Current situation of asthma–COPD overlap in Chinese patients older than 40 years with airflow limitation: a multicenter, cross-sectional, non-interventional study

Ther Adv Respir Dis

2020, Vol. 14: 1–16

DOI: 10.1177/1753466620961699

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Abstract

Background and aims: Asthma–chronic obstructive pulmonary disease (COPD) overlap (ACO) is poorly recognized in China. Our study determined the distribution of ACO and its clinical characteristics among patients (aged ⩾40 years) with airflow limitation at Chinese tertiary hospitals.

Methods: This cross-sectional, non-interventional study (NCT02600221), conducted between December 2015 and October 2016 in 20 Tier-3 Chinese hospitals, included patients aged ⩾40 years with post-bronchodilator (BD) $FEV_1/FVC < 0.7$. The primary variable was distribution of ACO in adults with post-BD forced expiratory volume /forced vital capacity (FEV_1/FVC) <0.7 based on Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2015 and 2017 reports. Other variables included determination of characteristics of ACO and its clinical recognition rate.

Results: In 2003 patients (mean age 62.30 ± 9.86 years), distribution of ACO, COPD and asthma were 37.40%, 48.50% and 14.10%, respectively. Proportions of patients with A, B, C and D grouping were 11.70%, 31.00%, 6.90% and 50.30% as per GOLD 2017, whereas they were 15.10%, 51.10%, 3.60% and 30.20% as per GOLD 2015. Similar clinical symptoms were reported in all three groups. A higher percentage of ACO patients presented with dyspnea, wheezing and chest tightness. Compared with the COPD group, a greater proportion of ACO patients reported wheezing (74.6% and 65.40%), while a lower proportion in the ACO group reported cough (79.40% *versus* 82.70%) and expectoration (76.50% *versus* 81.60%). Blood eosinophil count $\geqslant 0.3 \times 10^9$/L was observed in 34.6% of ACO patients. The clinical recognition rate of ACO was 31.4%.

Conclusion: Despite ACO affecting two-fifths of the study population, the initial diagnosis rate was low at 6% in China, thus warranting concerted efforts to improve ACO diagnosis.

ClinicalTrials.gov: [ClinicalTrials.gov identifier: NCT02600221] registered 22 October 2015, https://clinicaltrials.gov/ct2/show/NCT02600221

The reviews of this paper are available via the supplemental material section.

Keywords: asthma, asthma–COPD overlap, COPD, diagnosis, distribution

Received: 30 March 2020; revised manuscript accepted: 27 August 2020.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are highly prevalent chronic airway diseases, affecting approximately 339 million and 251 million people, respectively.[1,2] Both diseases lead to chronic airflow obstruction with distinct clinical features. In specific groups of patients, particularly aged ⩾40 years, overlapping symptoms of both asthma and COPD are reported,[3] which is commonly known as asthma–COPD overlap (ACO). Although ACO is clinically recognized, the definitive features are

ambiguous, leading to difficulty in reporting. The clinical definition provided by the Global Initiative for Chronic Obstructive Lung Disease, 2015 (GOLD) considers it as a clinical entity with airflow limitation and other features of COPD and asthma.[4] Due to the subjective nature of diagnosis of ACO, the global prevalence is reported to be between 15% and 55% with variation based on age and gender.[5] In China, the reported prevalence of ACO is 0.61%.[6]

Patients with ACO have reported more rapid disease progression, frequent exacerbations, increased comorbidities, and poorer health related quality of life and prognosis compared with asthma and COPD.[7–11] The clinical challenge in diagnosis of ACO is compounded by the lack of recommended biomarkers to differentiate ACO from asthma and COPD. But recently specific biomarkers including nitric oxide (FeNO), blood eosinophil count, sputum cell count and combined evaluation of serum periostin with serum chitinase-3-like protein 1 (YKL-40) were reported to be helpful in distinguishing ACO from asthma and COPD.[12] The clinical utility of these biomarkers has not been evaluated in larger real-world studies. In this pretext, the clinical diagnosis of ACO is facilitated by a multilevel approach consisting of clinical symptoms and spirometric parameters.[7,13]

Further, the clinical features associated with chronic airflow limitation diseases are also attenuated by lifestyle and patient demographic features, including smoking habit, which complicates the clinical diagnosis.[14] The clinical presentation of ACO is also compounded by the prevailing environmental factors, especially in China, with a relatively high respiratory disease burden.[15] Considering the fact that the initial diagnosis of chronic airway obstruction determines the therapeutic management, it is important to determine the incidence of ACO in China. As there are limited studies reporting the prevalence of ACO in China, further exploration of ACO distribution and identification of distinct risk factors is required for better clinical diagnosis and management of ACO. Therefore, this clinical practice-based multicenter, cross-sectional, non-interventional study (NIS) investigated the current situation of ACO in Chinese patients ⩾40 years of age, with airflow limitation, in terms of distribution, clinical characteristics, clinical recognition rate and the specific biomarkers.

Methods

Study design

This multicenter, cross-sectional NIS [ClinicalTrials.gov identifier: NCT02600221] was performed as a part of the routine clinical practice, in patients with airflow limitation in China. The enrollment criteria, baseline and diagnostic definitions have been reported previously.[16]

Study patients

The study collected data (e.g. medical records, patient- or physician-reported data) from consecutive outpatients with persistent airway limitation from 20 Tier-3 hospitals (most sophisticated and metropolis hospitals with multiple specialized departments having more than 500 beds) in China. The patients with the following presenting features were included in the study: (i) outpatients aged ⩾40 years; (ii) clinical diagnoses of asthma or COPD or ACO based on the syndromic criteria in the updated Global Initiative for Asthma (GINA) 2015 report[17] in the last 12 months; (iii) persistent airflow limitation (post-BD $FEV_1/FVC < 0.7$) and (iv) gave informed consent. Patients were excluded if they had participated in another clinical study in the last 3 months, were diagnosed with a chronic respiratory disease which influenced airflow, had acute exacerbation, or could not follow the procedures or answer the investigator's questions from the questionnaire. A two-tier approach to diagnosis of ACO was used in this study. While the initial inclusion was based on persistent airflow limitation (post-BD $FEV_1/FVC < 0.7$), the syndromic approach (Table 1) to chronic airflow obstruction as provided in the GINA 2015 report was used for the differential diagnosis of ACO.[18]

The study protocol was approved by the ethics committees of all the study sites according to the International Conference on Harmonization guidelines for Good Clinical Practice and conformed to the Declaration of Helsinki. All patients received information on the purpose and conduct of this study, and provided written, informed consent.

Observation indicators

The primary outcome was to understand the distribution of ACO in patients with airflow limitation aged ⩾40 years in China. The secondary outcomes included observation of the clinical characteristics

Table 1. Diagnostic algorithm followed in the study.

Feature	Asthma	COPD
Age of onset	Before the age of 20 years old	After the age of 40 years old
Pattern of symptoms	Variation over minutes, hours or days	Persistent despite treatment
	Worse during the night or early morning	Good and bad from time to time but symptoms persist and with exertional dyspnea
	Triggered by exercise, emotions including laughter, dust or exposure to allergens	Chronic cough and sputum preceded onset of dyspnea, unrelated to triggers
Lung function	Record of variable airflow limitation (spirometry or peak flow)	Record of persistent airflow limitation (FEV_1/FVC <0.7 post-BD)
Lung function between symptoms	Normal	Abnormal
Past history or family history	Previous diagnosis of asthma	Previous diagnosis of COPD, chronic bronchitis or emphysema
	Family history of asthma, and other allergic conditions (allergic rhinitis or eczema)	Heavy exposure to risk factor: tobacco smoke, biomass fuels
Disease course	No worsening of symptoms over time. Variation in symptoms either seasonally, or from year to year	Symptoms slowly worsening over time (progressive course over years)
	May improve spontaneously or have an immediate response to BD or to ICS over weeks	Rapid-acting BD treatment provides only limited relief
Chest X-ray	Normal	Severe hyperinflation

More than three positive features confirm diagnosis of chronic obstructive pulmonary disease (COPD) or asthma. If there is a similar number of positive features for both asthma and COPD, asthma–COPD overlap diagnosis is considered.
BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume/forced vital capacity; ICS, inhaled corticosteroid.

of Chinese ACO patients, including the demographic characteristics, symptoms (wheeze, cough, etc.), imaging features [computed tomography (CT), X-ray] and laboratory test results including specific biomarkers (blood eosinophils, exhaled NO, immunoglobulin; induced sputum eosinophils, neutrophils, etc.). The other important secondary outcome was to estimate the ACO clinical recognition rate: that is, the difference between the first diagnosis and the final diagnosis.

Statistical analysis

All the outcomes were determined in the full analysis set (FAS). Based on the assumption that ACO affects ~20% of Chinese patients ⩾40 years of age and with chronic airflow limitation,[17] an estimated sample size of 2000 patients was considered for inclusion to achieve a precision of 1.80% [half-length of 95% confidence interval (CI)]. Continuous data were presented as numbers, mean, standard deviation, median, minimum and maximum; whereas categorical data were presented as percentages and 95% CIs. Univariate and multivariable logistic regression analyses were used to find the risk factors associated with eosinophil (EOS) level ($\geqslant 0.3$ or <0.3). Statistical analysis was performed using Statistical Analysis System version 9.1. A p-value of <0.05 was considered to be statistically significant.

Results

Baseline characteristics of FAS

Of the 2016 recruited patients, 2003 patients were included in the FAS distributed across six regions of China. All the vital demographic details of the study population are presented in Table 2.

Table 2. Baseline characteristics and patient distribution.

Variables	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Age, years				
Mean (SD)	60.4 (9.65)	65.8 (8.61)	55.1 (9.23)	62.3 (9.86)
Median (range)	61 (40, 86)	66 (40, 98)	55 (40, 79)	63 (40, 98)
BMI, kg/m^2				
Mean (SD)	23.36 (3.523)	22.35 (3.715)	24.13 (3.395)	22.98 (3.658)
Median (range)	23 (14.3, 37.6)	22 (12.2, 38.4)	24 (15.9, 37.1)	22.8 (12.2, 38.4)
Gender				
Male	483 (64.50)	805 (82.90)	133 (47.00)	1421 (70.90)
Female	266 (35.50)	166 (17.10)	150 (53.00)	582 (29.10)
Smoking history				
History of smoking	432 (57.7)	794 (81.8)	96 (33.9)	1322 (66)
Duration of smoking	35.7 ± 12.08	38.5 ± 11.75	30.3 ± 11.94	37.0 ± 12.08
Smoking amount (cigarettes/year)	781 (541.2)	858 (576.6)	576 (473.6)	813 (563.0)
Race, *n* (%)				
Han	720 (96.10)	947 (97.50)	273 (96.50)	1940 (96.90)
Other	29 (3.90)	24 (2.50)	10 (3.50)	63 (3.10)
Living environment, *n* (%)				
Urban	392 (52.30)	540 (55.60)	181 (64.00)	1113 (55.60)
Rural	357 (47.70)	431 (44.40)	102 (36.00)	890 (44.40)
Education, *n* (%)				
Junior middle school or below	506 (67.60)	660 (68.00)	154 (54.40)	1320 (65.90)
Technical secondary school/senior high school	159 (21.20)	187 (19.30)	68 (24.00)	414 (20.70)
Technical college	51 (6.80)	65 (6.70)	32 (11.30)	148 (7.4)
Undergraduate	30 (4.00)	57 (5.90)	26 (9.20)	113 (5.6)
Graduate or above	3 (0.40)	2 (0.20)	3 (1.10)	8 (0.4)
Total family income, yuan/month, *n* (%)				
⩽3000	290 (38.70)	348 (35.80)	82 (29.00)	720 (35.90)
3001–5000	233 (31.10)	268 (27.60)	91 (32.20)	592 (29.60)
5001–10,000	162 (21.60)	249 (25.60)	70 (24.70)	481 (24.00)
10,001–15,000	37 (4.90)	64 (6.60)	22 (7.80)	123 (6.10)
>15,000	27 (3.6)	42 (4.3)	18 (6.40)	87 (4.30)

(Continued)

Table 2. (Continued)

Variables	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Primary health insurance, *n* (%)				
Labor expense medical insurance	25 (3.30)	66 (6.80)	16 (5.70)	107 (5.30)
Cooperative medical insurance	317 (42.30)	369 (38.00)	89 (31.40)	775 (38.70)
Employee medical insurance	230 (30.70)	361 (37.20)	119 (42.00)	710 (35.40s)
Commercial medical insurance	2 (0.30)	1 (0.10)	2 (0.70)	5 (0.20)
At own expense	140 (18.70)	123 (12.70)	52 (18.40)	315 (15.70)
Other	35 (4.70)	51 (5.30)	5 (1.80)	91 (4.50)
Therapeutic drug usage, *n* (%)	502 (67.0)	656 (67.6)	218 (77.0)	1376 (68.7)
ICS/LABA combination formulations	51.1%	46.3%	61.8%	50.3%
Anticholinergics	25.1%	43.5%	–	31.7%,
Leukotriene receptor antagonists	14.8%	–	27.6%	2.4%
Xanthines	–	18.1%	–	15.7%
Selective β2 adrenergic receptor agonists	–	–	6.3%	10.2%
Comorbidities, *n* (%)	279 (37.20)	415 (42.70)	92 (32.50)	786 (39.20)
Hypertension	121 (16.20)	415 (42.70)	92 (32.50)	356 (17.80)
CAD	34 (4.50)	72 (7.40)	7 (2.50)	113 (5.60)
Diabetes	26 (3.50)	35 (3.60)	6 (2.10)	67 (3.30)
Hyperlipidemia	8 (1.10)	20 (2.10)	5 (1.80)	33 (1.60)
Allergic rhinitis	33 (4.40)	22 (2.30)	18 (6.40)	62 (3.10)
History of acute exacerbation, *n* (%) (within 12 months prior to the visit)	319 (42.6)	395 (40.7)	96 (33.9)	–
Current respiratory symptoms, *n* (%)				
Cough	595 (79.40)	803 (82.70)	213 (75.30)	1611 (80.40)
Expectoration	573 (76.50)	792 (81.60)	198 (70.00)	1563 (78.00)
Dyspnea	557 (74.40)	677 (69.70)	180 (63.60)	1414 (70.60)
Wheeze	559 (74.60)	635 (65.40)	215 (76.00)	1409 (70.30)
Chest tightness	522 (69.70)	646 (66.50)	182 (64.30)	1350 (67.40)
Other	13 (1.70)	13 (1.30)	7 (2.50)	33 (1.60)

ACO, asthma–chronic obstructive pulmonary disease overlap; CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease; ICS: inhaled corticosteroid; LABA: long-acting β2 receptor agonist; SD, standard deviation.

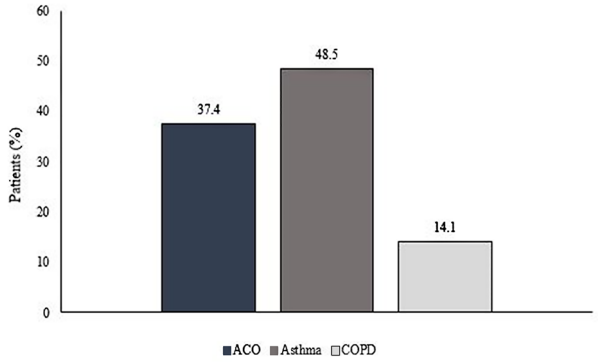

Figure 1. Distribution of asthma–chronic obstructive pulmonary disease overlap (ACO), asthma, and chronic obstructive pulmonary disease (COPD) in the study population.

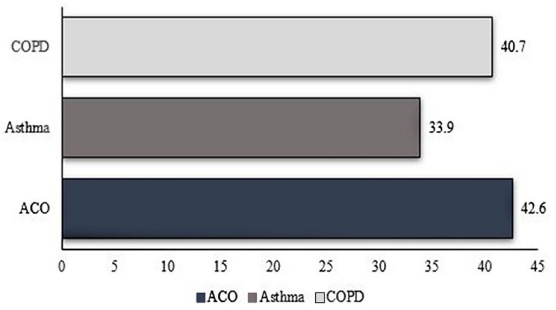

Figure 2. Proportion of patients with acute exacerbation history.
ACO, asthma–chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease.

Distribution of ACO in Chinese patients

ACO was reported in 749 patients (37.40%) in the FAS. Distribution of patients with only COPD was the highest among the study population at 971 (48.50%), while asthma patients formed the smallest group with 283 patients (14.10%) (Figure 1). According to the GOLD 2015 grouping, the proportions of ACO patients in A, B, C and D groups were 11.70%, 31.00%, 6.90% and 50.30% respectively while the GOLD 2017 grouping estimated 15.10%, 51.10%, 3.60% and 30.20% of ACO patients in A, B, C and D respectively.

Characteristics of Chinese ACO patients

History and symptoms. Patients with ACO ($n=749$) had a mean age of 60.40 ± 9.35 years, 64.50% male, 35.50% female (Table 2). A total of 432 (57.70%) patients had previous history of smoking with a mean duration of smoking history of 35.7 ± 12.08 years and mean yearly smoking of 781 ± 541.2 cigarettes/year. A total of 210/749 (28%) patients also had history of biomass fuel exposure. The proportion of patients with history of acute exacerbation was highest in the ACO group (Figure 2) (ACO *versus* COPD: $p=0.0756$; ACO *versus* asthma: $p=0.69$). The common respiratory symptoms in ACO patients included cough (79.40%), expectoration (76.50%) and wheezing (74.60%). The frequency of symptoms of ACO, asthma and COPD is shown in Table 2.

Imaging, biomarker and laboratory evaluation. Table 3 depicts the comparative results of the lung function tests. ACO patients reported a mean change of 8.23% in FEV_1 after bronchodilation. Other lung function parameters are presented in Table 4. Chest X-ray reported hyperinflation in 15.80% ACO patients, with severe hyperinflation reported in 8.50% patients (Table 5). In ACO patients, the high resolution CT (HRCT) findings included emphysema (47.80%), followed by chronic bronchitis (21.70%), bulla (16.10%) and bronchial wall thickening (obtained by calculating percentage of total airway cross-sectional area on CT and a mean value for each individual patient was calculated) (10.40%). Supplemental Material Table S1 online presents the laboratory findings in the ACO, asthma and COPD patients. Among the 205 ACO patients evaluated for blood EOS count, 71 patients (34.6%) reported a count of $\geqslant 0.3 \times 10^9$/L. The mean percentage of induced sputum EOS in ACO patients ($11.43 \pm 14.74\%$) was lower compared with the asthma group ($13.73 \pm 13.18\%$) but was higher than the COPD group ($2.97 \pm 2.95\%$). Further, there was no significant difference in acute exacerbation of ACO and COPD based on blood EOS count [$\geqslant 0.3 \times 10^9$/L *versus* $< 0.3 \times 10^9$/L; odds ratio (OR) = 0.94; 95% CI 0.715,1.237; $p=0.661$ and $\geqslant 0.3 \times 10^9$/L *versus* $< 0.3 \times 10^9$/L; OR = 1.24; 95% CI 0.876, 1.755; $p=0.226$ respectively] .

Risk factors for blood EOS ⩾0.3 in patients with ACO and COPD

Based on the univariate and multivariate analysis the risk factors for an increased EOS count included age of ⩽60 (OR 0.531; 95% CI 0.366, 0.773; $p=<0.001$); no smoking habit; history of allergic disease (univariate OR 2.388; 95% CI 1.563, 3.649;$p=<0.001$); initial diagnosis of

Table 3. Lung function test results – full analysis set.

	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Before bronchodilator inhalation				
FEV_1, %				
n	726	901	256	1883
Mean (SD)	47.34 (16.53)	45.59 (19.57)	55.41 (18.62)	47.60 (18.59)
Median	47.00	42.40	55.40	46.00
Range	(12.00, 92.00)	(9.80, 119.00)	(17.90, 103.30)	(9.80, 119.00)
FEV_1/FVC, %				
n	726	901	256	1883
Mean (SD)	50.21 (10.15)	47.90 (11.50)	55.63 (9.82)	49.84 (11.07)
Median	51.15	48.26	57.00	50.81
Range	(22.00, 75.90)	(19.30, 77.30)	(29.30, 89.40)	(19.30, 89.40)
After bronchodilator inhalation				
FEV_1, %				
n	748	971	283	2002
Mean (SD)	55.57 (17.87)	49.85 (20.175)	65.20 (19.243)	54.16 (19.894)
Median	55.45	47.00	66.80	53.00
Range	(16.00, 108.90)	(12.00, 117.10)	(22.00, 124.70)	(12.00, 124.70)
FEV_1/FVC, %				
n	749	971	283	2003
Mean (SD)	52.60 (10.59)	48.97 (11.62)	58.87 (9.14)	51.72 (11.416)
Median	53.80	49.06	61.10	53.00
Range	(21.00, 70.00)	(16.50, 69.90)	(30.80, 70.00)	(16.50, 70.00)
Before and after bronchodilator inhalation				
FEV_1 absolute changes, L				
n	726	901	256	1883
Mean (SD)	0.22 (0.16)	0.12 (0.11)	0.26 (0.207)	0.17 (0.16)
Median	0.21	0.10	0.23	0.14
Range		(–0.30, 0.90)		(–0.30, 1.10)
FEV_1 percent changes, %				
n	726	901	256	1883
Mean (SD)	19.77 (15.92)	11.56 (12.06)	20.11 (17.42)	15.89 (15.02)
Median	17.61	9.62	16.05	13.10
Range	(–22.60, 118.60)	(–14.90, 121.20)	(–10.70, 117.90)	(–22.60, 121.20)

ACO, asthma–chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; FEV_1/FVC, forced expiratory volume/forced vital capacity.

Table 4. FVC, FEF, MMEF Results – full analysis set.

	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Before bronchodilator inhalation				
FVC, %				
n	726	901	256	1883
Mean (SD)	74.99 (18.84)	74.73 (40.67)	80.18 (20.14)	75.57 (31.40)
Median	75.00	72.60	80.95	74.50
Range	(23.00, 133.10)	(12.70, 1110.2)	(33.7,128.2)	(12.70, 1110.2)
FEF75, %				
n	682	816	238	1736
Mean (SD)	20.73 (12.37)	20.81 (13.05)	24.12 (11.78)	21.23 (12.66)
Median	18.00	17.80	23.00	18.70
Range	(3.00, 58.00)	(2.00, 97.40)	(3.00, 88.10)	(2.00, 115.00)
MMEF25–75, %				
n	638	780	225	1643
Mean (SD)	18.45 (9.55)	17.74 (10.39)	24.76 (11.75)	18.97 (10.53)
Median	16.75	14.95	24.30	17.00
Range	(3.50, 65.00)	(3.50, 68.00)	(5.00, 71.00)	(3.50, 71.00)
After bronchodilator inhalation				
FVC, %				
n	748	971	283	2002
Mean (SD)	84.36 (19.21)	78.83 (21.95)	89.52 (19.67)	82.41 (20.99)
Median	84.50	78.00	89.00	82.00
Range	(29.00, 154.00)	(9.80, 119.00)	(35.10, 142.00)	(12.30, 158.60)
FEF75, %				
n	715	894	268	1877
Mean (SD)	24.24 (13.96)	22.60 (13.77)	28.54 (13.34)	24.07 (13.92)
Median	20.80	19.70	26.70	21.00
Range	(2.00, 135.00)	(1.00, 150.00)	(4.00, 99.20)	(1.00, 150.00)
MMEF25–75, %				
n	662	852	252	1766
Mean (SD)	22.81 (11.35)	20.07 (11.55)	30.83 (13.12)	22.63 (12.25)

(Continued)

Table 4. (Continued)

	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Median	21.00	17.00	30.15	20.00
Range	(4.00, 79.00)	(4.60, 70.00)	(5.10, 76.00)	(4.00, 79.00)
Other lung function test – full analysis set				
DLCO, %				
n	142	266	42	449
Mean (SD)	77.66 (28.56)	0.12 (0.11)	0.26 (0.207)	0.17 (0.16)
Median	76.40	62.55	92.00	69.50
Range	(91.10, 166.90)	(15.10, 242.80)	(32.00, 125.40)	(91.10, 242.80)
RV, %				
n	176	299	48	523
Mean (SD)	139.12 (52.28)	131.49 (49.45)	143.41 (49.18)	135.15 (52.65)
Median	128.35	124.10	127.05	126.00
Range	(31.10, 455.50)	(7.90, 332.00)	(61.50, 275.30)	(7.90, 455.50)
RV/TLC, %				
n	177	300	48	526
Mean (SD)	55.91 (20.07)	57.84 (20.92)	56.58 (20.19)	57.07 (21.26)
Median	54.01	54.50	52.79	54.04
Range	(27.00, 249.40)	(11.8, 202.80)	(31.00, 190.20)	(11.80, 249.40)

ACO, asthma–chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; DLCO, diffusion capacity of carbon monoxide; FEF, forced expiratory flow; FVC, forced vital capacity; MMEF, maximum-mid expiratory flow; RV, residual volume; TLC, total lung capacity.

asthma; and treatment with Ventolin or oral corticosteroid, while in multivariate analysis the risk factors included history of allergic disease and initial diagnosis of asthma. In COPD patients the risk factors included male gender and history of allergic disease (Table 6).

ACO clinical recognition rate

Among the 749 ACO patients, only 45 patients (6%) were diagnosed as ACO by the physicians during the initial visit. The clinical recognition rate for ACO was 31.4% (37.4–37.6%). The most common initial diagnoses of ACO were asthma (65.3%) followed by COPD (37.70%), chronic bronchitis (25.40%), emphysema (17.50%) and chronic bronchitis with emphysema (3.60%) (Supplemental Table S2).

Discussion

Owing to the overlap of symptoms, ACO does not represent a single disease or phenotype and mechanisms underlying this overlap are largely unknown. Therefore, a formal definition for ACO cannot be provided. However, GINA-GOLD 2017 provided a description of ACO for clinical use which is under big debate currently.[19] Further, ACO as a clinical entity worsens the quality of life and increases the cost burden of the individual diseases.[19] COPD may be over diagnosed in ageing populations or underdiagnosed in younger populations due to lack of precise methods in clinical practice.[21] Under regular clinical practice settings, COPD diagnosis is based on the fixed ratio $FEV_1/FVC < 0.70$ post-BD as well as other clinical features and epidemiological features. In

Table 5. Chest X-Ray and HRCT findings – full analysis set.

	ACO *n* = 749	COPD *n* = 971	Asthma *n* = 283	Total *N* = 2003
Chest X-ray				
n	165	232	49	446
Normal, *n* (%)	37 (22.40)	41 (17.70)	15 (30.60)	93 (20.90)
Hyperinflation, *n* (%)	26 (15.80)	60 (25.90)	0 (0)	86 (19.30)
Mild, *n* (%)	1 (0.60)	2 (0.90)	0 (0)	3 (0.70)
Moderate, *n* (%)	4 (2.40)	6 (2.60)	0 (0)	10 (2.20)
Severe, *n* (%)	14 (8.50)	36 (15.50)	0 (0)	50 (11.20)
Other abnormalities, *n* (%)	116 (70.30)	163 (70.30)	34 (69.40)	313 (70.20)
Chest HRCT				
n	230	347	87	664
Emphysema, *n* (%)	110 (47.80)	245 (70.60)	20 (23.00)	375 (56.50)
Chronic bronchitis, *n* (%)	50 (21.70)	103 (29.70)	8 (9.20)	161 (24.20)
Bulla, *n* (%)	37 (16.10)	91 (26.20)	2 (2.30)	130 (19.60)
Bronchial wall thickening, *n* (%)	24 (10.40)	32 (9.20)	5 (5.70)	61 (9.20)
Other abnormalities, *n* (%)	206 (89.60)	318 (91.60)	78 (89.70)	602 (90.70)
Chest X-ray or HRCT				
n	379	543	125	1047
Hyperinflation/emphysema, *n* (%)	135 (35.60)	300 (55.20)	20 (16.00)	455 (43.50)

ACO, asthma–chronic obstructive pulmonary disease overlap; COPD, chronic obstructive pulmonary disease; HRCT, high resolution computed tomography

the current study, diagnosis was based on these factors. Other diseases may also be associated with persistent airflow limitation such as bronchiectasis, diffuse panbronchiolobronchitis, bronchial asthma, etc. Hence, appropriate differential diagnosis was also used for confirmation, apart from assessment of pulmonary function (FEV_1/FVC <0.7). Further, patients with asthma may also develop airway remodeling as the disease progresses, leading to persistent airflow limitation. Hence differential diagnosis of ACO was not considered if the asthmatic patients did not have any risk factors for COPD, such as smoking. The disease history and clinical features, if they were in accordance with typical asthma, was also used for differential diagnosis, to rule out ACO. Further obvious wheezing in both lungs during acute exacerbation, even if the FEV_1/FVC <0.70, were diagnostic features for ruling out ACO. At present, there are no better alternative methods suitable for clinical practice. In the current study we employed a two-tier approach, that is, with airflow limitation (post-BD FEV_1/FVC <0.7) and clinical diagnosis as per syndromic criteria in the GINA 2015 updated report thereby limiting the overdiagnosis/underdiagnosis in ageing and younger populations respectively.[22]

Due to the increase in air pollution in China, the prevalence of chronic airflow limitation due to asthma and COPD has also been on the rise.[15,20–23] Due to the cumulative effect of increased pollution and limited prevalence data on ACO, China faces a challenge in the diagnosis and management of

Table 6. Analysis of risk factors for blood eosinophil in patients with ACO/COPD/asthma – full analysis set.

Variables	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Gender, male *versus* female	1.162	(0.780, 1.732)	0.461	1.612	(1.039, 2.499)	0.033
Age, >60 years *versus* ⩽60 years	0.531	(0.366, 0.773)	<0.001	–	–	–
History of allergic disease, with *versus* without	2.388	(1.563, 3.649)	<0.001	1.741	(1.097, 2.760)	0.019
Current state of smoking, smoking *versus* non-smoking	1.498	(1.022, 2.195)	0.038			
Asthma, with *versus* without	2.477	(1.693, 3.625)	<0.001	1.642	(0.998, 2.701)	0.051
COPD, with *versus* without	0.543	(0.369, 0.800)	0.002	0.603	(0.375, 0.971)	0.037
ACO, with *versus* without	1.248	(0.370, 4.207)	0.720	–	–	–
Ventolin, with *versus* without	2.848	(1.664, 4.876)	<0.001	2.317	(1.312, 4.090)	0.004
Oral hormone, with *versus* without	6.381	(1.225, 33.243)	0.028	–	–	–

ACO, asthma–chronic obstructive pulmonary disease overlap; CI, confidence interval; COPD, chronic obstructive pulmonary disease; OR, odds ratio.

ACO.[6] The results of our large, multicenter study provided the incidence of ACO among patients with chronic airway limitation using comprehensive diagnostic criteria recommended by the recent guidelines.[13]

In 2016, Sin *et al.* defined major and minor criteria based on spirometric analysis for defining ACO: (i) major criteria (post-BD FEV_1/FVC <0.7 in patients aged ⩾40 years; exposure to indoor/outdoor pollution or smoking ⩾10 packs of tobacco; history of asthma at <40 years of age or BDR >400 mL in FEV_1); (ii) minor criteria (history of atopy/allergic rhinitis; bronchodilator response (BDR) ⩾200 mL and 12% from baseline for ⩾2 weeks; peripheral blood EOS count ⩾300 cells/μL). Out of these, the patient must meet three major and one minor criterion to be confirmed as ACO.[13]

In this study, we included patients with chronic airflow limitation and analyzed the distribution of ACO, COPD and asthma using the syndromic criteria of GINA 2015. Therefore, this two-tier approach limits the overdiagnosis/underdiagnosis.[13] In the current study, two in five patients with chronic airway limitation were found to be with ACO, which is higher than in previous studies. In China, a small-scale study from Chinese Health Surveys reported only 0.61% patients to have ACO[6] whereas in a Taiwanese cohort study, 17.40% of the enrolled patients were diagnosed with ACO.[23] The reason for the observed difference might be due to the diagnostic criteria used in the previous studies. While in the Taiwanese study the diagnosis was based on physician-reported diagnosis of asthma in COPD patients, in our study, the diagnostic criteria were more comprehensive, taking into account the clinical features and the syndromic approach to ACO diagnosis. Hence, we presume, the incidence reported in our study may correspond with the actual prevalence. Further, a Finnish cross-sectional study reported ACO incidence in 27.40% of the enrolled patients who had previous smoking history.[27,28] Another study, in Korea, reported prevalence of ACO at 47.7% according to the modified Spanish criteria in COPD patients.[26] The results of our study suggest that the proportion of Chinese ACO patients with persistent airflow limitation (post-BD FEV_1/FVC <0.7) is higher than previously reported.[24,25,27] The incidence of ACO in the combined ACO + COPD cohort is 43.55%, which is higher than in the previous studies.[28–30] In the current study, around 68.7% patients in ACO, COPD and asthma groups were receiving drug therapies. The most commonly used drug therapies were inhaled cortiocosterioids/long-acting beta-agonists (ICS/LABA) and anticholinergics. Leukotriene receptor was also used in patients with asthma and ACO. As per the recent updated GINA 2020, ICS alone or in combination with long-acting beta-agonist/long-acting muscarinic antagonist (LABA/LAMA) are essential in reducing

exacerbations in asthma and ACO patients. Further, LABA/LAMA should not be used without ICS in asthma and ACO patients. In patients with COPD, initial treatment with LABA/LAMA is recommended with the addition of ICS in the case of hospitalization, ⩾2 exacerbations per year and blood EOSs ⩾300/μL. Further, ICS is not recommended as monotherapy without LABA/LAMA in patients with COPD. In our study, although leukotriene receptor antagonists were used, they are not recommended as first-line or initial treatment by GINA 2020. Similarly, anticholinergics like LAMA are recommended only in combination with ICS in asthma and ACO patients. But in our study, although anticholinergics were not used as monotherapy in asthma patients, in 25.1% of the ACO patients, they were used as monotherapy. Similarly, leukotriene receptor antagonists were used as monotherapy in ACO, COPD and asthma patients. This highlights the inconsistency between established guidelines and real-world clinical practice in China, and also highlights the need for standardized treatment strategies to prevent exacerbations in Chinese patients. The history of exacerbations was also relatively high in the ACO group in comparison with other groups, suggesting the increased disease burden in the ACO group. Further, before inhalation of bronchodilator, in patients with ACO, COPD and asthma, FEF75% was 20.73 ± 12.37, 20.81 ± 13.05 and 24.12 ± 11.78 respectively and MMEF 25–75 was 18.45 ± 9.55, 17.74 ± 10.39 and 24.76 ± 11.75 respectively. After inhalation of bronchodilator, in patients with ACO, COPD and asthma, both forced expiratory flow (FEF75%) and maximum-mid expiratory flow (MMEF 25–75 (%)) was increased. However, significant increase was observed in the asthma group, that is, 28.54 ± 13.34 and 30.83 ± 13.12. The observed increase in incidence might be due to the diagnostic criteria used in our study or might represent a paradigm shift in the incidence of ACO within the Chinese COPD cohort. In our study, approximately 42% of the ACO patients did not have previous smoking history and the biomass exposure in those patients could have predisposed them to ACO. Similar findings with regard to chronic airway restriction were also reported in previous studies. Wang *et al.* reported 28.8%, 28.2% and 17.6% patients without smoking history had GOLD stage I, II and III-IV COPD, respectively.[31]

The clinical diagnosis of ACO poses a diagnostic challenge due to the nature of ACO. However, analysis of common symptoms might help us in devising better diagnostic algorithms. In our study, the common respiratory symptoms of ACO and COPD patients included cough and expectoration, with dyspnea, wheeze and chest tightness as other prominent symptoms. Similar symptoms were also reported in the PLATIONO study, wherein cough (50.6% and 25.4%), phlegm (42.7% and 25.4%), wheezing (100% and 29.3%) and dyspnea (65.2% and 47.4%) were the common symptoms of ACO and COPD patients respectively.[32] The results of our study highlight the subtle difference in the respiratory symptoms of Chinese patients when compared with Western populations. Further, ACO patients complained of a higher rate of wheezing compared with COPD patients (74.6% *versus* 65.4%). Similar results have been reported in the RHINE and Swedish GA2LEN surveys wherein ACO patients had higher wheezing in comparison with the COPD patients (83.7% *versus* 48.9%).[33] Further, in our study, the prevalence of allergic rhinitis was found to be lower than in previous studies. A probable reason for the observed difference could be lack of awareness in the patient population.

Blood EOS concentrations are considered as good predictors of acute exacerbations in COPD patients, which was established without taking into account ACO. Sin *et al.* in 2016 proposed peripheral blood EOS count of ⩾300 cells/μL as one of the minor criteria for diagnosing ACO,[37] whereas the Spanish consensus had proposed sputum eosinophilia of >3% as a major criterion for ACO.[35] The precise role of blood EOSs in the differentiation of ACO from COPD and asthma is not yet revealed. In our study, ACO patients had lower mean blood EOS count and mean percentage of induced sputum EOS compared with asthma patients, but was much higher than in COPD patients. Hence, EOS count in blood and induced sputum could be used in the differential diagnosis of ACO and COPD. Analysis of acute exacerbations also revealed lack of association with higher blood EOS count in ACO patients, which is unlike COPD. In contrast to the studies that reported increased EOS count in elderly patients (>60 years)[36] and smokers,[37,38] our study demonstrated a lower EOS count in these cohorts. This partly explains that blood EOSs are generally not high in the Chinese population and hence blood EOS count is not suggested to be used to guide treatment. Some of the experts have recommended the diagnosis of ACO with an increase of

15% and 400 mL in FEV_1.[39,40] On the other hand, several studies reported the same extent of response in the case of COPD patients.[41–43] In our study, FEV_1 variability was evident in the ACO and the COPD group, with higher FEV_1 noticed in the ACO group in comparison with the COPD group.

The reported radiological characteristics of ACO included lower emphysema index, greater post-BD variations in air trapping, larger variations of sagittal-lung CT measurements[39,44] and reduced cross-sectional area of pulmonary vessels ($<5\,mm^2$).[45] The HRCT findings in our study demonstrated bronchial wall thickening in 10.4% of the ACO patients, which was slightly more than that reported in COPD patients. Our findings were similar to those reported by Suzuki *et al.* (ACO *versus* COPD: $79.10 \pm 4.00\%$ *versus* $76.90 \pm 3.40\%$, $p = 0.001$).[46] However, the current radiological features reported are too few to recommend a pathognomonic radiological characteristic in ACO. As the peripheral blood EOS count of $\geqslant 0.3 \times 10^9$/L was not suitable in Chinese ACO patients, other methods including the FEV_1 and HRCT findings may be used as an alternative diagnostic aid in the Chinese population. Further studies are required to validate our results.

In our study, the initial physician reported diagnosis rate of ACO was 6.0% in the ACO group, which was higher than the rate reported from other studies. But, 65.3% and 37.7% of the ACO patients were also previously diagnosed as asthma and COPD, which emphasizes the diagnostic conundrum of ACO. The rates of initial diagnosis in Chinese patients in previous studies is also low, mainly due to lack of consensus on the precise diagnostic algorithm. A multi-tier approach to diagnosis might improve the rate of diagnosis facilitating and adequate management of ACO.

Strengths and limitations

The main strength of our study includes the comprehensive diagnostic algorithm taking into account the syndromic criteria for determining the distribution of ACO in China, in a large cohort of patients with chronic airway limitation. This study also provided the distribution of COPD and asthma, both of which are on the rise in China. This real-world study also reported the clinical characteristics and potential biomarkers associated with ACO which could be incorporated into the diagnostic algorithm for better initial diagnosis. Most importantly this is the first report on the actual clinical distribution of ACO in China, which will assist in devising better management strategies.

Our study also has a few limitations. As this is a NIS, data may not have been available and collected for all variables in the enrolled patients. Further, the study was conducted only in tertiary hospitals, which may not represent the prevalence and diagnosis of ACO at a primary-level hospital. Since ACO is a newly defined condition, its diagnosis and management in the lower-ranked primary hospitals might be worse due to lower physician awareness. Last, only symptom frequency statistics were available, with no data available on the severity of the symptom and quality of life.

Conclusion

In conclusion, though the distribution of ACO was nearly two-fifths of the study population, the initial diagnosis rate was very low at 6%. Hence, there is a critical need to improve the diagnosis of ACO in China. The clinical, radiographical and laboratory findings of our study will serve as a benchmark for the physicians in diagnosing and managing ACO efficiently in China.

Acknowledgements

The authors would like to thank all investigators and patients for participating in this study.

Author contribution(s)

Jian Kang: Conceptualization; Data curation; Formal analysis; Methodology; Writing-original draft; Writing-review & editing.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Data sharing, data availability, data citation statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

Ethical approval and consent to participate

The study was approved by ethics committees of all the study sites according to the International Conference on Harmonization guidelines for Good Clinical Practice and conformed to the Declaration of Helsinki. All patients received information on the purpose and conduct of this study, and provided written, informed consent.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was funded by AstraZeneca, China and National Key R&D Program of China 2016YFC1304500.

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Supplemental material

The reviews of this paper are available via the supplemental material section.

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