Prevalence of Asthma-COPD Overlap in COPD and Severe Asthma Cohorts

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Abstract

Background: Asthma and chronic obstructive pulmonary disease (COPD) are airway diseases with similar clinical manifestations, despite differences in pathophysiology. Asthma-COPD overlap (ACO) is a condition characterized by overlapping clinical features of both diseases. There have been few reports regarding the prevalence of ACO in COPD and severe asthma cohorts. ACO is heterogeneous; patients can be classified on the basis of phenotype differences. This study was performed to analyze the prevalence of ACO in COPD and severe asthma cohorts. In addition, this study compared baseline characteristics among ACO patients according to phenotype.

Methods: Patients with COPD were prospectively enrolled into the Korean COPD subgroup study (KOCOSS) cohort. Patients with severe asthma were prospectively enrolled into the Korean Severe Asthma Registry (KoSAR). ACO was defined in accordance with the updated Spanish criteria. In the COPD cohort, ACO was defined as bronchodilator response (BDR) ≥ 15% and ≥ 400 mL from baseline or blood eosinophil count ≥ 300 cells/μL. In the severe asthma cohort, ACO was defined as age ≥ 35 years, smoking ≥ 10 pack-years, and post-bronchodilator forced expiratory volume in 1 s/forced vital capacity < 0.7. Patients with ACO were divided into four groups according to smoking history (threshold: 20 pack-years) and blood eosinophil count (threshold: 300 cells/μL).

Results: The prevalence of ACO significantly differed between the COPD and severe asthma cohorts (19.8% [365/1839] vs. 12.5% [104/832], respectively, $P < 0.001$). The numbers of patients in each group were as follows: Group A (smoking 10–20 pack-years and blood eosinophil count ≥ 300 cells/μL), 42 (9.1%); Group B (smoking 10–20 pack-years and eosinophil count < 300 cells/μL), 17 (3.7%); Group C (smoking ≥ 20 pack-years and eosinophil count ≥ 300 cells/μL), 341 (73.8%); and Group D (smoking ≥ 20 pack-years and eosinophil count < 300 cells/μL), 62 (13.4%). Age, sex, BDR, comorbidities, and medications significantly differed among the four groups.

Conclusion: The prevalence of ACO differed between COPD and severe asthma cohorts. ACO patients can be classified into four phenotype groups, such that each phenotype exhibits distinct characteristics.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both airway diseases with similar clinical manifestations, despite different pathophysiologies. Asthma-COPD overlap (ACO) is a condition that is characterized by overlapping clinical features from both diseases.[1] There have been increasing numbers of studies regarding the classification and clinical features of ACO.[2] However, there remains no consensus regarding definite diagnostic criteria; the reported prevalences of ACO vary widely according to the diagnostic criteria used.[3–9] Although there have been many reports of studies in asthma and COPD cohorts, there have been few reports regarding the prevalence of ACO in combined COPD and severe asthma cohorts.

Asthma and COPD are heterogeneous disorders with variable phenotypes, and there are several phenotypes of ACO. To our knowledge, there have been few studies of the clinical characteristics of ACO phenotypes.[2, 10, 11] There have been several attempts to classify the phenotypes of ACO, but a consensus has not yet been reached concerning appropriate classification criteria. Patients with ACO can be classified according to differences in ACO phenotype, mainly on the basis of eosinophilic inflammation and smoking history.[12] Using these criteria, COPD patients have been classified and compared according to phenotype, revealing differences in clinical features.[10] There have been no studies in which participants were divided into different phenotype groups in cohorts of severe asthma and COPD patients.

This study was performed to analyze the prevalence of ACO in COPD and severe asthma cohorts. In addition, this study compared baseline characteristics among ACO patients according to phenotype.

Material And Methods

Study population

Patients with COPD were prospectively enrolled into the Korean COPD subgroup study (KOCOSS) cohort, a multicenter cohort study of COPD patients recruited from 54 medical centers in South Korea. In this study, we extracted KOCOSS data from the cohort enrolled between April 2012 and September 2020. Inclusion criteria were South Korean patients age ≥ 40 years with post-bronchodilator forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) < 70% of the normal predicted value.

Patients with severe asthma were prospectively enrolled into the Korean Severe Asthma Registry (KoSAR) of the Korean Academy of Asthma, Allergy, and Clinical Immunology, the Working Group on Severe Asthma. The KoSAR is a prospective multicenter observational study for adult severe refractory asthma from 31 institutions in Korea. In total, 832 patients with severe asthma enrolled between January 2010 and February 2021 were included in this study. The inclusion criteria were patients with severe asthma, defined as follows: treatment by asthma specialists under regular follow-up for at least 1 year or inability to consistently achieve a well-controlled status after Global Initiative for Asthma treatment steps 4 or 5; alternatively, achievement of well-controlled status after Global Initiative for Asthma treatment step 4 or 5 but presentation to an emergency department more than once annually, receipt of steroid burst treatment more than three times annually, asthma worsening on tapering of oral corticosteroids or inhaled corticosteroids, or near-fatal asthma attack onset at any time in the past.

Definitions

ACO was defined in accordance with the updated Spanish criteria.[13] In the COPD cohort, ACO was defined as bronchodilator response (BDR) ≥ 15% and ≥ 400 mL from baseline or blood eosinophil count ≥ 300 cells/μL. In the severe asthma cohort, ACO was defined as age ≥ 35 years, smoking ≥ 10 pack-years, and post-bronchodilator FEV_1/FVC < 0.7.

Classification of ACO phenotype

Patients with ACO were divided into four groups according to smoking history (threshold: 20 pack-years) and blood eosinophil count (threshold: 300 cells/μL): Group A (smoking 10–20 pack-years and blood eosinophil count ≥ 300 cells/μL); Group B (smoking 10–20 pack-years and eosinophil count < 300 cells/μL); Group C (smoking ≥ 20 pack-years and eosinophil count ≥ 300 cells/μL); and Group D (smoking ≥ 20 pack-years and eosinophil count < 300 cells/μL). Patients with blood eosinophil count ≥ 300 cells/μL at the time of enrollment were classified as the high blood eosinophil group. Characteristics were analyzed and compared among the four groups.

Clinical evaluation

Demographic information (e.g., sex, age, smoking history, comorbidities, body mass index [BMI], and questionnaire results [asthma control test and COPD assessment test]) was collected along with the results of pulmonary function and laboratory tests, as well as details concerning medication use.

Statistical analysis

Categorical data were analyzed using the χ^2 test or Fisher's exact test. For normally distributed data, Student's *t*-test or one-way analysis of variance was used for between-group comparisons. For non-normally distributed data, the Mann–Whitney U test or the Kruskal–Wallis test was used for between-group comparisons. All statistical analyses were performed using SPSS (version 23.0; SPSS Inc., Chicago, IL, USA). In all analyses, $P < 0.05$ was considered to indicate statistical significance.

Ethics statement

For both KOCOSS and KoSAR patients, written informed consent was obtained from all study participants. Ethics approval for the both cohorts was obtained from the ethics committee at each center. We also received approval from each center to use clinical record for their subjects for the study while maintaining patient confidentiality with regard to the data. The official name of each approving ethics committee is listed in Supplementary materials.

Results

Patients and comorbidities

The prevalence of ACO significantly differed between the COPD and severe asthma cohorts (19.8% [365/1839] vs. 12.5% [104/832], respectively, $P < 0.001$) (Fig. 1). In total, 462 ACO patients were divided into four groups: Group A, 42 (9.1%); Group B, 17 (3.7%); Group C, 341 (73.8%); and Group D, 62 (13.4%) (Fig. 2). Table 1 shows the baseline characteristics of the four phenotype groups. The mean age significantly differed among groups ($P < 0.001$). Patients in Group C were oldest and patients in group B were youngest. The proportion of men significantly differed among groups ($P < 0.001$). The proportion of men was high in Group C (almost all patients were men in that group); Group B had the highest

proportion of women. Smoking histories significantly differed between Groups C and D (48.99 ± 23.95 and 44.83 ± 29.88 pack-years, respectively) and between Groups A and B (15.22 ± 3.33 and 13.92 ± 3.01 pack-years, respectively) ($P < 0.001$ for each pairwise comparison). Among all patients, 39.0% had hypertension and 15.8% had diabetes, but these parameters did not significantly differ among groups. The proportion of allergic rhinitis significantly differed among groups ($P < 0.001$); Group B exhibited the highest proportion (40%). There were no significant differences in congestive heart failure, gastroesophageal reflux disease, atopic dermatitis, or osteoporosis among groups (Table 2).

Table 1
Demographic and clinical characteristics of ACO phenotype groups ($n = 462$)

	ACO phenotype group				*P*-value
	A	B	C	D	
n	42	17	341	62	
Age (years)	65.45 ± 10.16	57.47 ± 12.83	67.75 ± 8.02	63.98 ± 9.44	< 0.001
Male	39 (92.9%)	14 (82.4%)	337 (98.8%)	56 (90.3%)	< 0.001
Smoking (%)					
Ex-smoker	27 (64.3%)	11 (64.7%)	241 (70.7%)	51 (82.3%)	0.166
Current-smoker	15 (35.7%)	6 (35.3%)	100 (29.3%)	11 (17.7%)	
Pack-years	15.22 ± 3.33	13.92 ± 3.01	48.99 ± 23.95	44.83 ± 29.88	< 0.001
BMI (kg/m^2)	23.71 ± 3.21	23.03 ± 2.30	23.15 ± 3.61	23.89 ± 3.29	0.377
ACT	18.00 ± 6.86	17.93 ± 4.50	17.09 ± 5.96	19.96 ± 3.56	0.104
CAT	14.23 ± 9.25	9.00 ± 7.07	14.63 ± 7.99)	13.87 ± 7.66	0.771
Data are expressed as mean ± standard deviation or number (%)					
ACO, asthma-chronic obstructive pulmonary disease overlap; ACT, asthma control test; BMI, body mass index; CAT, chronic obstructive pulmonary disease assessment test.					

Table 2
Comorbidities in ACO phenotype groups

	ACO phenotype group				*P*-value
	A	B	C	D	
DM	8 (19.0%)	2 (11.8%)	53 (15.5%)	10 (16.1%)	0.937
HTN	17 (40.5)	4 (23.5%)	134 (39.3%)	25 (40.3%)	0.728
CHF	1 (2.4%)	0 (0.0%)	11 (3.25)	2 (3.2%)	1
GERD	7 (16.7%)	0 (0.0%)	1 (0.3%)	5 (8.1%)	0.297
Allergic rhinitis	11 (26.2%)	8 (47.1%)	46 (13.5%)	21 (33.9%)	< 0.001
Atopic dermatitis	1 (2.4%)	2 (11.8%)	13 (3.8%)	3 (4.8%)	0.416
Osteoporosis	5 (11.9%)	2 (11.8%)	11 (3.2%)	3 (4.8%)	0.007
BRE on CT findings	4 (9.5%)	1 (5.9%)	23 (6.7%)	23 (6.7%)	9 (14.5)

ACO, asthma-chronic obstructive pulmonary disease overlap; BRE, bronchiectasis; CHF, congestive heart failure; CT, computed tomography; GERD, gastroesophageal reflex disease; DM, diabetes mellitus; HTN, hypertension.

Pulmonary function tests and laboratory findings

Table 3 shows the results of pulmonary function tests and laboratory findings among the four phenotype groups. Post-bronchodilator FVC (L, % predicted) and FEV_1 (L, % predicted) did not significantly differ among the four groups. The FEV_1/FVC ratio was lower in Groups C and D (longer smoking history) than in Groups A and B (shorter smoking history). BDR (%) was lowest in Group A and highest in Group D; BDR (mL) was lowest in Group C and highest in Group B. The differences in BDR (mL) and BDR (%) were statistically significant ($P < 0.001$ for both comparisons among groups). There were no differences in white blood cell counts between groups, but there were significant differences among groups in blood eosinophil counts ($P < 0.001$). BDR was lower in the high blood eosinophil count group, but this difference was not statistically significant. Immunoglobulin E levels did not significantly differ among the four groups ($P = 0.869$).

Table 3
Lung function and laboratory findings in ACO phenotype groups

	ACO phenotype group				*P*-value
	A	B	C	D	
Pulmonary function test					
Post-BD FVC (L)	3.41 ± 0.92	3.49 ± 1.11	3.40 ± 0.76	3.38 ± 0.87	0.965
Post-BD FVC (%)	82.59 ± 18.61	80.55 ± 19.49	80.86 ± 15.92	82.27 ± 16.40	0.866
Post-BD FEV_1 (L)	1.83 ± 0.63	1.90 ± 0.59	1.75 ± 0.58	1.71 ± 0.49	0.866
Post-BD FEV_1 (%)	60.87 ± 17.66	57.71 ± 14.48	58.29 ± 18.27	56.02 ± 16.00	0.594
Post-BD FEV_1/FVC	53.65 ± 11.13	55.06 ± 8.41	51.25 ± 12.03	51.52 ± 11.44	0.386
BDR (%)	4.90 ± 7.25	16.43 ± 16.87	5.64 ± 11.22	17.39 ± 26.74	< 0.001
BDR (mL)	80.95 ± 135.37	238.24 ± 247.97	76.42 ± 211.28	218.23 ± 216.95	< 0.001
Laboratory findings					
WBC	8136.90 ± 2223.02	7920.00 ± 2659.19	8049.88 ± 2245.73	8431.13 ± 2672.10	0.675
Eos	571.61 ± 259.17	129.85 ± 93.83	553.50 ± 384.84	148.26 ± 85.97	< 0.001
IgE	463.17 ± 649.19	416.80 ± 324.15	351.56 ± 511.73	254.50 ± 233.68	0.671
CRP	2.78 ± 4.19	1.11 ± 2.32	2.37 ± 5.68	2.27 ± 4.34	0.861

Data are expressed as mean ± standard deviation.

ACO, asthma-chronic obstructive pulmonary disease overlap; BD, bronchodilator; BDR, bronchodilator response; CRP, C-reactive protein; Eos, eosinophils; IgE, immunoglobulin E; WBC, white blood cells.

Inhaler use

Table 4 shows the use of inhalers in the four phenotype groups. The patterns of inhaler use differed among the four phenotype groups. The frequency of inhaled corticosteroid (ICS) + long-acting beta

agonist (LABA) use was highest in Group C, followed by Group A. The difference in ICS + LABA use among the four groups was statistically significant ($P < 0.001$). The frequency of ICS + LABA + long-acting muscarinic antagonist (LAMA) use was highest in Group C, followed by Groups A, D, and B. There was no significant difference in triple inhaler use among the four groups ($P = 0.196$).

Table 4
Inhaler use in ACO phenotype groups

	ACO phenotype group				*P*-value
	A	B	C	D	
ICS + LABA only	11 (26.2%)	0 (0.0%)	107 (31.4%)	7 (11.3%)	0.001
ICS + LABA + LAMA	7 (16.7%)	1 (5.9%)	69 (20.2%)	6 (9.7%)	0.196

ACO, asthma-chronic obstructive pulmonary disease overlap; ICS, inhaled corticosteroid; LABA, long-acting beta agonist; LAMA, long-acting muscarinic antagonist.

Discussion

Gibson et al. first proposed the definition of ACO using the combined physiological criteria for COPD and asthma.[14] Since then, various alternative definitions of ACO have been proposed.[9, 13, 15] Moreover, several studies investigated the prevalence of ACO using these various definitions.[16] The opinion of a specialist, albeit subjective, may also be an important criterion in ACO diagnosis.[16] In another study, smoking history was considered the most important factor by a specialist in ACO diagnosis.[17] Therefore, this study examined the prevalence of ACO using the updated Spanish ACO guidelines, which require a smoking history ≥ 10 pack-years for definitive diagnosis. To our knowledge, this is the first study to investigate the prevalence of ACO in two combined nationwide cohorts. The results showed that the prevalence of ACO was significantly higher in the COPD cohort than in the severe asthma cohort (19.8% vs. 12.5%, respectively, $P < 0.001$). The prevalence in the COPD cohort was comparable with the prevalence reported in previous studies; in contrast, the prevalence in the severe asthma cohort was lower than in previous studies where smoking history was not an essential component of the diagnosis of ACO.

ACO has characteristics of both asthma and COPD, and its phenotype is defined based on the predominant feature. Therefore, many studies have attempted to classify ACO patients according to their phenotype. One study classified ACO patients based on smoking and wheezing,[11] while another classified ACO patients into four phenotypes using clustering analysis according to age, BMI, exacerbation, smoking, dyspnea score, and comorbidities.[2] Rhee suggested classification of ACO patients into four phenotypes based on simple blood eosinophil count and smoking history.[12] These criteria are similar to the updated Spanish ACO guidelines used in the present study. Analysis of single-center COPD patients based on the suggested classification revealed differences in lung function, medication use, exacerbation, and baseline characteristics.[10] In the present study, COPD and severe asthma patients were classified according to ACO phenotypes. Group C (smoking ≥ 20 pack-years and

eosinophil count ≥ 300 cells/μL) comprised the largest proportion, similar to previous findings. Furthermore, the phenotype of patients in Group C was consistent with ACO, because those patients exhibited features of both asthma and COPD. A notable finding in this study was the distinct inhaler use pattern in each group. Consistent with previous studies, ICS + LABA (a treatment mainly used in asthma) was the most common drug combination overall; it was also used at different frequencies by patients in each phenotype group. There was an asthma-predominant group and a COPD-predominant group; specialists prescribed ICS + LABA only or ICS + LABA + LAMA differently for these groups. For each ACO phenotype, factors related to asthma were investigated; differences were observed in the proportions of features suggestive of asthma for each type.

The multicenter and nationwide enrollment of ACO patients within a large population of asthma and COPD patients represents a major strength of the present study, leading to analysis based on large cohorts of severe asthma and COPD patients. In addition, both cohorts were well controlled with few missing values and high data reliability. Our study provided valuable information regarding the prevalence of ACO and insightful data concerning the characteristics of different ACO phenotype groups. Phenotype classification based on underlying disease physiology is important for the proper management of individual patients.[12]

This study had several limitations. First, the majority of patients in this study were men. However, the Korean statistics in 2019 indicated that smoking rates were 35.3% and 3.7% in adult men and women, respectively. Overall, the smoking rate of women in Korea is very low; therefore, the relative number of women among patients in this study was not very small. Second, this was a cross-sectional study. Comparison of exacerbations could not be analyzed because prospective follow-up examinations were not included in the KoSAR data. Third, the study may have been subject to bias because all patients were enrolled from specialist centers; the results may have been biased toward patients with higher disease severity.

Conclusion

The prevalence of ACO differed between COPD and severe asthma cohorts. ACO patients can be classified into four phenotype groups, each of which showed different characteristics. However, further studies regarding ACO phenotypes are required.

Abbreviations

ACO: Asthma-COPD overlap

ACT: asthma control test

BD: bronchodilator

BDR: Bronchodilator response

BMI: Body mass index

BRE: bronchiectasis;

CAT: chronic obstructive pulmonary disease assessment test

CHF: congestive heart failure;

COPD: Chronic obstructive pulmonary disease

CRP: C-reactive protein;

CT: computed tomography;

DM: diabetes mellitus;

Eos: eosinophils;

FEV_1: forced expiratory volume in 1 s

FVC: forced vital capacity

GERD: gastroesophageal reflex disease;

HTN: hypertension

ICS: inhaled corticosteroid

IgE: immunoglobulin E;

KOCOSS: Korean COPD subgroup study

KoSAR: Korean Severe Asthma Registry

LABA: long-acting beta agonist

LAMA: long-acting muscarinic antagonist

WBC: white blood cells.

Declarations

Ethics approval and consent to participate

This study was conducted in accordance with the amended Declaration of Helsinki. All patients submitted written informed consent at study enrollment. Ethical approval was collected from the Ethics Committee of each participating medical center.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interest

The authors declare that they have no competing interests.

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Author's contributions

HSJ: Substantial contribution to the conception, study design, interpretation of data, drafted work and revision. PSY, PSY, CYS, JKS involved in data curation and interpretation of data. PSY involved in data analysis. KSH, YKH involved in writing the manuscript. RCK: Contribution to the study design, data analysis, drafting, revision, final approval, and accountability of all aspects of the work. All authors have approved the final version of the work.

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Figures

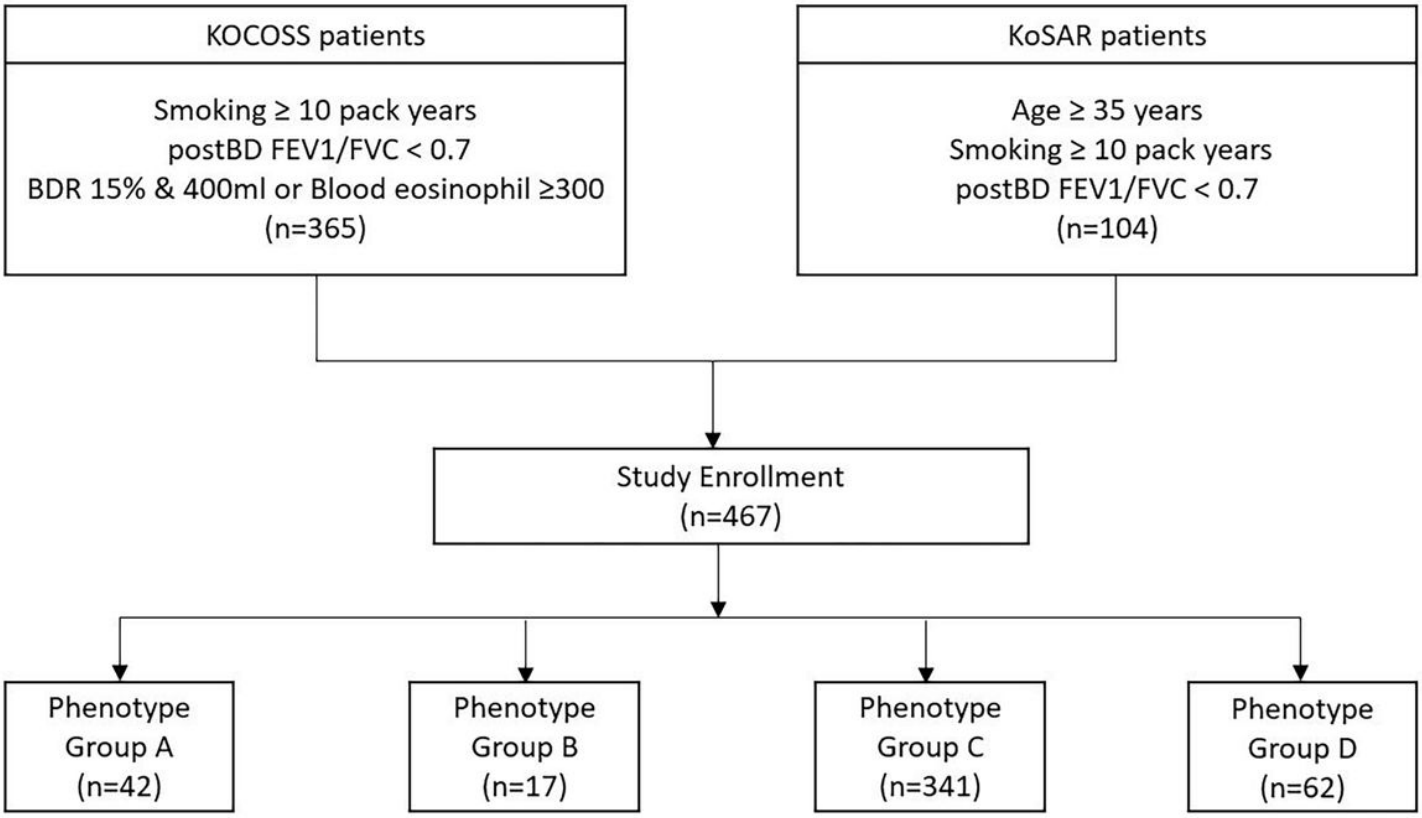

Figure 1

Flow diagram for participant enrollment Group A, smoking 10–20 pack-years and blood eosinophil count ≥ 300 cells/μL; Group B, smoking 10–20 pack-years and eosinophil count < 300 cells/μL; Group C, smoking ≥ 20 pack-years and eosinophil count ≥ 300 cells/μL; Group D, smoking ≥ 20 pack-years and eosinophil count < 300 cells/μL. Abbreviations: BD, bronchodilator; BDR, bronchodilator response; KOCOSS, Korean Chronic Obstructive Pulmonary Disease Subgroup Study; KoSAR, Korean Severe Asthma Registry.

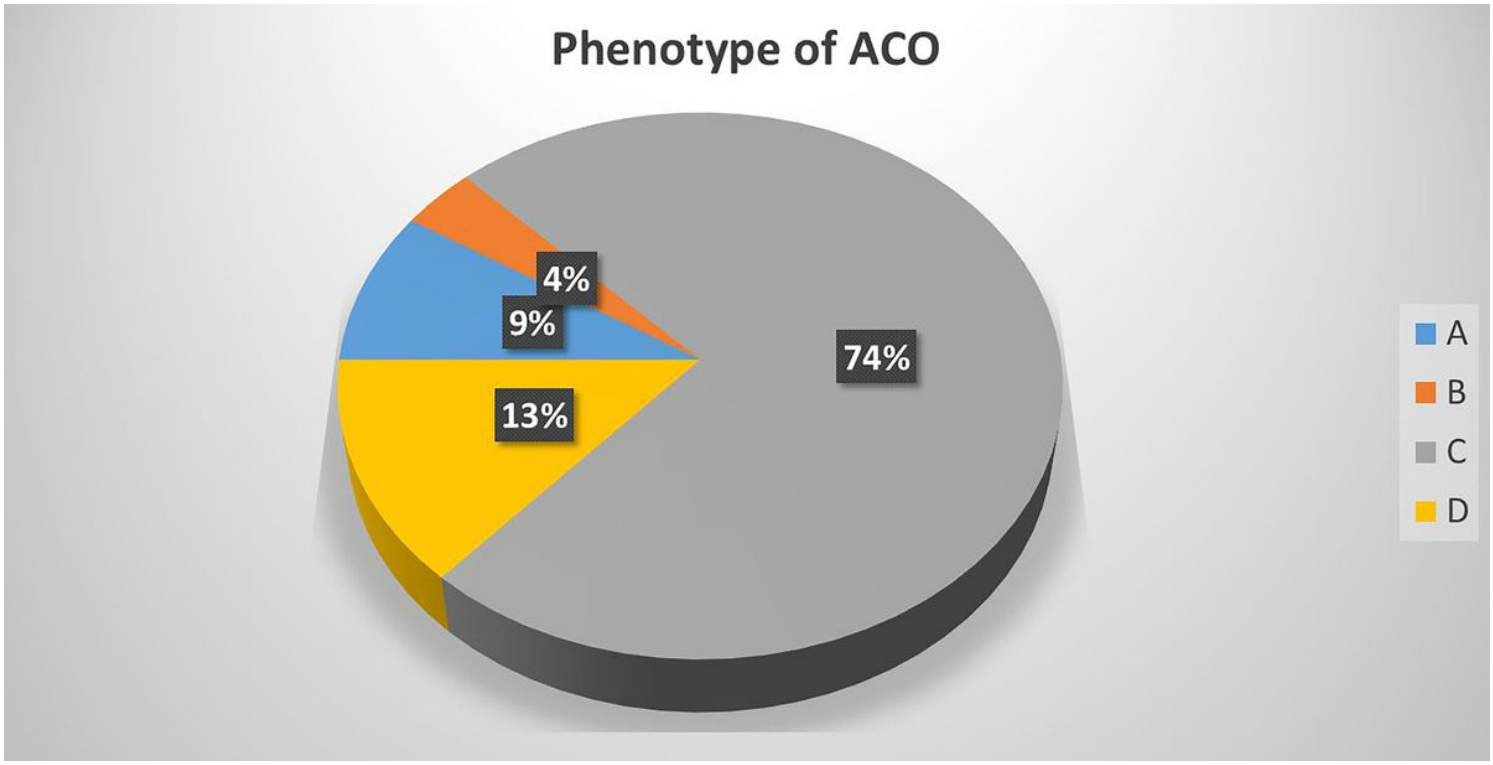

Figure 2

Distributions of patients in four ACO phenotype groups Group A, smoking 10–20 pack-years and blood eosinophil count ≥ 300 cells/μL; Group B, smoking 10–20 pack-years and eosinophil count < 300 cells/μL; Group C, smoking ≥ 20 pack-years and eosinophil count ≥ 300 cells/μL; Group D, smoking ≥ 20 pack-years and eosinophil count < 300 cells/μL. Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap

Supplementary Files

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