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Differences in prevalence of asthma–COPD overlap according to different criteria

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Abstract

Asthma and chronic obstructive pulmonary disease (COPD) are common chronic airway diseases. Overlap in the clinical features of these 2 diseases is observed in many cases, and thus, the concept of asthma–COPD overlap (ACO) has recently been proposed. However, the definition of ACO and the clinical significance remains to be determined.

We evaluated the prevalence and risk of acute exacerbation in ACO among Korean COPD patients as defined by modified Spanish criteria and American Thoracic Society (ATS) Roundtable criteria.

The prevalence of ACO was 47.7% (660/1383) by modified Spanish criteria and 1.9% (26/1383) by ATS Roundtable criteria. ACO, regardless of criteria, did not significant affect the exacerbation risk during at least 1-year follow-up period.

Substantial discrepancies were found in the prevalence and outcome of ACO according to different diagnostic criteria, which would compromise implementation of ACO before the definition is established.

Abbreviations: % pred = % predicted, ACO = asthma–COPD overlap, ATS = American Thoracic Society, BDR = bronchodilator response, CAT = COPD Assessment Test, CI = confidence interval, COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, HR = hazard ratio, ICS/LABA = inhaled corticosteroid/long-acting beta 2 agonist, IgE = immunoglobulin E, IRR = incidence rate ratio, KOCOSS = Korean COPD subtype study, LAMA = long-acting muscarinic antagonist, mMRC = modified medical research council dyspnea.

Keywords: acute exacerbation, asthma–COPD overlap, chronic obstructive lung disease, prevalence

1. Introduction

Recently published guidelines for asthma[1] and chronic obstructive pulmonary disease (COPD)[2] have introduced asthma–COPD overlap (ACO), which is a condition having clinical features of both asthma and COPD.

Typically, asthma and COPD can be easily distinguished from each other. Asthma is a chronic airway disease that typically develops in childhood and is often accompanied by allergic conditions.[1] Patients with asthma have type 2 inflammation promoted by helper T cells and eosinophils[3] and usually present variable and episodic symptoms.[4] COPD is also a chronic airway disease that is related to the smoking history of an individual.[4] Airway inflammation predominantly caused by neutrophils and type 1 T cells is observed in COPD,[3,5] leading to persistent and progressive symptoms.[4]

However, both asthma and COPD commonly occur worldwide,[6,7] and patients with these diseases present with similar respiratory symptoms related to airway obstruction. Advanced cases of COPD often have variable airflow obstruction, whereas those of asthma may be related to persistent airflow obstruction.[8] Thus, ACO was introduced some years ago,[9,10] and several studies report that patients with ACO have different clinical characteristics and courses.[9,11–13] Because treatment for ACO may be different from that for typical COPD or asthma,[14,15] the early and appropriate diagnosis of ACO may contribute to an improvement in the clinical outcomes of patients with ACO.

However, the acceptance of this condition as a unique disease entity in clinical practice is problematic and requires further study.[4,8,16] For example, issues that require investigation include the numbers of COPD patients diagnosed with ACO, and whether these patients have a clinical course and treatment reversibility distinguishable from those of patients with COPD. Most importantly, however, the definition of ACO has not been established although several diagnostic criteria exist.[17]

Editor: Jian Liu.

The authors report no conflicts of interest.

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Medicine (2018) 97:36(e12049)

Received: 22 February 2018 / Accepted: 1 August 2018

http://dx.doi.org/10.1097/MD.0000000000012049

Although it is expected that clinical features, prevalence, prognosis, and treatment reversibility will vary according to different diagnostic criteria,[18] little research has been conducted on this issue. Therefore, in this prospective cohort study, we investigated the prevalence and risk of exacerbation according to 2 distinct ACO diagnostic criteria: modified Spanish criteria[11] and American Thoracic Society (ATS) Roundtable criteria.[19]

2. Methods

We analyzed data from KOCOSS (Korean COPD subtype study NCT02800499), which is a prospective and observational study enrolling COPD patients from 28 hospitals in Korea.[20] All patients enrolled KOCOSS were provided written informed consent. COPD was defined as a post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7 in patients aged >40 years and with >10 pack-years of smoking history.

ACO is defined based on either the modified Spanish criteria (at least 1 major criterion or at least 2 minor criteria in COPD patients)[11] or ATS Roundtable criteria (all 3 major criteria and at least 1 minor criterion).[19] The modified Spanish criteria are as follows: major criteria: bronchodilator response (BDR) to salbutamol >400 mL and 15% and previous history of asthma; minor criteria: serum immunoglobulin E (IgE) >100 IU/mL or history of atopy , blood eosinophils >5%, and 2 separate BDR $>$ 12% and 200 mL. When the patient fulfills at least 1 major or 2 minor criteria, they are diagnosed as ACO. ATS Roundtable are as follows: major criteria: persistent airflow limitation and aged $\geq$40 years, smoking >10 pack-years or equivalent air pollution exposure, and documented history of asthma before 40 years of age or BDR $>$ 400 mL; minor criteria: documented history of atopy or allergic rhinitis, 2 separate BDR $>$ 12% and 200 mL, and blood eosinophil count of $\geq 300/\mu$L. We first calculated the prevalence of ACO according to these criteria. Next, the ACO and non-ACO groups were compared. Chi-square tests or Fisher's exact tests were applied for categorical variables, and Student's *t* tests or Mann–Whitney tests were used for continuous variables. Third, we investigated the risk of exacerbation in each group. Exacerbation was defined as COPD symptom aggravation requiring systemic corticosteroids, antibiotics, or hospitalization. Time to initial exacerbation was analyzed using the Cox proportional hazard model. Incidence rates were analyzed using the negative binomial regression model adjusted by covariates, including age, sex, body mass index (BMI), total symptom score for dyspnea (St. George's Respiratory Questionnaire [SGRQ], COPD Assessment Test [CAT], and mMRC [the modified medical research council dyspnea scale]), initial FEV_1 (%), use of inhaled corticosteroid/long-acting beta 2 agonist (ICS/LABA), and use of long-acting muscarinic antagonist (LAMA). $P<.05$ was considered statistically significant. All statistical analyses were performed using STATA version 14.2 (StataCorp, College Station, TX).

This study was approved by the Institutional Review Board (IRB) of each hospital (Gacheon University Gil Medical Center, Gangnam Severance Hospital, Kyung Hee University Hospital at Gangdong, Sungkyunkwan University Kangbuk Samsung Hospital, Kangwon National University Hospital, Konkuk University Hospital, Konkuk University Chungju Hospital, Kyungpook National University Hospital, Gyeongsang National University Hospital, Korea University Anam Hospital, Dongguk University Gyeongju Hospital, Dong-A University Hospital, Pusan National University Hospital, The Catholic University of Korea Bucheon St. Mary's Hospital, Soonchunhyang University Hospital Bucheon, Seoul National University Bundang Hospital, Bundang CHA Hospital, Eulji General Hospital, Seoul National University Hospital, Seoul Metropolitan Government Seoul National University Boramae Medical Center, Samsung Medical Center, The Catholic University of Korea Seoul St. Mary's Hospital, Asan Medical Center, The Catholic University of Korea St. Paul's Hospital, The Catholic University of Korea St. Vincent's Hospital, Severance Hospital, Soonchunhyang University Seoul Hospital, Ajou University Hospital, The Catholic University of Korea Yeouido St. Mary's Hospital, Yeungnam University Medical Center, Ulsan University Hospital, Wonju Severance Christian Hospital, The Catholic University of Korea Uijeongbu St. Mary's Hospital, Ewha Womans University Mokdong Hospital, Incheon St. Mary's Hospital, Inha University Hospital, Ilsan Paik Hospital, Chonnam National University Hospital, Chonbuk National University Hospital, Jeju National University Hospital, Soonchunhyang University Hospital Cheonan, Hallym University Gangnam Sacred Heart Hospital, Hallym University Kangdong Sacred Heart Hospital, Hallym University Dongtan Sacred Heart Hospital, Hallym University Chuncheon Sacred Heart Hospital, Hallym University Sacred Heart Hospital, Hanyang University Guri Hospital). Also, we obtained the approval of patient's medical records from each center and maintained confidentiality.

3. Results

In total, 1383 COPD patients were included, of which 660 (47.7%) met the modified Spanish criteria and 26 (1.9%) met the ATS Roundtable criteria. Among the patients who fulfilled the ATS Roundtable criteria, age was significantly lower for ACO than for non-ACO patients (64.8 ± 1.7 vs 69.5 ± 0.2, $P<.01$). Furthermore, the change in FEV_1 following salbutamol treatment (BDR, %) was higher in ACO than in non-ACO patients (19.1 ± 2.9 vs 7.1 ± 0.2, $P<.01$). Other demographic characteristics—SGRQ, CAT, mMRC, spirometry measurements, and previous history of acute exacerbation–were similar between ACO and non-ACO groups. (Table 1)

The prevalence of ACO as defined by modified Spanish criteria and ATS Roundtable criteria was 47.7% and 1.9%, respectively. Six hundred fifteen patients (46.5% among those for whom records were available) had a history of asthma but only 33 (2.4%) patients reported asthma documentation before 40 years of age (adjusted to 27 [2.0%] showing BDR $>$ 400 mL). Because participants in the KOCOSS study underwent annual spirometry testing, there were no cases with 2 separate tests at baseline and thus no patients were classified as meeting the criterion "two separate BDR $>$ 12% and 200 mL" (Table 2).

Patients with ACO according to the modified Spanish criteria (adjusted hazard ration [HR], 0.73; 95% confidence interval [CI] = 0.50–1.08; adjusted incidence rate ratio [IRR], 0.82; 95% CI = 0.55–1.23) and ATS Roundtable criteria (adjusted HR, 0.63; 95% CI = 0.19–2.10; adjusted IRR 0.46; 95% CI = 0.11–1.90) did not affect exacerbation risk (Table 3).

4. Discussion

Our study showed a substantial difference in the prevalence of ACO according to the 2 diagnostic criteria in COPD patients. The prevalence of ACO was 47.7% when the modified Spanish criteria were applied, but only 1.9% on ATS Roundtable criteria.

Table 1

Baseline characteristics of patients with and without diagnosis for asthma-chronic obstructive pulmonary disease overlap.

Variables	Total (n = 1383)	Modified Spanish criteria		P value	ATS Roundtable criteria		P value
		ACO (n = 660)	Non-ACO (n = 476)		ACO (n = 26)	Non-ACO (n = 1338)	
Age	69.3 ± 7.6	69.7 ± 0.3	69.0 ± 0.4	.13	64.8 ± 1.7	69.5 ± 0.2	<.01
Sex (male)	1264 (92.7%)	606 (91.8%)	445 (93.5%)	.29	26 (100%)	1238 (92.5%)	.25
Pack-year	41.6 ± 26.7	41.3 ± 1.1	42.7 ± 1.3	.42	39.5 ± 5.4	41.6 ± 0.7	.69
BMI, kg/m^2	22.8 ± 3.4	22.7 ± 0.1	23.0 ± 0.2	.14	23.1 ± 0.6	22.8 ± 0.1	.61
FEV_1 (L)	1.5 ± 0.5	1.4 ± 0.02	1.4 ± 0.02	.65	1.5 ± 0.1	1.5 ± 0.01	.77
FEV_1% pred	54.7 ± 17.5	53.9 ± 0.7	54.9 ± 0.8	.35	52.2 ± 2.9	54,9 ± 0.5	.43
FVC (L)	3.04 ± 0.79	3.0 ± 0.03	3.1 ± 0.04	.11	3.1 ± 0.2	3.0 ± 0.02	.91
FVC % pred	80.9 ± 17.7	80.1 ± 0.7	82.2 ± 0.8	.05	76.6 ± 3.5	81.1 ± 0.5	.21
FEV_1/FVC % pred	61.0 ± 42.0	58.2 ± 1.0	63.4 ± 4.4	.21	57.0 ± 6.6	61.1 ± 1.8	.81
BDR %	7.3 ± 0.3	8.3 ± 0.4	7.2 ± 0.4	.07	19.1 ± 2.9	7.1 ± 0.2	<.01
mMRC	1.5 ± 0.9	1.5 ± 0.04	1.5 ± 0.04	.87	1.3 ± 0.2	1.5 ± 0.03	.21
SGRQ total	34.9 ± 19.0	34.6 ± 0.8	35.1 ± 0.9	.67	32.9 ± 4.4	34.8 ± 0.5	.62
CAT total	15.9 ± 7.9	15.6 ± 0.3	16.1 ± .4	.32	16.8 ± 1.5	15.8 ± 0.2	.52
Total exacerbation in the past year (/yr)	2.1 ± 2.1	2.0 ± 0.1	2.2 ± 0.2	.42	1.4 ± 0.4	2.1 ± 0.1	.42
Severe exacerbation in the past year (/yr)	0.7 ± 1.1	0.8 ± 0.1	0.6 ± 0.1	.06	0.3 ± 0.2	0.7 ± 0.1	.31

% pred = % predicted, ACO = Asthma-chronic obstructive pulmonary disease overlap, ATS = American thoracic society, BDR = bronchodilator response, BMI = body mass index, CAT total = COPD Assessment Test total, FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, mMRC = The modified medical research council dyspnea scale, SGRQ total = St George's Respiratory Questionnaire total.

Table 2

Patients fulfilling the modified Spanish and American thoracic society Roundtable criteria for asthma-chronic obstructive pulmonary disease overlap.

Modified Spanish criteria	Meeting criterion (n)
Major (1) Previous history of asthma	615 (46.5%)
Major (2) BDR > 15% and 400 mL	27 (2.0%)
Minor (1) Serum IgE > 100 IU, or history of atopy	270 (74.0%)
Minor (2) 2 separate BDR > 12% and 200 mL	0
Minor (3) Blood eosinophils > 5%	206 (18.4%)
ACOS	660 (47.7%)
ATS Roundtable criteria	
Major (1) Post-BDR FEV_1/FVC < 0.7 and age > 40 years	1383 (100%)
Major (2) Smoking > 10 PY or air pollution ≥ 10 PY	1383 (100%)
Major (3) Asthma < 40 years or BDR > 400 mL in FEV_1	60 (4.4%)
Minor (1) History of atopy or allergic rhinitis	165 (12.5%)
Minor (2) Two separate BDR > 12% and 200 mL	0
Minor (3) Blood eosinophil count > 300/μL	277 (24.8%)
ACO	26 (1.9%)

ACO = asthma-chronic obstructive pulmonary disease overlap, ATS = American thoracic society, BDR = bronchodilator response, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, IgE = immunoglobulin E, PY = pack-year.

ACO, regardless of criteria, did not affect the exacerbation risk during the follow-up period.

According to previous reports,[13,19,21–24] the prevalence of ACO among COPD patients ranged from 3.3% to 54.6%. However, no study to date has compared prevalence according to different criteria. In addition, no study has reported the prevalence of ACO according to ATS Roundtable criteria among COPD patients. This is the first report, to our knowledge, to compare 2 diagnostic criteria of ACO, and the first on the prevalence of ACO according to ATS Roundtable criteria among COPD patients from a prospective cohort.

The substantial discrepancy in the prevalence of ACO in our study could have been affected by several factors. First, around half of the patients with COPD in our study reported a history of asthma, which resulted in a high percentage fulfilling the first major criterion of the modified Spanish criteria. While previous studies [12,24–26] reported that many COPD patients had a history of asthma, the percentage of those with such a history among our COPD patients was relatively high. This may be due to the fact that cheonsik, the Korean word for asthma, could have been confused with COPD, heart failure, or chronic respiratory conditions in Korea, and the condition is thought to be part of the "normal" aging process and is frequently accepted as part of

Table 3

The risk of moderate-to-severe exacerbation of chronic obstructive pulmonary disease according to asthma-chronic obstructive pulmonary disease criteria.

Time to first moderate-to-severe exacerbation				
	Crude HR (95% CI)	P value	Adjusted HR (95% CI)*	P value
ACO according to modified Spanish criteria	0.75 (0.54–1.03)	.079	0.73 (0.50–1.08)	.11
ACO according to ATS Roundtable criteria	0.49 (0.18–1.34)	.162	0.63 (0.19–2.10)	.449
Incidence rate of moderate-to-severe exacerbation				
	Crude IRR (95% CI)	P value	Adjusted IRR (95% CI)*	P value
ACO according to modified Spanish criteria	0.84 (0.57–1.24)	.391	0.82 (0.55–1.23)	.335
ACO according to ATS Roundtable criteria	0.43 (0.11–1.72)	.230	0.46 (0.11–1.90)	.282

ACO = asthma-chronic obstructive pulmonary disease overlap, ATS = American thoracic society, CI = confidence interval, HR = hazard ratio, IRR = incidence rate ratio.

* Models adjusted for age, sex, body mass index, total St. George's Respiratory Questionnaire score, initial forced expiratory volume in 1 second (%), use of inhaled corticosteroid/long-acting beta 2 agonist, and use of long-acting muscarinic antagonist.

growing old.[24,26] The possibility that cheonsik is not the specific term for asthma can be illustrated by the fact that the percentage of patients with documented asthma history before 40 years of age was relatively small, resulting in the low percentage of major ATS roundtable criteria recorded. Our results show the weakness of diagnosis based on self-reported history. In fact, the revised Global Initiative for Asthma guidelines state the importance of objective measurement of variable expiratory airflow limitation, in combination with symptoms.[1] In addition, only a small proportion of COPD patients had bronchodilator reversibility >400 mL, which contributed to the low rate of fulfillment for the major ATS Roundtable criteria. These findings correspond to previous studies, which reported that 4.7% (39/831) of COPD patients had BDR > 15% and 400 mL,[11] and 1.17% of those with mild COPD had BDR > 15%.[12] In fact, this cut-off value (>400 mL) used to determine the presence of asthma does not have any supporting evidence. Both modified Spanish[11] and ATS Roundtable criteria[19] define minor ACO criteria with BDR >12%, 200 mL on 2 separate visits, but the basis for this is also unclear.

Most previous studies have shown worse outcomes in ACO patients compared with non-ACO COPD patients.[9,12,13,23] On the other hand, a CHAIN cohort study reported enhanced survival in the ACO group.[11] Our study did not find any statistically significant effects of ACO on exacerbation risk. These differences may depend on the differences in the definition criteria for ACO used in studies. However, interestingly, even when the target studies were confined to those applying modified Spanish criteria as criteria for ACO[11,23] including the current study, different results were observed. It suggests ACO might not be a good prognostic factor. Further studies are needed.

Our study has several limitations. First, data were missing on serum IgE, eosinophil count, and age at diagnosis of asthma. However, we found no significant difference between patients with and without missing data regarding baseline clinical characteristics. Second, the number of patients diagnosed with ACO according to ATS Roundtable criteria was low, and only 5 patients experienced acute exacerbation; this could have resulted in low statistical power.

In conclusion, the prevalence of ACO and clinical outcomes varied markedly according to diagnostic criteria. This may be due to the dependence on self-reported history in the diagnostic criteria, which suggests the requirement of objective measurement-based diagnosis. This substantial discrepancy would hinder the implementation of ACO before determination of the definition.

Author contributions

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