Analysis of Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome Defined on the Basis of Bronchodilator Response and Degree of Emphysema

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Abstract

Rationale: Despite the increasing recognition of asthma–chronic obstructive pulmonary disease overlap syndrome (ACOS) as a clinical entity, it remains poorly characterized due to a lack of agreement on its definition and diagnostic criteria.

Objectives: The aim of this study was to use spirometry and computed tomography (CT) to help better define ACOS as well as to classify subjects with ACOS based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) letter grade.

Methods: We analyzed 10,192 subjects enrolled in the COPDGene Study. Subjects were non-Hispanic white or African American current or former smokers aged 45–80 years with at least a 10-pack-year smoking history. Subjects were categorized as having either ACOS with a bronchodilator response or chronic obstructive pulmonary disease with emphysema on the basis of spirometry, high-resolution CT, and a history of asthma or hay fever.

Measurements and Main Results: Subjects with ACOS were younger (60.6 vs. 65.9 years old; $P < 0.0001$), more likely to be African American (26.8% vs. 14.4%; $P < 0.0001$), had a higher body mass index (29.6 vs. 25.1 kg/m^2; $P < 0.0001$), and were more likely to be current smokers (50.9% vs. 20.7%; $P < 0.0001$). The majority of subjects with ACOS were categorized as GOLD grade B. Despite less severe spirometry and CT findings in subjects with ACOS, there was no significant difference in severe or frequent exacerbations.

Conclusions: Bronchodilator responsiveness and degree of emphysema can help define ACOS. When defined on the basis of bronchodilator responsiveness and degree of emphysema, patients with ACOS represent a unique and high-risk group with distinct clinical features.

Keywords: asthma–COPD overlap syndrome; chronic obstructive pulmonary disease; asthma; Global Initiative for Chronic Obstructive Lung Disease letter grade; bronchodilator responsiveness

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Asthma and chronic obstructive pulmonary disease (COPD) are chronic diseases characterized by airway inflammation and airflow obstruction, which are common in the general population. Asthma is typically characterized by reversible airflow obstruction, whereas COPD is characterized mainly by irreversible airflow obstruction. However, there can be significant overlap between these two diseases that has led to the recognition of asthma–COPD overlap syndrome (ACOS).

Nearly one-fourth of patients with COPD report a history of asthma (1). Features of both asthma and COPD are associated with a poorer quality of life, a more rapid decline in lung function, a higher mortality (2, 3), and use of a greater amount of healthcare resources than asthma or COPD alone (4). In a number of studies, researchers have attempted to better define this distinct subset of patients; however, conflicting data have been published. One possible reason for this is the lack of agreement on a definition of and diagnostic criteria for ACOS. Drafters of the Global Initiative for Asthma and Global

Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recently acknowledged the disease entity of ACOS and provided some insight into the diagnosis; however, a consensus on the diagnostic criteria remains elusive (5, 6). The authors of a number of papers have attempted to define ACOS, including Soler-Cataluña and colleagues, who defined major and minor criteria to better diagnose ACOS (7). The major criteria include a positive bronchodilator test (increase in FEV_1 ⩾15% and ⩾400 ml), eosinophilia in sputum, and a personal history of asthma. Minor criteria include elevated total IgE, a personal history of atopy, and a positive bronchodilator test (increase in FEV_1 ⩾12% and ⩾200 ml) on two or more occasions.

Other reasons why there are conflicting data are that a dual diagnosis of asthma and COPD is often an exclusion criterion for many studies, and, for those studies in which patients with ACOS are included, the overlap group is often defined as those with COPD and a prior history of asthma. Asthma and COPD both involve airway inflammation and share many features that can lead to a misdiagnosis. Researchers in a number of studies have evaluated patients with a diagnosis of asthma in the primary care setting. When objective testing is performed, a significant number of patients have a diagnosis other than asthma (8, 9). Similar results have been shown in patients with a prior history of COPD (10, 11).

On the basis of these studies, it appears that relying solely on an individual's self-reported history of asthma is not an adequate criterion for an accurate diagnosis of asthma or ACOS. The majority of past ACOS studies have been focused on clinical features, risk factors, or quality of life. Hardin and colleagues previously described the clinical features of ACOS in the COPDGene Study (12, 13). In their cohort, the ACOS group was defined as subjects with COPD and a previous diagnosis of asthma received before the age of 40 years. Although the present study includes the same COPDGene cohort that was used by Hardin and colleagues in previous studies (12, 13), the criteria used to define ACOS were very different and included a prior history of asthma along with bronchodilator response and radiographic imaging.

The aim of this study was to determine if bronchodilator responsiveness and degree of emphysema on the basis of high-resolution computed tomography (HRCT) can help define the clinical, physiologic, and radiographic features of patients with ACOS. In addition, to our knowledge, no study to date has included an evaluation of ACOS and classification based on GOLD letter grade. In this study, we also classified patients with ACOS based on GOLD letter grade.

Methods

Subjects and Procedures

We performed a retrospective analysis of the COPDGene Study, a multicenter prospective observational study involving 21 clinical centers and 10,192 subjects. The study details have been described previously (14) and are available at the COPDGene website (http://www.copdgene.org/). Briefly, enrolled subjects were self-identified non-Hispanic white or African American current or former smokers between the ages of 45 and 80 years with at least a 10-pack-year history of smoking. Exclusion criteria were pregnancy, history of a respiratory disorder other than asthma, prior lobectomy or lung volume reduction procedure, undergoing cancer treatment, or known or suspected lung cancer. Institutional review board approval was obtained for all participating centers, and all subjects signed informed consent prior to enrollment.

At the time of enrollment, all subjects completed standardized questionnaires regarding medical history, respiratory symptoms, medication use, and exacerbation history, including frequency and severity of exacerbations. Exacerbations were defined as episodes during which the subject experienced shortness of breath or change in sputum production that required treatment with antibiotics and/or systemic steroids. Subjects were defined as frequent exacerbators if they had experienced at least two exacerbations in the year prior to enrollment. Severe exacerbations were defined as those exacerbations that required a visit to an emergency room or hospitalization. Subjects also performed standardized spirometry and underwent HRCT of the chest. All subjects provided inspiratory and expiratory computed tomographic (CT) scans, and 3D Slicer software was used to determine the presence and quantify the percent emphysema and gas trapping.

The degree of emphysema was defined as the percentage of lung with attenuation values less than or equal to −950 Hounsfield units on inspiratory images, and the degree of gas trapping was defined as the percentage of lung with attenuation values less than or equal to −856 Hounsfield units on expiratory images. VIDA software (VIDA Diagnostics, Coralville, IA) was used to calculate the wall thickness of a hypothetical airway with a 10-mm internal perimeter, as well as to quantify wall area percentage of segmental airways. For this study, the cutoff point for percent emphysema on CT scans for categorizing subjects as having either ACOS or COPD alone was 15%. This value is based on the results of a previous study in the COPDGene cohort performed by Hardin and colleagues (12), who found that in subjects with ACOS the average percent emphysema on CT scans was less than 15%, whereas in those with COPD alone it was greater than 15%.

Statistical Analysis

The primary analysis included all subjects enrolled in COPDGene. Using a self-reported history or prior physician diagnosis of asthma or hay fever, along with spirometry and CT scan features, patient data were analyzed to determine which subjects met the criteria for ACOS with bronchodilator response (ACOS-BDR) or COPD with emphysema.

Subjects were categorized as having ACOS-BDR if they met either one of two criteria: (*1*) a history of asthma or hay fever, evidence of obstructive lung disease noted on spirometry (FEV_1/FVC, <0.7) with improvement in FEV_1 greater than 200 ml and greater than 12% following bronchodilator administration, and less than 15% emphysema on HRCT; or (*2*) evidence of obstructive lung disease noted on spirometry with improvement in FEV_1 greater than 400 ml and greater than 15% following bronchodilator administration, regardless of history of asthma or hay fever; and less than 15% emphysema on the basis of HRCT. Subjects were categorized as having COPD with emphysema if they had obstructive lung disease noted on spirometry with a post-bronchodilator improvement in FEV_1 less than 400 ml and less than 15% with no history of asthma or hay fever, as well as greater than 15% emphysema on the basis of HRCT. The spirometry values used to determine whether subjects met the criteria for ACOS-BDR versus COPD with emphysema were similar to the values proposed by Soler-Cataluña and colleagues (7) and the most recent GOLD guidelines (6).

Data were analyzed by using JMP software version 10.0.2 (SAS Institute, Cary, NC). Data were analyzed by using the chi-square test for categorical variables and the *t* test for continuous variables. Linear and logistic regression models were performed to adjust for potentially cofounding variables. The following parameters were adjusted for age, race, sex, body mass index (BMI), total pack-years of smoking, current smoking, and FEV_1 percent predicted value: body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index; St. George's Respiratory Questionnaire (SGRQ) score; 6-minute walk test; severe exacerbations; and at least two exacerbations in the year prior to enrollment. Percent emphysema and percent gas trapping on the basis of CT scans were adjusted for the same variables as previously mentioned as well as for type of CT scanner used.

Results

Demographics

Of the 10,192 subjects enrolled, 385 and 620 met the criteria for ACOS-BDR and COPD with emphysema, respectively. Compared with subjects with COPD with emphysema, subjects with ACOS-BDR were younger (60.6 vs. 65.9 years old; $P < 0.0001$), more likely to be African American (26.8% vs. 14.4%; $P < 0.0001$), and had a higher BMI (29.6 vs. 25.1 kg/m^2; $P < 0.0001$). Subjects with ACOS-BDR were also more likely to be current smokers (50.9% vs. 20.7%; $P < 0.0001$) but had less overall total pack-years of smoking (48 vs. 55.7; $P < 0.0001$) and were less likely to be on supplemental oxygen (10.9% vs. 45.2%; $P < 0.0001$). Subjects with ACOS-BDR also had greater incidence of obstructive sleep apnea (OSA) (19.5% vs. 11.1%; $P = 0.0002$), gastroesophageal reflux disease (32.7% vs. 24.9%; $P = 0.007$), and diabetes mellitus (15.3% vs. 6.5%; $P < 0.0001$) (Table 1). Subjects with ACOS-BDR were less likely to be on a long-acting β-agonist (LABA) (6.8% vs. 13.9%; $P = 0.006$), a long-acting muscarinic antagonist (20% vs. 60.8%; $P < 0.0001$), or a combination LABA/inhaled corticosteroid (29.9% vs. 55.6%; $P < 0.0001$) (Table 2).

Quality of Life

In univariate analysis, subjects with ACOS-BDR had a better quality of life and less dyspnea than those with COPD with emphysema, as evidenced by a lower SGRQ score (37.3 vs. 42.5; $P = 0.0002$) and a lower modified Medical Research Council dyspnea scale score (1.8 vs. 2.4; $P < 0.0001$), respectively. Subjects with ACOS-BDR were able to ambulate greater distances in their 6-minute walk test than those subjects with COPD with emphysema (1,313.4 vs. 1,130.4 ft; $P < 0.0001$). ACOS-BDR was also associated with a lower predicted mortality on the basis of BODE index (1.9 vs. 3.8; $P < 0.0001$). There was no significant difference between the two groups with regard to severe exacerbations or frequent exacerbations (Table 1). We found similar results when we adjusted for age, race, sex, BMI, total pack-years of smoking, and current smoking.

However, when we adjusted for FEV_1 percent predicted in addition to age, race,

Table 1. Characteristics of subjects with chronic obstructive disease with emphysema and asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response

	COPD (*n* = 620)	ACOS-BDR (*n* = 385)	*P* Value*
Demographics			
Age, yr	65.9 (7.6)	60.6 (9.02)	<0.0001
Sex			0.17
Male	386 (62.3)	223 (57.9)	
Female	234 (37.7)	162 (42.1)	
Race			<0.0001
White	531 (85.7)	282 (73.3)	
African American	89 (14.4)	103 (26.8)	
BMI	25.1 (4.8)	29.6 (6.3)	<0.0001
Pack-years of smoking	55.7 (27.3)	48 (26.1)	<0.0001
Current smoker	128 (20.7)	196 (50.9)	<0.0001
Oxygen therapy	280 (45.2)	42 (10.9)	<0.0001
SGRQ score	42.5 (19.6)	37.3 (22.4)	0.0002
mMRC dyspnea scale score	2.4 (1.3)	1.8 (1.4)	<0.0001
BODE index	3.8 (2.1)	1.9 (1.7)	<0.0001
6 MWT, ft	1,130.4 (395.2)	1,313.4 (355.1)	<0.0001
Two or more exacerbations/yr	108 (17.4)	58 (15.1)	0.33
Severe exacerbations†	148 (23.9)	80 (20.8)	0.26
GOLD letter grade			<0.0001
A	76 (12.3)	121 (31.4)	
B	93 (15)	154 (40)	
C	47 (7.6)	10 (2.6)	
D	404 (65.2)	100 (26)	
GOLD stage			<0.0001
I	36 (5.8)	66 (17.1)	
II	147 (23.7)	245 (63.6)	
III	239 (38.6)	71 (18.4)	
IV	198 (31.9)	3 (0.8)	
Comorbidities			
Cardiac‡	118 (19)	76 (19.7)	0.78
Sleep apnea	69 (11.1)	75 (19.5)	0.0002
Diabetes	40 (6.5)	59 (15.3)	<0.0001
Hypertension	264 (42.6)	188 (48.8)	0.05
Hypercholesterolemia	223 (36)	154 (40.9)	0.2
GERD	154 (24.9)	126 (32.7)	0.007

Definition of abbreviations: 6MWT = 6-minute walk test; ACOS-BDR = asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response; BMI = body mass index; BODE index = body mass index, airflow obstruction, dyspnea, and exercise capacity index; COPD = chronic obstructive pulmonary disease; GERD = gastroesophageal reflux disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; mMRC = modified Medical Research Council; SGRQ = St. George's Respiratory Questionnaire.

Values are presented as mean (SD) or count (percent).

*By *t* test or chi-square test.

†Severe exacerbations were defined as the presence of a COPD exacerbation resulting in presentation to an emergency room or a hospital admission in the year prior to presentation.

‡Cardiac comorbidity was defined as having a history of coronary artery disease, prior myocardial infarction, congestive heart failure, history of a cerebrovascular accident, or history of peripheral vascular disease.

Table 2. Respiratory medication use in subjects with chronic obstructive disease with emphysema and those with asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response

	COPD	ACOS-BDR	*P* Value*
SABA	402 (65.9)	228 (59.8)	0.05
SAMA	54 (9.1)	45 (12.1)	0.13
SABA/SAMA	145 (24.3)	74 (20)	0.13
LABA	83 (13.9)	25 (6.8)	0.006
LAMA	369 (60.8)	74 (20)	<0.0001
Theophylline	30 (5.1)	11 (3)	0.12
ICS	79 (13.3)	55 (15)	0.46
LABA/ICS	339 (55.6)	111 (29.9)	<0.0001
Oral steroid	36 (6.1)	19 (5.2)	0.55

Definition of abbreviations: ACOS-BDR = asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response; COPD = chronic obstructive pulmonary disease; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LAMA = long-acting muscarinic antagonist; SABA = short-acting β-agonist; SAMA = short-acting muscarinic antagonist.
Values are presented as count (percent).
*By *t* test or chi-square test.

sex, BMI, total pack-years of smoking, and current smoking, we observed no significant difference between the two groups in SGRQ score, BODE index, or 6-minute walk distance. There were significant differences in severe exacerbations and frequent exacerbations, as subjects with ACOS-BDR were more likely to experience severe exacerbations (odds ratio, 0.58; 95% confidence interval, 0.37–0.9; $P = 0.01$) and to have frequent exacerbations (odds ratio, 0.48; 95% confidence interval, 0.29–0.8; $P = 0.005$) (Table 3)

Spirometry and HRCT

Compared with subjects with COPD with emphysema, subjects with ACOS-BDR had a higher FEV_1/FVC (0.6 vs. 0.4; $P < 0.0001$), FEV_1 (percent predicted, 65.7% vs. 42.2%; $P < 0.0001$), and FVC (percent predicted, 86.6% vs. 76.2%; $P < 0.0001$). Subjects with ACOS-BDR had less emphysema (4.3% vs. 27.8%; $P < 0.0001$) and less gas trapping (25.8% vs. 57.9%; $P < 0.0001$) visualized on their CT scans, but they had more airway disease as evidenced by a greater 10-mm internal perimeter (3.74 vs. 3.69; $P < 0.0001$) and greater segmental wall area (63.4% vs. 61.8%; $P < 0.0001$) (Table 4). When adjusted for age, race, sex, BMI, total pack-years of smoking, current smoking, FEV_1 percent predicted, and type of CT scanner used, subjects with ACOS-BDR had 16.9% less emphysema ($P < 0.0001$) and 15.8% less gas trapping ($P < 0.0001$) on the basis of CT scans (Table 3).

GOLD Letter Grade

The distribution of subjects with ACOS-BDR versus COPD with emphysema according to GOLD letter grade is shown in Figure 1. Most notable is the large percentage of subjects with ACOS-BDR categorized as GOLD grade B. In subgroup analysis, subjects with ACOS-BDR who were current smokers were more likely to be categorized as GOLD grade B than non–GOLD grade B (57.1% vs. 46.8%; $P = 0.05$).

Discussion

Our results demonstrate that there are distinct features that can help identify patients with ACOS. These subjects are more likely to be younger, African American, and current smokers, as well as to have a higher BMI, than subjects with COPD with emphysema. Subjects with ACOS-BDR also have less severe airflow obstruction noted on spirometry and less emphysema and gas trapping noted on CT scans. In a recent study, Gao and colleagues also found that subjects with ACOS had less emphysema than those with COPD and suggested that CT densitometry can be used to characterize ACOS as a distinct phenotype from COPD (15).

Despite the less severe spirometric and CT findings, subjects with ACOS-BDR were just as likely as those with COPD with emphysema to experience frequent exacerbations as well as severe exacerbations. When outcomes were adjusted for age, race, sex, BMI, total pack-years of smoking, and current smoking, the results remained unchanged. However, after we adjusted for FEV_1 percent predicted in addition to age, race, sex, BMI, total pack-years of smoking, and current smoking, we found that subjects with ACOS-BDR were more likely than those with COPD with emphysema to experience frequent exacerbations as well as severe exacerbations. This indicates that there are factors other than degree of airflow obstruction contributing to exacerbations in patients with ACOS-BDR. Possible explanations for this may be the higher incidence of gastroesophageal reflux disease, OSA, and current smoking in subjects with ACOS-BDR, all of which

Table 3. Adjusted analysis of outcomes between subjects with chronic obstructive disease with emphysema and those with asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response

Outcome	Parameter Estimate (SE) or OR (95% CI)*	*P* Value
BODE index	0.18 (0.1)	0.07
SGRQ score	−1.7 (1.5)	0.23
6MWT, ft	−10.8 (26.4)	0.68
Severe exacerbations	0.58 (0.37–0.9)	0.01
Two or more exacerbations/yr	0.48 (0.29–0.8)	0.005
Percent emphysema, −950 HU†	16.9 (0.63)	<0.0001
Percent gas trapping, −856 HU†	15.8 (0.92)	<0.0001

Definition of abbreviations: 6MWT = 6-minute walk test; BODE index = body mass index, airflow obstruction, dyspnea, and exercise capacity index; CI = confidence interval; OR = odds ratio; SGRQ = St. George's Respiratory Questionnaire.
*All outcomes were adjusted for age, race, sex, body mass index, total pack-years of smoking, current smoking, and FEV_1 percent predicted.
†Siemens 64 sensation scanners gave aberrant lung density measurements and therefore this scanner type was adjusted as a covariate.

Table 4. Spirometry and computed tomography findings in subjects with chronic obstructive disease with emphysema and those with asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response

	COPD	ACOS-BDR	*P* Value*
COPD characteristics			
FVC, % predicted	76.2 (21.5)	86.6 (17.7)	<0.0001
FEV_1, % predicted	42.2 (20.7)	65.7 (17.4)	<0.0001
FEV_1/FVC	0.4 (0.1)	0.6 (0.09)	<0.0001
CT characteristics			
Percent emphysema, −950 HU	27.8 (10)	4.3 (3.7)	<0.0001
Percent gas-trapping, −856 HU	57.9 (13.5)	25.8 (13.6)	<0.0001
Airway wall thickness, Pi10	3.69 (0.13)	3.74 (0.17)	<0.0001
Segmental airway wall area, %	61.8 (3.1)	63.4 (3.2)	<0.0001

Definition of abbreviations: ACOS-BDR = asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response; COPD = chronic obstructive pulmonary disease; CT = computed tomography; HU = Hounsfield units; Pi10 = square root wall area of an airway of 10-mm internal perimeter.
Values are presented as mean (SD) or count (percent).
*By *t* test or chi-square test.

are risk factors associated with exacerbations. Another possible explanation may be the role of small airway disease in subjects with ACOS-BDR.

As expected, subjects with ACOS-BDR had less emphysema and gas trapping noted on CT scans, as that was predetermined in the definition. However, the degree of emphysema and gas trapping were disproportionate between the two groups. Subjects with ACOS-BDR had a higher proportion of gas trapping in relation to the degree of emphysema than did subjects with COPD with emphysema, and they also had increased small airway wall thickening. This suggests that ACOS-BDR is associated with a higher incidence of small airway disease, as well as proportionally smaller airway obstruction, than is COPD with emphysema. This is not unexpected, since gas trapping in patients with asthma is associated with duration of asthma, persistent airflow obstruction (FEV_1/FVC), atopy, and prior history of pneumonia (16). Many of the same features are present in patients with ACOS and similar to those of the subjects with ACOS-BDR in this study. Gas trapping in patients with asthma is also associated with increased airway neutrophilic inflammation (16).

While asthma and COPD both involve airway inflammation, airway inflammation is considered mainly to be eosinophilic and CD4 cell driven in asthma and neutrophilic and CD8 cell driven in COPD (17–19). However, studies have shown that there is an increase in neutrophils in the airways of patients with asthma with incomplete reversibility, and the degree of neutrophilia is related to FEV_1 decline (20–22). It has also been shown that in patients with asthma who smoke there is an increase in neutrophils in the airways similar to that seen in patients with COPD (23, 24). The rate of FEV_1 decline is also accelerated in patients with asthma who smoke compared with patients with asthma who do not (25). It is therefore likely that current smoking in subjects with ACOS, coupled with the long duration of asthma, leads to inflammation and small airway remodeling with development of symptoms earlier in the disease course than that seen in those with COPD with emphysema.

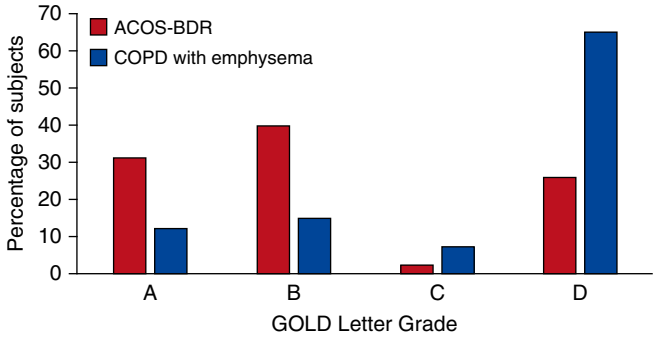

Figure 1. Percentage of include subjects by Global Initiative for Chronic Obstructive Lung Disease (GOLD) letter grade. ACOS-BDR = asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response; COPD = chronic obstructive pulmonary disease.

The majority of subjects with ACOS-BDR, when categorized on the basis of spirometry alone, were classified as GOLD stage I or II. However, when categorized by GOLD letter grade, nearly half of the subjects with ACOS-BDR were classified as GOLD grade B, indicating a high degree of symptoms despite less severe airflow obstruction (Figure 2). Furthermore, nearly two-thirds of those with ACOS-BDR were classified as GOLD grade B or D, indicating this as a cohort with a high degree of disease instability and symptomatology. Subjects with ACOS-BDR who were current smokers were also more likely to be categorized as GOLD grade B, suggesting that current smoking is a contributing factor to the increased symptoms and unstable nature of ACOS. On the basis of these findings, patients with ACOS are a particularly high-risk group.

In a study by Agusti and colleagues (26) in which they examined the characteristics, stability, and outcomes related to the GOLD letter grades in subjects with COPD, patients classified as grades A and D were relatively stable over time, whereas those categorized as grades B and C had more temporal variability. As expected, the hospitalization and mortality rates were lowest in GOLD grade A and highest in grade D. However, the rates of hospitalization and mortality were similar in GOLD grades B and C, despite grade B subjects' having less severe airflow obstruction and fewer exacerbations. They noted that those in GOLD grade B had higher prevalence of comorbidities and systemic inflammation than those in grade C. Lange and colleagues (27) also noted that patients in grade B had significantly more comorbidities, mainly cardiovascular disease and cancer. They also noted that patients in GOLD grade B had a significantly higher mortality than patients in grade C. It is therefore not surprising that, in our present study, we found a large

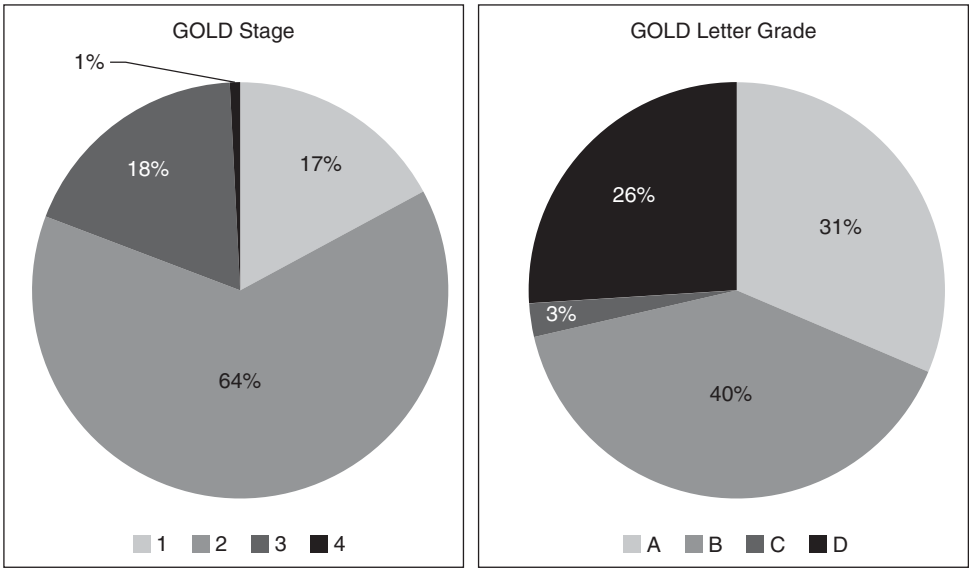

Figure 2. Distribution of subjects with asthma–chronic obstructive pulmonary disease overlap syndrome with bronchodilator response by Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage and letter grade.

number of patients with ACOS-BDR categorized as GOLD grade B, as they have a higher incidence of cardiac risk factors, including OSA, diabetes mellitus, obesity, and current smoking.

Limitations

We performed a retrospective analysis, and we were limited in our ability to examine long-term data. Long-term data and outcomes for COPDGene were not available at the time of this study. Our criteria for asthma and hay fever were based on a patient's self-reported history or prior physician diagnosis, which could be subject to recall bias or incorrect diagnoses.

Although our study has limitations, it does provide some novel data. We were able to demonstrate that there are distinct clinical features that can help identify subjects with ACOS-BDR. Subjects with ACOS-BDR are likely to be younger, African American, and current smokers, as well as to have a higher BMI with less emphysema and more small airway disease noted on CT scans, than those with COPD with emphysema. These results are similar to those of previous studies in which investigators have evaluated clinical features associated with ACOS, including those by Hardin and colleagues, who used the COPDGene cohort (12, 13).

However, our study demonstrates additional features that can help identify subjects with ACOS and provide further insight into this complex disease. First, we categorized subjects with ACOS-BDR on the basis of GOLD letter grade. We were able to show that the majority of subjects with ACOS-BDR were categorized as GOLD grade B, a highly unstable group with severe symptoms despite less severe airflow obstruction. Second, we found that subjects with ACOS-BDR had a number of significant comorbidities, many of which are known risk factors associated with exacerbations. In addition, current smoking appears to be a factor that drives symptoms in these subjects and categorizes them as GOLD grade B. Despite the large number of ACOS-BDR subjects classified as GOLD grade B, only a small percentage of them were being treated with a LABA or long-acting muscarinic antagonist. Early and aggressive treatment with combination therapy may help alleviate symptoms and decrease exacerbations. Recognition and treatment of comorbidities and aggressive smoking cessation may also play a key role in preventing exacerbations and alleviating the morbidity associated with ACOS; however, future studies on the treatment of ACOS are needed.

Conclusions

ACOS remains difficult to define, partly due to lack of diagnostic criteria. Bronchodilator responsiveness and degree of emphysema on the basis of HRCT can provide objective measures that can help define ACOS, which is important, given the high morbidity and unstable nature of the disease. When defined on the basis of bronchodilator responsiveness and degree of emphysema, patients with ACOS represent a unique and high-risk group with distinct clinical features. These patients deserve special attention, and practitioners need to be diligent in evaluation of them. ■

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