identifying the sputum eosinophilia in stable COPD patients [31-34]. Similar to these studies, present study demonstrated a signficant correlation between sputum and blood eosinophil results.

The studies demonstrated that the prevalence of ACO increased with increasing age. Present study determined that ACO patients was younger than COPD patients however this difference was not statistically significant. The frequency of exacerbations in ACO patients was significantly higher than asthma and COPD in our study correlated with the literature reviews [35,36]. Biomass smoke exposure, is oftenly overlooked in women who live at rural areas such as villages and also most important etiological factor for the diagnosis of COPD, However, the lack of the consensus on the diagnostic criteria for ACO makes the diagnosis difficult. Especially women who were exposed to biosmoke should be evaluated in terms of airway disease, not only asthma or COPD, but also ACO should be considered and treatment protocol should be arranged accordingly [37].

There were some limitations in this study. Firstly, this was a not a large population study however the ACO was a novel concept diagnosis and larger populations are required to obtain clues in the differential diagnosis of asthma, COPD and ACO. Secondly, we have not evaluate exhaled nitric oxide, DLco and DLco/alveolar volume in the differential diagnosis.

Conclusion

Biomass smoke exposure in women population is revealed as a significant factor for the diagnosis of ACO due to common used in rural areas for cooking or heating. Laboratory markers may be effective for, estimating the exacerbation time, separating the differences in airway diseases and resulted to the real diagnosis.

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Conflict of interest
The author has no conflicts of interest to declare.

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