The value of bronchodilator response in FEV1 and FeNO for differentiating between chronic respiratory diseases: an observational study

Zhaoqian Gong[1†], Junwen Huang[1†], Guiling Xu[1†], Ying Chen[1], Maosheng Xu[1], Yanyan Ma[1], Wenqu Zhao[1], Yanhong Wang[1], Jianpeng Liang[1], Chunquan Ou[2], Laiyu Liu[1], Shaoxi Cai[1] and Haijin Zhao[1*]

Abstract

Background There is no uniform standard for a strongly positive bronchodilation test (BDT) result. In addition, the role of bronchodilator response in differentiating between asthma, chronic obstructive pulmonary disease (COPD), and asthma–COPD overlap (ACO) in patients with a positive BDT result is unclear. We explored a simplified standard of a strongly positive BDT result and whether bronchodilator response combined with fractional exhaled nitric oxide (FeNO) can differentiate between asthma, COPD, and ACO in patients with a positive BDT result.

Methods Three standards of a strongly positive BDT result, which were, respectively, defined as post-bronchodilator forced expiratory volume in 1-s responses (ΔFEV_1) increasing by at least 400 mL + 15% (standard I), 400 mL (standard II), or 15% (standard III), were analyzed in asthma, COPD, and ACO patients with a positive BDT result. Receiver operating characteristic curves were used to determine the optimal values of ΔFEV_1 and FeNO. Finally, the accuracy of prediction was verified by a validation study.

Results The rates of a strongly positive BDT result and the characteristics between standards I and II were consistent; however, those for standard III was different. $\Delta FEV_1 \geq 345$ mL could predict ACO diagnosis in COPD patients with a positive BDT result (area under the curve [AUC]: 0.881; 95% confidence interval [CI] 0.83–0.94), with a sensitivity and specificity of 90.0% and 91.2%, respectively, in the validation study. When ΔFEV_1 was < 315 mL combined with FeNO < 28.5 parts per billion, patients with a positive BDT result were more likely to have pure COPD (AUC: 0.774; 95% CI 0.72–0.83).

Conclusion The simplified standard II can replace standard I. ΔFEV_1 and FeNO are helpful in differentiating between asthma, COPD, and ACO in patients with a positive BDT result.

Keywords Chronic airway disease, ACO, Diagnosis, Bronchodilator response, Asthma–COPD overlap, Forced expiratory volume in 1 s, Fractional exhaled nitric oxide

†Zhaoqian Gong, Junwen Huang and Guiling Xu have contributed equally to this article.

*Correspondence:
Haijin Zhao
haijin99@sina.com
Full list of author information is available at the end of the article

Background

Asthma and chronic obstructive pulmonary disease (COPD) are heterogeneous lung diseases [1], and they can coexist in some given patients, namely asthma–COPD overlap (ACO). Although some consensus documents raise different criteria for diagnosing ACO, there is still a lack of widely accepted and simplified criteria [2–4]. The European Consensus for ACO in 2016 is one of the most recognized criteria [4]. The prevalence of ACO in asthma and COPD is similar, ranging from 20 to 30% [5]. ACO has a higher symptom burden and more frequent and severe exacerbations than asthma or COPD [6, 7]. Additionally, the treatment of ACO is different from that of COPD; patients with ACO are recommended to use inhaled corticosteroids (ICS) combined with inhaled bronchodilators [8, 9] and might benefit from biologics used in patients with severe asthma [10, 11]. Therefore, it is of great importance to determine a simplified and accurate method for differentiating ACO from COPD.

The bronchodilation test (BDT), which evaluates airway reversibility, is not only an important diagnostic base of asthma, but it also plays a critical role in differentiating between ACO and COPD [12]. However, nearly one-third of patients with COPD have a positive BDT result [13–15]. The Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2022 [16] also proposed that COPD alone often shows a positive BDT result when the baseline forced expiratory volume in 1 s (FEV_1) is poor. As a major index for diagnosis of ACO according to the guidelines and consensus [4, 17–19], a strongly positive BDT result can be considered to differentiate ACO from COPD. Currently, there are three major criteria for a strongly positive BDT result: standard I [20–22], post-bronchodilator forced expiratory volume in 1 s response ($\Delta FEV_1 > 400$ mL + 15%); standard II [23], $\Delta FEV_1 > 400$ mL; and standard III [24], $\Delta FEV_1 > 200$ mL + 15%. However, it is unclear which one is more suitable in diagnosing ACO. Although the positive BDT result alone is limited in differentiating between asthma, COPD, and ACO, COPD has a lower ΔFEV_1 (in mL) than asthma and ACO, and bronchodilator response (BDR) was helpful in the early screening of ACO [25]. Besides, BDR was vital in identifying different phenotypes of ACO [26]. Therefore, it is necessary to further explore the role of BDR in differentiating between asthma, COPD, and ACO in patients with a positive BDT result and determine whether there is a better predictive threshold.

The inflammatory biomarker fractional exhaled nitric oxide (FeNO) has been reported as an indicator for differentiating between ACO and COPD; one study reported its optimal cut-off value as 39.5 parts per billion (ppb) (sensitivity, 58.3%; specificity, 84.9%) [27], whereas another study reported its optimal cut-off value as 25.0 ppb (sensitivity, 60.6%; specificity, 87.7%) [28]. The two aforementioned studies showed a low sensitivity, indicating that FeNO alone is useful but difficult to use for differentiating between ACO and COPD. Recently, Wang reported that ΔFEV_1 and FeNO were significantly different in ACO compared with COPD alone, which indicated that BDR combined with FeNO may be helpful in the early screening of ACO [25]. However, there is still a lack of an optimal value of ΔFEV_1 for differentiating between asthma, COPD, and ACO in patients with a positive BDT result. It needs to be clarified whether ΔFEV_1 combined with FeNO have advantages in differentiating between asthma, COPD, and ACO.

This study included patients with a positive BDT result to explore a simplified standard for a strongly positive BDT result and the value of ΔFEV_1 in BDT and FeNO for differentiating between asthma, COPD, and ACO. We assumed that BDR in FEV_1 and FeNO are helpful in differentiating between asthma, COPD, and ACO in patients with a positive BDT result, which contributes to the early screening of ACO.

Methods

Study design and patients

To explore a simplified standard for a strongly positive BDT result and the value of ΔFEV_1, this cross-sectional study included patients admitted to our hospital's outpatient respiratory clinic from January 2019 to January 2021. The participants were diagnosed with asthma, COPD, or ACO. The diagnosis of asthma was defined by the Global Initiative for Asthma (GINA) guidelines [29], requiring: (1) a history of asthmatic symptoms (wheezing, shortness of breath, with or without chest tightness or cough) relieved spontaneously or by medication; (2) variable expiratory airflow limitation (BDR of $FEV_1 > 200$ mL and 12%). The diagnosis of COPD was based on the GOLD guidelines, indicating a post-bronchodilator FEV_1/forced vital capacity (FVC) < 0.70 [30]. The diagnosis of ACO was based on the European Consensus 2016 criteria, major criteria [4]: (1) post-bronchodilator FEV_1/FVC < 0.70 in individuals > 40 years old; (2) at least 10 pack-years of tobacco smoking or equivalent exposure history; (3) history of asthma before age of 40 years or BDR of $FEV_1 > 400$ mL. Minor criteria included: (1) history of atopy or allergic rhinitis; (2) positive BDT result on two or more visits; (3) blood eosinophil count (BEC) ≥ 300 cells/μL. Patients who met all three major criteria and at least one minor criterion were diagnosed with ACO. Patients included were newly diagnosed and without inhalant treatment, or those who did not receive inhalant treatment for at least 4 weeks prior to enrollment, including long-acting muscarinic antagonist

(LAMA), long-acting beta-2 agonist (LABA) orICS. All patients had a positive BDT result. The exclusion criteria were as follows: (1) acute attack of respiratory system; (2) active pulmonary tuberculosis, interstitial pneumonia, fungal infection and lung tumors; (3) refuse to sign informed consent. This study was approved by the ethics committee (Code No. NFEC-2021-142).

Clinical information from electronic medical records, including demographic data, spirometry data, BDT result, FeNO value, BEC, and percentage were collected. To verify the results, a validation study included patients who were admitted to the respiratory clinic from June 2021 to December 2022.

Definition of the study groups

Three criteria were used to define a strongly positive BDT result in accordance with the GINA, National Institute for Health and Clinical Excellence, and American Thoracic Society (ATS) guidelines: standard I, $\Delta FEV_1 > 400$ mL + 15%; standard II, $\Delta FEV_1 > 400$ mL; and standard III, $\Delta FEV_1 > 200$ mL + 15%. Patients were grouped according to whether they had a strongly positive BDT result.

Spirometry, BDT, FeNO, and BEC

Spirometry was strictly measured by spirometers (Jaeger MasterScreen, Germany) with reference to the ATS criterion. A positive BDT result was defined as follows: $\Delta FEV_1 \geq 200$ mL + 12% after inhaling 400 μg of salbutamol. The FeNO detection was measured by a NIOX VERO analyzer (Aerocrine AB, Solna, Sweden) with reference to the ATS/European Respiratory Society criterion. The count and percentage of blood eosinophil was read by the automatic hematology analyzer.

Statistical analysis

Statistical analysis was performed using SPSS statistics for Windows, version 24.0 (IBM Corp.). Data are presented as mean ± standard deviation for continuous variables and as median (first quartile, third quartile) for categorical variables. Comparisons between continuous variables were performed using the Student's t-test or Mann–Whitney U test; the Chi-square test was used to analyze categorical variables. The factors of $\Delta FEV_1 \geq 400$ mL in ACO patients were analyzed using the COX regression model. All variables detected in the univariate analyses (with a *P*-value less than 0.1) were included in the multivariate analysis. Predictive values of single or combined measurements were calculated by constructing receiver operating characteristic (ROC) curves and measuring areas under the curve (AUCs). A two-sided *P*-value < 0.05 was considered significant.

Results

Study participants

A total of 633 patients were enrolled from the hospital's outpatient respiratory clinic. Finally, only 397 patients were eligible, including 192 (48.4%) with asthma, 135 (34.0%) with COPD, and 70 (17.6%) with ACO. The study flow chart is shown in Fig. 1.

Demographic and clinical characteristics

The clinical characteristics of the participants are shown in Table 1. Patients with asthma were younger, female-dominant, had lower smoking pack-years, and better spirometric indices (including FEV_1, FVC, %FEV_1, %FVC, and FEV_1/FVC) than those with COPD or ACO. FEV_1, FVC, %FEV_1, and FEV_1/FVC values of patients with COPD were lower than those of patients with ACO. Patients with ACO and asthma had a higher BDR in ΔFEV_1 (mL) than those with COPD; the BDR in ΔFEV_1 was highest in patients with ACO. Patients with asthma had a lower ΔFVC (mL) value than those with COPD and ACO; however, there was no difference in ΔFVC (mL) between patients with COPD and those with ACO. FeNO levels were lower in patients with COPD than in other patients, but there was no difference in FeNO levels between patients with asthma and those with ACO. The BEC was higher in patients with asthma than in those with COPD; however, there was no significant difference between patients with ACO and those with asthma or COPD. There was also no statistical difference in blood eosinophil percentage between patients with asthma, ACO, and COPD.

Difference analysis of a strongly positive BDT rate under different standards

The strongly positive BDT rates in patients with asthma, COPD, and ACO under different standards are shown in Fig. 2 and Additional file 1. In the asthma group, 66 (34.4%), 74 (38.5%), and 135 (70.3%) patients had a strongly positive BDT rate under standards I, II, and III, respectively; those respective values were 4 (3.0%), 4 (3.0%), and 103 (76.3%) in the COPD group and 40 (57.1%), 42 (60.0%), and 61 (87.1%) in the ACO group. Under standards I and II, the ACO group had the highest strongly positive BDT rate, followed by the asthma group, and there were statistical differences between the three diseases (*P* < 0.05). Under standard III, the ACO group had a higher strongly positive BDT rate than the asthma group (*P* = 0.005), but there was no statistical difference between the COPD group and the other two groups. All three diseases had a higher strongly positive BDT rate in standard III than the other two standards (*P* < 0.001). However, there was no statistical difference in the strongly positive BDT rate between standards I and
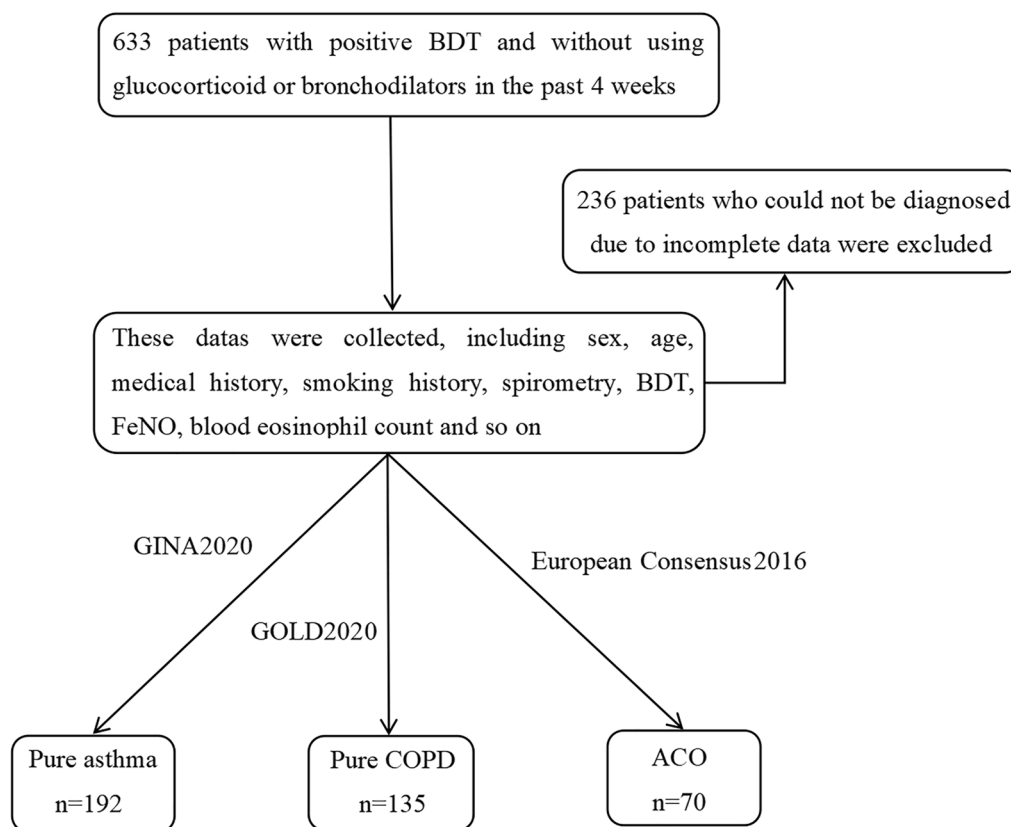
Fig. 1 Study flowchart. BDT, bronchodilation test; FeNO, fractional exhaled nitric oxide; GINA, Global Initiative for Asthma; GOLD, Global Initiative for Chronic Obstructive Lung Disease; COPD, chronic obstructive pulmonary disease; ACO, asthma–chronic obstructive pulmonary disease overlap

II among the three diseases (asthma, COPD, and ACO: $P = 0.396$, $P = 1.000$, and $P = 0.731$, respectively).

Comparison of clinical characteristics under different standards

The comparison of clinical characteristics of asthma, COPD, and ACO under standards I, II, and III is shown in Additional files 2, 3 and 4, respectively. The clinical characteristics between the two groups with a strongly positive BDT result or not were consistent between standards I and II; however, clinical characteristics in standard III were different from those in standard I or II. Under standards I and II, asthma patients with a strongly positive BDT result were younger, more male-dominant, and had higher smoking pack-years and higher FEV_1 and FVC values than those with COPD or ACO. Under any standard, there was no between-group difference in FeNO levels. However, under standard III, all patients with a strongly positive BDT result had poor pulmonary function, including FEV_1, FVC, %FEV_1, %FVC, and FEV_1/FVC.

Factors associated with $\Delta FEV_1 \geq 400$ mL in ACO patients

The univariate and multivariate analysis with $\Delta FEV_1 \geq 400$ mL in ACO patients is shown in Table 2. In the univariate Cox regression analysis, only FVC and ICS/LABA/LAMA (yes vs. no) were an independent predictor of $\Delta FEV_1 \geq 400$ mL in ACO patients [FVC: HR = 1.97, 95% CI 1.04–3.71, $P = 0.037$; ICS/LABA/ LAMA (yes vs. no): HR = 0.12, 95% CI 0.01–0.94, $P = 0.044$]. The multivariate Cox regression analysis found that FVC was significantly correlated with $\Delta FEV_1 \geq 400$ mL in ACO patients (HR = 2.71, 95% CI 1.31–5.63, $P = 0.007$). And the inhalation therapy of ICS/LABA/LAMA (yes vs. no) was also correlated with $\Delta FEV_1 \geq 400$ mL in ACO patients ($P = 0.013$).

Predictive value of ΔFEV_1 alone or combined with FeNO for the diagnosis of ACO or asthma in patients with a positive BDT result

The predictive value of ΔFEV_1 alone or combined with FeNO was evaluated using ROC curves, adjusted by covariates. Only ΔFEV_1 could predict the diagnosis of ACO in COPD patients with a positive BDT result, with a cut-off value of 345 mL (AUC: 0.881; 95% CI 0.83–0.94)

Gong *et al. European Journal of Medical Research*   (2024) 29:97

Page 5 of 10

Table 1 Patient characteristics

	Asthma group (*N* = 192)	COPD group (*N* = 135)	ACO group (*N* = 70)	*P*-value
Age, year	46.0 (33.0, 55.5)	61.0 (56.0, 66.0)	56.0 (50.5, 62.3)	< 0.001
Sex (female/male), *N*	121/71	19/116	7/63	< 0.001
BMI, kg/m^2	23.5 ± 3.5	22.9 ± 3.8	23.7 ± 2.9	0.178
Smoking history				
Current or ex-smoker/nonsmoker, *N*	38/154	111/24	53/17	< 0.001
Smoking pack-years	0.0 (0.0, 0.0)	30.0 (10.0, 40.0)	20.0 (0.0, 31.3)	< 0.001
Pulmonary function grading (normal/mild/moderate/ moderate to severe/severe/extremely severe), *N*	32/70/37/26/21/7	0/19/30/22/41/23	0/23/17/9/12/9	< 0.001
Post-bronchodilation spirometry				
FEV$_1$, L	1.91 (1.43, 2.44)	1.43 (1.02, 1.71)	1.75 (1.24, 2.08)	< 0.001
Predicted FEV$_1$, %	69.7 ± 18.4	53.5 ± 18.1	61.7 ± 21.3	< 0.001
FVC, L	3.08 (2.53, 3.74)	2.90 (2.55, 3.34)	3.23 (2.55, 3.62)	0.004
Predicted FVC, %	96.5 ± 18.4	86.8 ± 17.9	90.4 ± 21.4	< 0.001
FEV$_1$/FVC, %	60.7 ± 11.3	48.1 ± 11.6	53.9 ± 11.4	< 0.001
ΔFEV$_1$, mL	340.0 (280.0, 480.0)	260.0 (230.0, 290.0)	425.0 (327.5, 530.0)	< 0.001
ΔFVC, mL	210.0 (92.5, 367.5)	300.0 (170.0, 470.0)	425.0 (117.5, 567.5)	< 0.001
Standard I, *N*(%)	66 (34.4)	4 (3.0)	40 (50.7)	< 0.001
Standard II, *N*(%)	74 (38.5)	4 (3.0)	42 (60)	< 0.001
Standard III, *N*(%)	135 (70.3)	103 (76.3)	61 (87.1)	0.019
FeNO, ppb	44.0 (17.0, 78.3)	21.0 (14.0, 51.0)	32.5 (20.8, 54.3)	0.003
Blood parameters				
Total eosinophils, /μL	340 (175, 493)	230 (130, 410)	255 (133, 465)	0.107
%Eosinophils	5.1 ± 3.5	3.9 ± 2.9	4.5 ± 3.4	0.251

Data are shown as frequency, mean ± SD, median (first quartile, third quartile), or frequency (percentage). COPD, chronic obstructive pulmonary disease; ACO, asthma–chronic obstructive pulmonary disease overlap; BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; SD, standard deviation
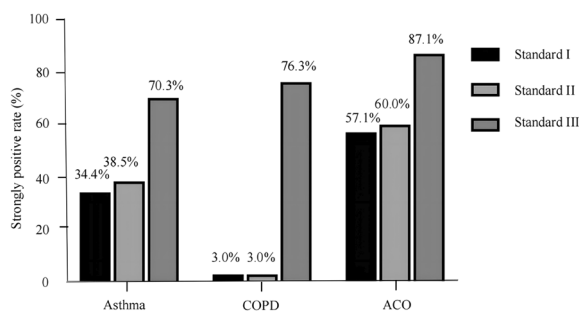

Fig. 2 Strongly positive BDT rates in the asthma, COPD, and ACO groups under three different standards. COPD, chronic obstructive pulmonary disease; ACO, asthma–chronic obstructive pulmonary disease overlap; BDT, bronchodilation test

(Fig. 3). Table 3 shows the sensitivity, specificity, positive predictive value, negative predictive value, and Youden index of each cut-off value for ΔFEV$_1$.

After excluding patients with ACO, ΔFEV$_1$ (AUC: 0.613; 95% CI 0.55–0.68) and FeNO (AUC: 0.765; 95% CI 0.71–0.82) could predict the diagnosis of asthma in patients with a positive BDT result (Table 4). The AUC for ΔFEV$_1$ combined with FeNO was 0.774 (95% CI 0.72–0.83), which was significantly higher than that of ΔFEV$_1$ or FeNO alone; the cut-off values for ΔFEV$_1$ and FeNO were 315 mL and 28.5 ppb, respectively (Table 4 and Fig. 4).

Validation study

To verify the reliability of the prediction model, we continued to recruit 209 patients from June 2021 to December 2022, including 132 with asthma, 57 with COPD, and 20 with ACO. The clinical characteristics of the three diseases were broadly in line with our original study (Additional file 5). Surprisingly, ΔFEV$_1$ ≥ 345 mL could predict the diagnosis of ACO in COPD patients with a positive BDT result, with a great sensitivity and specificity of 90.0% and 91.2%, respectively, in external validation (Additional file 6). Additionally, ΔFEV$_1$ < 315 mL combined with FeNO < 28.5 ppb could eliminate asthma diagnosis in patients with a positive BDT result, with a high specificity of 87.0% but a low sensitivity of 54.2% (Additional file 7).

Gong *et al. European Journal of Medical Research*   (2024) 29:97

Page 6 of 10

Table 2 Univariate and multivariate associations with $\Delta FEV_1 \geq 400$ mL in ACO patients

Variable	Univariate analysis HR (95% CI)	P-value	Multivariate analysis HR (95% CI)	P-value
Age (year)	0.97 (0.92–1.02)	$P = 0.187$		
Sex (female vs. male)	1.40 (0.29–6.81)	$P = 0.679$		
BMI (kg/m^2)	0.96 (0.81–1.13)	$P = 0.598$		
Smoking index (pack-year)	1.00 (0.97–1.02)	$P = 0.765$		
FEV_1 (mL)	1.71 (0.77–3.78)	$P = 0.188$		
Predicted FEV_1 (%)	1.01 (0.99–1.03)	$P = 0.421$		
FVC (mL)	1.97 (1.04–3.71)	$P = 0.037$	2.71 (1.31–5.63)	$P = 0.007$
Predicted FVC (%)	1.02 (0.99–1.04)	$P = 0.132$		
FEV_1/FVC (%)	1.00 (0.96–1.05)	$P = 0.982$		
FeNO (ppb)	1.00 (0.99–1.02)	$P = 0.519$		
Total eosinophils (/μL)	1.00 (0.99–1.00)	$P = 0.543$		
Eosinophils (%)	0.99 (0.72–1.35)	$P = 0.937$	0.06 (0.01–0.55)	$P = 0.013$
ICS/LABA/LAMA (yes vs. no)	0.12 (0.01–0.94)	$P = 0.044$		

HR, relative risk; 95% CI, 95% confidence interval; BMI, body mass index; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist
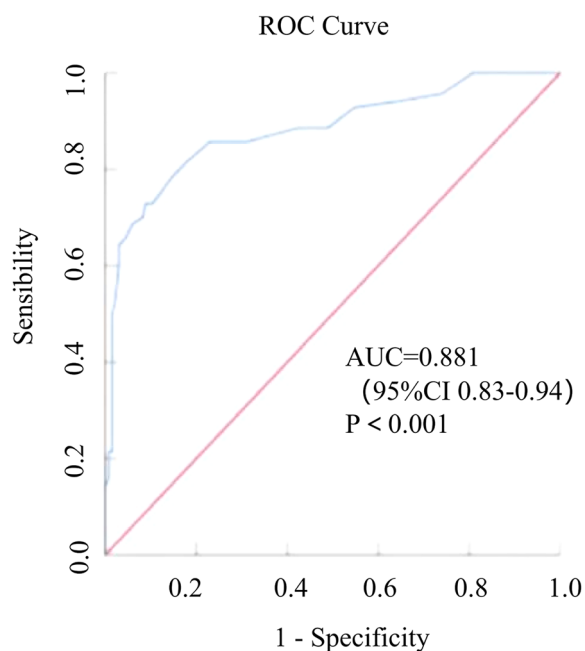

Fig. 3 ROC curves for ΔFEV_1 in predicting ACO diagnosis for COPD with a positive BDT result. ROC, receiver operating characteristic; ΔFEV_1, post-bronchodilator forced expiratory volume in 1 s response; COPD, chronic obstructive pulmonary disease; ACO, asthma–chronic obstructive pulmonary disease overlap; BDT, bronchodilation test

Discussion

This is the first study to compare three criteria of a strongly positive BDT result in chronic airway disease patients with a positive BDT result. This study demonstrated that standard II ($\Delta FEV_1 > 400$ mL) can effectively replace standard I ($\Delta FEV_1 > 400$ mL + 15%).

In this study, patients with COPD were older, male-dominant, smoker-dominant, and had poorer baseline lung function than patients with asthma, which is consistent with previous studies' findings [31, 32]. Compared with patients with COPD, those with ACO were younger and had better baseline lung function. A previous study reported that patients with ACO were younger than those with COPD, but they had a lower FEV_1 [7]. Herein, patients with ACO and those with asthma had a higher BDR (mL in FEV_1) than those with COPD, which is in line with previous studies' findings [32, 33]. We found a significant difference in BECs between patients with asthma and those with COPD, but there was no difference between patients with ACO and those with COPD or asthma. We thought the reason for this phenomenon was that the positive BDT result and exposure to tobacco smoke reduced the difference in BECs between ACO and COPD or asthma [34–36]. Peng reported that patients with ACO had higher BECs than those with COPD [37]. However, there was no difference in BECs among the asthma, COPD, and ACO groups in the real-world study cohort, NOVELTY [6]. Additionally, patients with asthma and those with ACO had higher FeNO levels than those with COPD, which is similar to previous studies' results [38, 39]. Therefore, BDR combined with the biomarkers of type 2 airway inflammation may be a useful tool in distinguishing between COPD and ACO or asthma.

A large multicenter study [40] reported that in 1106 participants with low FEV_1 values (mL), the

Table 3 Predictive values for predicting ACO diagnosis from COPD in patients with a positive BDT result

ΔFEV_1 (mL)	Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index
345	72.9	91.1	81.0	86.6	0.640
355	70.0	91.9	81.7	85.5	0.619
365	68.6	94.1	85.7	85.2	0.627
375	67.1	94.8	87.0	84.8	0.619
385	65.7	95.6	88.5	84.3	0.613

COPD, chronic obstructive pulmonary disease; ACO, asthma–chronic obstructive pulmonary disease overlap; BDT, bronchodilation test; FEV_1, forced expiratory volume in 1 s; PPV, positive predictive values; NPV, negative predictive values

Table 4 Predictive values for predicting asthma diagnosis in patients with a positive BDT result

	AUC	Cutoff value	Sensibility (%)	Specificity (%)	PPV (%)	NPV (%)	Youden index	*P*-value
FeNO (ppb)	0.613 (95% CI 0.55–0.68)	28.5	61.9	63.2	70.9	53.4	0.251	0.001
ΔFEV_1 (mL)	0.765 (95% CI 0.71–0.82)	315	59.7	86.4	85.0	59.3	0.461	< 0.001
FeNO + ΔFEV_1	0.774 (95% CI 0.72–0.83)	–	61.3	86.4	93.4	52.2	0.477	< 0.001

BDT, bronchodilation test; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; AUC, area under the curve; PPV, positive predictive values; NPV, negative predictive values
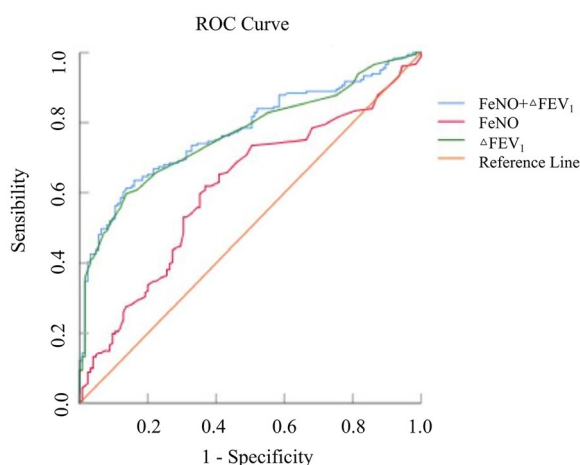

Fig. 4 ROC curves for the model of ΔFEV_1 combined with FeNO in predicting the diagnosis of asthma. ROC, receiver operating characteristic; ΔFEV_1, post-bronchodilator forced expiratory volume in 1 s response; FeNO, fractional exhaled nitric oxide; BDT, bronchodilation test. $AUC_{FeNO+\Delta FEV1} = 0.774$ (95% CI 0.72–0.83); $AUC_{FeNO} = 0.613$ (95% CI 0.55–0.68); $AUC_{\Delta FEV1} = 0.765$ (95% CI 0.71–0.82)

FEV_1 increased by 12–44.7% relative to the baseline but < 200 mL, and $\Delta FEV_1\%$ increased with the level of airflow obstruction but decreased with severe obstruction, indicating that patients with severe obstruction rarely meet standard I. Thus, our result that standard II can replace standard I is clinically significant. However, there is still a lack of relevant research on the specific value of BDR in distinguishing between ACO and COPD with a positive BDT result.

Here, we firstly showed that $\Delta FEV_1 \geq 345$ mL could help physicians to distinguish ACO from COPD in patients with a positive BDT result. To verify the accuracy of this conclusion, we strictly recruited 20 ACO, 57 COPD, and 132 asthma patients with a positive BDT result; we found that $\Delta FEV_1 \geq 345$ mL was an excellent marker in distinguishing ACO from COPD. Similarly, a previous study showed that patients with ACO had a significantly higher ΔFEV_1 value (mL) than those with COPD [25]. Moreover, some guidelines have suggested BDR ≥ 400 mL as the basis for distinguishing ACO from COPD, but in clinical practice, very few patients with COPD meet this criterion. It is very important to determine whether $\Delta FEV_1 \geq 345$ mL could distinguish ACO from COPD in patients with a positive BDT result. Another study revealed that lung function parameters are potentially important tools in discriminating between asthma, ACO, and COPD [41]. COPD and asthma are characterized by incompletely reversible and reversible airflow obstruction, respectively [22, 42]. ACO shares the airflow obstruction characteristics of both asthma and COPD [22]. Thus, BDR is a key differential tool for distinguishing between COPD and ACO, especially in patients with a positive BDT result.

Alcázar-Navarrete [43] reported that an FeNO level of ≥ 19 ppb could distinguish ACO from COPD. Takayama [28] showed that COPD patients without treatment can be diagnosed as having ACO when the FeNO level is ≥ 25 ppb. In this study, patients with ACO had higher FeNO levels than those with COPD, but FeNO had no value in predicting ACO from COPD, which was inconsistent with previous studies' findings [38, 44]. This result

Gong *et al. European Journal of Medical Research*   (2024) 29:97

Page 8 of 10

is likely due to the fact that patients had a positive BDT result, which can weaken the difference of the FeNO level between ACO and COPD. In the present study, most patients with a positive BDT result and airway limitation were diagnosed with COPD instead of asthma when $\Delta FEV_1 < 315$ mL was combined with an FeNO level < 28.5 ppb, which was verified by the validation study. This indicates that our prediction model is more meaningful in excluding a diagnosis.

This study has a few potential limitations, which should be considered. First, this is a single-center design, so multicenter studies are needed to confirm our findings. Secondly, all patients in this study are with a positive BDT result.

Conclusions

Our study showed that the simplified standard II could replace the common standard I as the criterion of a strongly positive BDT result. Additionally, ΔFEV_1 alone or combined with FeNO are helpful in differentiating between asthma, COPD, and ACO in patients with a positive BDT result.

Abbreviations

COPD	Chronic obstructive pulmonary disease
ACO	Asthma–chronic obstructive pulmonary disease overlap
BDT	Bronchodilation test
GOLD	Global Initiative for Chronic Obstructive Lung Disease
FEV_1	Forced expiratory volume in 1 s
ΔFEV_1	Postbronchodilator forced expiratory volume in 1-s response
FVC	Forced vital capacity
BDR	Bronchodilator response
FeNO	Fractional exhaled nitric oxide
GINA	Global initiative for asthma
BEC	Blood eosinophil count
ATS	American Thoracic Society
ROC	Receiver operating characteristic
AUC	Area under the curve
ICS	Inhaled corticosteroids
LABA	Long-acting beta-2 agonist
LAMA	Long-acting muscarinic antagonist
HR	Relative risk
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-024-01679-w.

Additional file 1. Difference analysis of strongly positive asthma, COPD, and ACO rates under different standards.

Additional file 2. Clinical characteristics of different groups based on standard I.

Additional file 3. Clinical characteristics of different groups based on standard II.

Additional file 4. Clinical characteristics of different groups based on standard III.

Additional file 5. Patient characteristics in the validation study.

Additional file 6. The accuracy of $\Delta FEV_1 \geq 345$ mL predicts the diagnosis of ACO from COPD with positive BDT.

Additional file 7. The accuracy of ΔFEV_1 and FeNO in excluding asthma from patients with a positive BDT.

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

Declarations

Ethics approval and consent to participate
This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Nanfang Hospital, Southern Medical University (Code No. NFEC-2021-142). All patients have signed informed consent.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Author details
[1]Chronic Airways Diseases Laboratory, Department of Respiratory and Critical Care Medicine, Nanfang Hospital, Southern Medical University, Guangzhou 510515, China. [2]Department of the Biostatistics, Guangdong Provincial Key Laboratory of Tropical Disease Research, School of Public Health, Southern Medical University, Guangzhou, China.

References
1. Postma DS, Reddel HK, ten Hacken NHT, van den Berge M. Asthma and chronic obstructive pulmonary disease. Clin Chest Med. 2014;35:143–56. https://doi.org/10.1016/j.ccm.2013.09.010.
2. Barczyk A, Maskey-Warzęchowska M, Górska K, Barczyk M, Kuziemski K, Śliwiński P, et al. Asthma–COPD overlap—a discordance between patient populations defined by different diagnostic criteria. J Allerg Clin Imm In Practice. 2019. https://doi.org/10.1016/j.jaip.2019.04.022.
3. Leung JM, Sin DD. Asthma–COPD overlap syndrome: pathogenesis, clinical features, and therapeutic targets. BMJ. 2017. https://doi.org/10.1136/bmj.j3772.
4. Sin DD, Miravitlles M, Mannino DM, Soriano JB, Price D, Celli BR, et al. What is asthma−copd overlap syndrome? Towards a consensus definition from a round table discussion. Eur Resp J. 2016;48:664–73. https://doi.org/10.1183/13993003.00436-2016.

Gong *et al. European Journal of Medical Research*   (2024) 29:97

Page 9 of 10

5. Mekov E, Nuñez A, Sin DD, Ichinose M, Rhee CK, Maselli DJ, et al. Update on asthma–COPD overlap (ACO): a narrative review. Int J Chronic Obstr Pul Dis. 2021;16:1783–99. https://doi.org/10.2147/copd.s312560.

6. Reddel HK, Vestbo J, Agustí A, Anderson GP, Bansal AT, Beasley R, et al. Heterogeneity within and between physician-diagnosed asthma and/or COPD: novelty cohort. Eur Resp J. 2021;58:2003927. https://doi.org/10.1183/13993003.03927-2020.

7. Barrecheguren M, Pinto L, Mostafavi-Pour-Manshadi S, Tan WC, Li PZ, Aaron SD, et al. Identification and definition of asthma–COPD overlap: the cancold study. Respirology. 2020;25:836–49. https://doi.org/10.1111/resp.13780.

8. Lee S-Y, Park HY, Kim EK, Lim SY, Rhee CK, Hwang YI, et al. Combination therapy of inhaled steroids and long-acting beta2-agonists in asthma and COPD overlap syndrome. Int J Chron Obstr Pul Dis. 2016;11:2797–803. https://doi.org/10.2147/copd.s114964.

9. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2023. https://ginasthma.org/. Accessed 2023 Oct 24.

10. Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma–COPD overlap: post hoc analysis of Prospero. J Allerg Clin Immun. 2019. https://doi.org/10.1016/j.jaci.2018.11.032.

11. Pérez de Llano L, Dacal Rivas D, Marina Malanda N, Plaza Moral V, Gullón Blanco JA, Muñoz-Esquerre M, et al. The response to biologics is better in patients with severe asthma than in patients with asthma–COPD overlap syndrome. J Asth Allerg. 2022;15:363–9. https://doi.org/10.2147/jaa.s338467.

12. Annangi S, Coz-Yataco AO. Clinical implications of bronchodilator testing: diagnosing and differentiating COPD and asthma–COPD overlap. Resp Care. 2022;67:440–7. https://doi.org/10.4187/respcare.09215.

13. Marín JM, Ciudad M, Moya V, Carrizo S, Bello S, Piras B, et al. Airflow reversibility and long-term outcomes in patients with COPD without comorbidities. Resp Med. 2014;108:1180–8. https://doi.org/10.1016/j.rmed.2014.05.006.

14. Guo X, Deng N, Chen Q, Yu H, Ding X, Hu S, et al. Application of inflammatory markers in induced sputum in stable chronic obstructive pulmonary disease patients with positive bronchodilation tests. Curr Med Sci. 2019;39:560–7. https://doi.org/10.1007/s11596-019-2074-7.

15. Wang Z, Xu Z, Sun G, Bao H. Clinical and airway inflammation features of COPD patients with positive bronchodilator test. J Col Phys Surg Pak. 2019;29(08):741–5. https://doi.org/10.29271/jcpsp.2019.08.741.

16. Global Initiative for Chronic Obstructive Lung Disease. The global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. 2022. https://goldcopd.org/archived-reports/. Accessed 2023 Oct 24.

17. Cosio BG, Soriano JB, López-Campos JL, Calle-Rubio M, Soler-Cataluna JJ, de-Torres JP, et al. Defining the asthma–COPD overlap syndrome in a COPD cohort. Chest. 2016;149:45–52. https://doi.org/10.1378/chest.15-1055.

18. Plaza V, Álvarez F, Calle M, Casanova C, Cosío BG, López-Viña A, et al. Consensus on the asthma–COPD overlap (ACO) between the Spanish COPD guidelines (GesEPOC) and the Spanish guidelines on the management of asthma (GEMA). Arch Bronconeumol. 2017;53:443–9. https://doi.org/10.1016/j.arbr.2017.06.001.

19. Cataldo D, Corhay JL, Derom E, Louis R, Marchand E, Michils A, et al. A Belgian survey on the diagnosis of asthma and COPD overlap syndrome. Int J Chronic Obstr Pul Dis. 2017;12:601–13. https://doi.org/10.2147/copd.s124459.

20. Koblizek V, Chlumsky J, Zindr V, Neumannova K, Zatloukal J, Zak J, et al. Chronic obstructive pulmonary disease: official diagnosis and treatment guidelines of the Czech pneumological and Phthisiological Society; a novel phenotypic approach to COPD with patient-oriented care. Biomed Pap. 2013;157:189–201. https://doi.org/10.5507/bp.2013.039.

21. Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, et al. Documento de Consenso Sobre el Fenotipo Mixto Epoc-Asma En La Epoc. Arch Bronconeumol. 2012;48:331–7. https://doi.org/10.1016/j.arbres.2011.12.009.

22. Global Initiative for Asthma. Global strategy for asthma management and prevention. 2022. https://ginasthma.org/. Accessed 2023 Oct 24.

23. Intermediate care-hospital-at-home in chronic obstructive pulmonary disease: British Thoracic Society Guideline. Thorax. 2007;62:200–10. https://doi.org/10.1136/thx.2006.064931.

24. British Thoracic Society; Scottish Intercollegiate Guidelines Network. British guideline on the management of asthma. Thorax. 2003;58(Suppl 1):i1–94. https://doi.org/10.1136/thorax.58.suppl_1.1i.

25. Wang J, Wang W, Lin H, Huan C, Jiang S, Lin D, et al. Role of pulmonary function and FeNO detection in early screening of patients with ACO. Exp Therap Med. 2020;20:830–7. https://doi.org/10.3892/etm.2020.8762.

26. Joo H, Park S-Y, Park SY, Park SY, Kim S-H, Cho YS, et al. Phenotype of asthma–COPD overlap in COPD and severe asthma cohorts. J Korean Med Sci. 2022. https://doi.org/10.3346/jkms.2022.37.e236.

27. Li M, Yang T, He R, Li A, Dang W, Liu X, et al. The value of inflammatory biomarkers in differentiating asthma–COPD overlap from COPD. Int J Chronic Obstr Pul Dis. 2020;15:3025–37. https://doi.org/10.2147/copd.s273422.

28. Takayama Y, Ohnishi H, Ogasawara F, Oyama K, Kubota T, Yokoyama A. Clinical utility of fractional exhaled nitric oxide and blood eosinophils counts in the diagnosis of asthma–COPD overlap. Int J Chronic Obstr Pul Dis. 2018;13:2525–32. https://doi.org/10.2147/copd.s167600.

29. Global Initiative for Asthma. Global strategy for asthma management and prevention; 2020. https://ginasthma.org/. Accessed 2023 Oct 24. Global Initiative for Asthma.

30. Global Initiative for Chronic Obstructive Lung Disease. The global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease; 2020. https://goldcopd.org/archived-reports/. Accessed 2023 Oct 24.

31. Tamura K, Shirai T, Hirai K, Nakayasu H, Takahashi S, Kishimoto Y, et al. Mucus plugs and small airway dysfunction in asthma, COPD, and asthma–COPD overlap. Allerg Asth Immun Res. 2022;14:196. https://doi.org/10.4168/aair.2022.14.2.196.

32. Proboszcz M, Goryca K, Nejman-Gryz P, Przybyłowski T, Górska K, Krenke R, et al. Phenotypic variations of mild-to-moderate obstructive pulmonary diseases according to airway inflammation and clinical features. J Inflamm Res. 2021;14:2793–806. https://doi.org/10.2147/jir.s309844.

33. Kumar K, Gupta PP, Verma AK, Yadav R. Assessment of prevalence and characteristics of asthma–COPD overlap among patients with chronic airflow obstruction. Monaldi Arch Chest Dis. 2022. https://doi.org/10.4081/monaldi.2022.2323.

34. Chou KT, Su KC, Hsiao YH, Huang SF, Ko HK, et al. Post-bronchodilator reversibility of FEV(1) and eosinophilic airway inflammation in COPD. Arch Bronconeumol. 2017;53(10):547–53. https://doi.org/10.1016/j.arbres.2017.01.014.

35. Zhao B, Zheng H, Li X, Zheng R. Evaluation of the peripheral blood eosinophil count as a predictor for fractional exhaled nitric oxide or bronchodilator reversibility test outcome. Allergy Asthma Proc. 2021;42(3):228–34. https://doi.org/10.2500/aap.2021.42.210016.

36. Jacinto T, Malinovschi A, Janson C, Fonseca J, Alving K. Differential effect of cigarette smoke exposure on exhaled nitric oxide and blood eosinophils in healthy and asthmatic individuals. J Breath Res. 2017;11(3):36006. https://doi.org/10.1088/1752-7163/aa746b.

37. Peng J, Wang M, Wu Y, Shen Y, Chen L. Clinical indicators for asthma–COPD OVERLAP: a systematic review and meta-analysis. Int J Chronic Obstr Pul Dis. 2022;17:2567–75. https://doi.org/10.2147/copd.s374079.

38. Shrestha SK, Shrestha S, Sharma L, Pant S, Neopane A. Comparison of fractional exhaled nitric oxide levels in chronic obstructive pulmonary disease, bronchial asthma and healthy subjects of Nepal. J Breath Res. 2017;11:047101. https://doi.org/10.1088/1752-7163/aa7e63.

39. Zhang C, Zhang M, Wang Y, Su X, Lei T, Yu H, et al. Diagnostic value of fractional exhaled nitric oxide in differentiating the asthma–COPD overlap from COPD: a systematic review and meta-analysis. Expert Rev Resp Med. 2021;16:679–87. https://doi.org/10.1080/17476348.2022.2011221.

40. Quanjer PH, Ruppel GL, Langhammer A, Krishna A, Mertens F, Johannessen A, et al. Bronchodilator response in FVC is larger and more relevant than in FEV 1 in severe airflow obstruction. Chest. 2017;151:1088–98. https://doi.org/10.1016/j.chest.2016.12.017.

41. Kraemer R, Gardin F, Smith H-J, Baty F, Barandun J, Piecyk A, et al. Functional predictors discriminating asthma–COPD overlap (ACO) from chronic obstructive pulmonary disease (COPD). Int J Chronic Obstr Pul Dis. 2022;17:2723–43. https://doi.org/10.2147/copd.s382761.

42. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global initiative for chronic obstructive lung disease 2023 report: GOLD executive summary. Am J Respir Crit Care Med. 2023;207:819–37. https://doi.org/10.1164/rccm.202301-0106PP.

43. Alcázar-Navarrete B, Romero-Palacios PJ, Ruiz-Sancho A, Ruiz-Rodriguez O. Diagnostic performance of the measurement of nitric oxide in exhaled air in the diagnosis of COPD phenotypes. Nitric Oxide. 2016;54:67–72. https://doi.org/10.1016/j.niox.2016.02.003.
44. Miskoff JA, Dewan A, Chaudhri M. Fractional exhaled nitric oxide testing: diagnostic utility in asthma, chronic obstructive pulmonary disease, or asthma–chronic obstructive pulmonary disease overlap syndrome. Cureus. 2019. https://doi.org/10.7759/cureus.4864.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.