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The characteristics of the frequent exacerbators with chronic bronchitis phenotype and the asthma-chronic obstructive pulmonary disease overlap syndrome phenotype in chronic obstructive pulmonary disease patients
A meta-analysis and system review

Jian-Jun Wu, PhD[a], Hong-Ri Xu, PhD[a], Ying-Xue Zhang, MM[a], Yi-Xuan Li, MM[a], Hui-Yong Yu, PhD[a], Liang-Duo Jiang, PhD[b,*], Cheng-Xiang Wang, PhD[a,*], Mei Han, PhD[c,*]

Abstract

To investigate the difference of clinical characteristics between chronic obstructive pulmonary disease (COPD) patients with the frequent exacerbators with chronic bronchitis (FE-CB) phenotype and those with the asthma-COPD overlap syndrome (ACO) phenotype.

We searched CNKI, Wan Fang, Chongqing VIP, China Biology Medicine disc, PubMed, Cochrane Library, and EMBASE databases for studies published as of April 30, 2019. All studies that investigated COPD patients with the FE-CB and ACO phenotypes and which qualified the inclusion criteria were included. Cross-sectional/prevalence study quality recommendations were used to measure methodological quality. RevMan5.3 software was used for meta-analysis.

Ten studies (combined n = 4568) qualified the inclusion criteria. The FE-CB phenotype of COPD was associated with significantly lower forced vital capacity percent predicted (mean difference [MD] −9.05, 95% confidence interval [CI] [−12.00, −6.10], $P < .001$, I^2 = 66%), forced expiratory volume in 1 second (FEV_1) (MD −407.18, 95% CI [−438.63, −375.72], $P < .001$, I^2 = 33%), forced expiratory volume in 1 second percent predicted (MD −9.71, 95% CI [−12.79, −6.63], $P < .001$, I^2 = 87%), FEV_1/forced vital capacity (MD −5.4, 95% CI [−6.49, −4.30], $P < .001$, I^2 = 0%), and body mass index (BMI) (MD −0.81, 95% CI [−1.18, −0.45], $P < .001$, I^2 = 44%) as compared to the ACO phenotype. However, FE-CB phenotype was associated with higher quantity of cigarettes smoked (pack-years) (MD 6.45, 95% CI [1.82, 11.09], $P < .001$, I^2 = 73%), COPD assessment test score (CAT) (MD 4.04, 95% CI [3.46, 4.61], $P < .001$, I^2 = 0%), mMRC score (MD 0.54, 95% CI [0.46, 0.62], $P < .001$, I^2 = 34%), exacerbations in previous year (1.34, 95% CI [0.98, 1.71], $P < .001$, I^2 = 68%), and BMI, obstruction, dyspnea, exacerbations (BODEx) (MD 1.59, 95% CI [1.00, 2.18], $P < .001$, I^2 = 86%) as compared to the ACO phenotype.

Compared with the ACO phenotype, COPD patients with the FE-CB phenotype had poorer pulmonary function, lower BMI, and higher CAT score, quantity of cigarettes smoked (pack-years), exacerbations in previous year, mMRC score, and BODEx.

This study is an analysis of published literature, which belongs to the second study. Therefore, this study does not require the approval of the ethics committee. The findings will be disseminated through a peer-reviewed journal publication or conference presentation.

1. Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease.[1–3] Recognition of the COPD phenotype may help recognize this heterogeneity and facilitate diagnosis and treatment.[4] The phenotype of COPD refers to the comprehensive clinical characterization of this condition vis-à-vis presence of single disease or multiple diseases. It can help clarify the differences between COPD patients with respect to clinical prognosis, symptoms, acute exacerbations, therapeutic response, disease progression rate, and mortality risk.[5] This is because these may have the same biological or physiological mechanisms. COPD phenotype may play an important role in facilitating individualized treatment, improving the quality of life, and reducing the burden of disease. However, there is no consensus on the classification of COPD phenotype in academic circles; in addition, the criteria and definitions are not standardized.[6] In 2013, the Spanish guidelines for the management of chronic obstructive pulmonary disease (GesEPOC) established for the first time an individualized drug treatment based on the clinical phenotype.[7] This approach was later adopted by other national guidelines and has since been consistently supported by new evidence. The guidelines propose 4 phenotypes: infrequent exacerbators with either chronic bronchitis or emphysema (non-exacerbator, NON-AE), frequent exacerbators with emphysema predominant, frequent exacerbators with chronic bronchitis predominant (FE-CB), and asthma-COPD overlap (ACO). The GesEPOC 2017 guidelines made certain modifications to the COPD phenotypes in the original guidelines according to risk stratification and clinical manifestations. The revised guidelines provide a better characterization of the phenotypes and have helped improve the individualized treatment of COPD. For example, ACO manifests stronger bronchial eosinophilic inflammation than any other phenotype. Inhaled corticosteroid and long-acting beta2 agonist, as the preferred treatment for ACO, can improve lung function and respiratory symptoms and reduce the number of acute exacerbations.[8]

FE-CB and ACO are 2 important phenotypes in the GesEPOC guidelines. Their clinical features are controversial in many aspects, such as lung function, body mass index (BMI), and performance in the COPD assessment test (CAT). In some studies, COPD patients with the FE-CB phenotype had significantly poorer lung function than those with the ACO phenotype[9,10]; however, another study found no difference in lung function between the 2 groups.[11] Among the clinical phenotypes of COPD, active smokers were found more likely to have frequent acute exacerbation phenotypes than non-smokers, with worse quality of life, and modified British Medical Research Council dyspnea scale (mMRC) score.[12] A Polish study also found that smoking index of patients with FE-CB phenotype was significantly higher than that of ACO, while BMI of patients with ACO was significantly higher than that of FE-CB phenotype.[9]

Patients with the FE-CB phenotype had more symptoms, often accompanied by anxiety and depression, while patients with the ACO phenotype were significantly younger, and the time of diagnosis of COPD was earlier than those with other COPD phenotypes, and they were often accompanied by allergic diseases and obesity. In several studies, the CAT scores of patients with the FE-CB phenotype were significantly higher than that of ACO phenotype,[9,13] while an Australian study[10] found no significant difference in this respect.

It is apparent that the different clinical phenotypes have different clinical characteristics. However, the clinical characteristics of each COPD phenotype are not well characterized, which calls for further in-depth studies to better guide clinical diagnosis and individualized treatment. The purpose of this study was to explore the difference of clinical characteristics between the FE-CB and ACO phenotypes of COPD, and to provide evidence for further study. The results of this study are expected to explain the clinical characteristics of these 2 phenotypes in a relatively comprehensive way, thus contributing to the provision of individualized treatment options. This has positive implications for reducing the number of acute episodes, delaying progression, improving prognosis, and delaying lung function decline and improving quality of life in patients with these 2 phenotypes. In addition, comprehensive judgment based on the clinical features of COPD phenotype, such as CAT, BMI, lung function, mMRC, smoking index, number of acute exacerbations, is helpful to judge the severity and prognosis of patients.

2. Research methods

This meta-analysis was conducted in accordance with meta-analysis of observational studies in epidemiology, and the literature search and screening protocol were pre-established.

2.1. Search strategy

The followed databases were searched for relevant articles published in English and Chinese language as of April 30, 2019: CNKI, Wan Fang, Chongqing VIP, China Biology Medicine disc, PubMed, Cochrane Library, and EMBASE. The following keywords or combinations were used to retrieve studies: "Chronic Obstructive Pulmonary Disease" or "COPD;" merging "ACOS" or "Asthma-COPD Overlap Syndrome" or "ACO" or "asthma–COPD overlap;" merging "exacerbators with chronic bronchitis" or "frequent exacerbators with chronic bronchitis" or "frequent exacerbator phenotype with chronic bronchitis" or "exacerbator phenotype with chronic bronchitis" or "exacerbator with chronic bronchitis." In addition, the reference lists of relevant reviews and meta-analyses were manually screened to avoid any omissions (see Text, Supplemental Text 1, http://links.lww.com/MD/D379, which shows the detailed search strategies).

2.2. Inclusion and exclusion criteria

Inclusion criteria:

(1) COPD patients;
(2) FE-CB phenotype and ACO phenotype characteristics were reported;
(3) main outcomes: lung function tests including forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), forced vital capacity percent predicted (FVC%pred), forced expiratory volume in 1 second percent predicted (FEV_1% pred), FEV_1/FVC. Secondary outcomes: quantity of cigarettes smoked (pack-years), CAT score, BMI, frequency of acute exacerbations, and mMRC score. Only studies that reported at least 1 of the main outcomes were included.
(4) Clinical randomized trials, semi-randomized trials, prospective cohort studies, and retrospective case analysis.

Exclusion criteria:

(1) copied or plagiarized literature;
(2) obvious inconsistencies in the data or suspicion of modification of data without authorization.
(3) studies with incomplete data or for which comprehensive information could not be obtained from the original author.

2.3. Data extraction and quality assessment

Two researchers independently performed literature screening and data extraction. Disagreements, if any, were resolved by consensus or by participation of a third co-author (Hong-Ri Xu). The methodological quality of the included studies was evaluated by the cross-sectional/prevalence study quality recommendations of the American Agency for Healthcare Research and Quality (AHRQ). There are 11 items in total. If the answer was "no" or "unclear," the item was scored as "0;" if the answer was "yes," the item was scored as "1." The quality of each included study was evaluated as follows: low quality = 0 to 3; moderate quality = 4 to 7; high quality = 8 to 11.

2.4. Observation indicators

The data extracted from the observation indicators mainly included information pertaining to the researchers (name of authors, publication time, language, country, type of study), and the research (sample size, average age, lung function, quantity of cigarettes smoked [pack-years], CAT score, BMI, etc).

2.5. Publication bias assessment

If there were more than 10 studies included in the meta-analysis, the data were evaluated for publication bias. Publication bias was assessed by viewing the symmetry of the funnel plot and using the Begg and Mazumdar[14] rank correlation method and the Harbord et al[15] modified linear regression method.

2.6. Data analysis

Rev Man 5.3 software was used for statistical analysis. Statistical heterogeneity among studies was evaluated by I^2. In the event of no significant heterogeneity ($P > .1$ and $I^2 < 50\%$), the fixed-effect model was used for meta-analysis. In case of statistically significant heterogeneity ($P < .1$ and $I^2 > 50\%$), the random effect model was used for meta-analysis. Continuous variables were evaluated by mean difference (MD). Results are expressed with 95% confidence intervals (CIs). $P < .05$ was considered as statistically significant.

3. Results

3.1. Literature search

A total of 372 articles were retrieved on database search. After review of titles and abstracts, 356 were eliminated for various reasons (Fig. 1). Full-text of the remaining 17 articles were reviewed, after which 7 articles were excluded (see Table, Supplemental Table 1, http://links.lww.com/MD/D380. List of excluded full-text articles.) and 10 articles were included. Figure 1 shows a schematic illustration of the literature search and the study selection criteria.

3.2. Basic characteristics of the included studies

Ten studies with a combined study population of 4568 patients were included in this study[11,16–24]; these included 3047 patients with the FE-CB phenotype and 1521 patients with ACO phenotype. The characteristics of the included studies are shown in Table 1.

3.3. Quality evaluation

According to the AHRQ, out of the 10 studies, no studies were evaluated as low quality, 7 were moderate quality, and 3 were high quality. The methodological quality evaluation of the included studies is shown in Table 2.

3.4. Comparison of the characteristics of COPD patients with the FE-CB and the ACO phenotypes

3.4.1. FVC%pred. Six studies[16,19–23] had reported the FVC% pred values of COPD patients with the FE-CB and ACO phenotypes. In 4 studies,[19,21–23] FVC%pred of the FE-CB phenotype was significantly lower than that of ACO phenotype, while other 2 studies[16,20] found no significant between-group difference in this respect. Owing to significant heterogeneity between the samples, the random effect model was used for analysis. Meta-analysis showed that the FVC%pred of FE-CB phenotype was lower than that of ACO phenotype (MD −9.05, 95% CI [−12.00, −6.10], $P < .001$, $I^2 = 66\%$) (Fig. 2). Sensitivity analysis suggested that heterogeneity was mainly derived from the study by Corlateanu et al.[19] Even after exclusion of this study, the FVC%pred of FE-CB phenotype was lower than that of the ACO phenotype (MD −8.52, 95% CI [−10.11, −6.93], $P < .001$, $I^2 = 28$) (see Figure, Supplemental Fig. 1, http://links.lww.com/MD/D381, which shows the sensitivity analysis of FVC%pred).

3.4.2. FEV_1. Three studies[18,23,24] had reported FEV_1 values of COPD patients with the FE-CB and ACO phenotypes. In all 3 studies, the FEV_1 of FE-CB phenotype was significantly lower than that of the ACO phenotype. There was no heterogeneity among the samples. Fixed-effect model was used for analysis. Meta-analysis showed that FEV_1 of COPD patients with the FE-CB phenotype was lower than that of ACO phenotype (MD −407.18, 95% CI [−438.63, −375.72], $P < .001$, $I^2 = 33\%$) (Fig. 3).
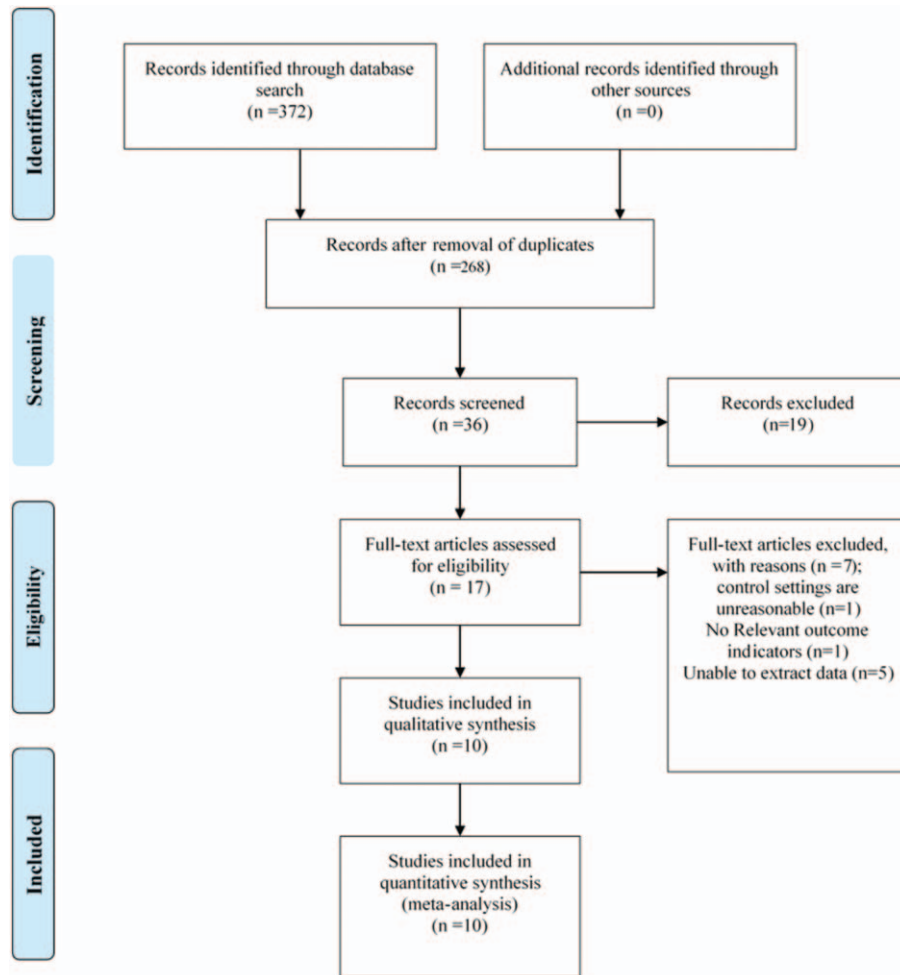
Figure 1. Schematic illustration of the study design literature search and the study selection criteria.

3.4.3. FEV₁%pred. Ten studies[11,16–24] reported FEV_1%pred of COPD patients with the FE-CB and ACO phenotypes. In 6 studies,[19–24] the FEV_1%pred of FE-CB phenotype was significantly lower than that of the ACO phenotype, while the other 4 studies[11,16–18] found no significant between-group difference in this respect. Owing to significant heterogeneity between the samples, the random effect model was used for analysis. Meta-analysis showed that the FEV_1%pred of the FE-CB phenotype was lower than that of the ACO phenotype (MD -9.71, 95% CI [-12.79, -6.63], $P < .001$, $I^2 = 87\%$) (Fig. 4). No evidence for publication bias was observed in the funnel plot (Fig. 5) or Begg ($P = .371$, Fig. 6) or Egger tests ($P = .371$, Fig. 7). Sensitivity analysis suggested that the heterogeneity was mainly derived from the studies by Arkhipov et al[17] and Qing et al.[24] After excluding the results of these studies, the FEV_1%pred of FE-CB phenotype was still lower than that of the ACO phenotype (MD -11.30, 95% CI [-12.71, -9.90], $P < .001$, $I^2 = 48\%$) (see Figure, Supplemental Fig. 2, http://links.lww.com/MD/D382, which shows the sensitivity analysis of FEV_1%pred).

3.4.4. FEV₁/FVC. Five studies[16,19–21,23] had reported FEV_1/FVC of COPD patients with the FE-CB and ACO phenotypes. In 4 studies,[19,21–23] the FEV_1/FVC of the FE-CB phenotype was

significantly lower than that of the ACO phenotype, while 1 other study[16] found no significant between-group difference in this respect. There was no heterogeneity among the samples. Fixed-effect model was used for analysis. Meta-analysis showed that the FEV_1/FVC of FE-CB phenotype was lower than that of ACO phenotype (MD -5.4, 95% CI [-6.49, -4.30], $P < .001$, $I^2 = 0\%$) (Fig. 8).

3.4.5. Quantity of cigarettes smoked (pack-years), CAT score, mMRC score, exacerbations in previous year, BMI, BODEx. All details of outcomes were found in Table 3, Supplemental Figure and Supplemental Table (see Figure, Supplemental Figs. 3–8, http://links.lww.com/MD/D383, which shows the forest plot of other indexes. Supplemental Figs. 9–10, http://links.lww.com/MD/D384, the sensitivity analysis of pack-years and exacerbations in previous year. Supplemental Table 2, http://links.lww.com/MD/D385. Other indices in different phenotype).

4. Discussion

COPD patients with the FE-CB phenotype had lower FVC%, FEV_1, FEV_1%, FEV_1/FVC, and BMI as compared to those with

Table 1

**Characteristics of the included studies.**

Author	Year	Country	Language	Research type	Cases (ACOS/FE-CB)	Age, yr (ACOS/FE-CB)	Evaluation indices
Alcázar-Navarrete, B	2016	Spain	English	Cross-sectional observation study	22/34	68 ± 8.0 72 ± 10.4	$FEV_1\%$, FEV_1/FVC, FVC%, CAT, pack-years, BMI
Arkhipov, V	2017	Russia	English	Cross-sectional observation study	143/415	60.5 ± 10.7 64.6 ± 8.5	$FEV_1\%$, pack-years, BMI, CAT
Calle Rubio, M	2017	Spain	English	Cross-sectional observation study	42/188	64.2 ± 9 69.5 ± 8.6	FEV_1, pack-years, CAT, mMRC, $FEV_1\%$, BODEx, exacerbations in previous year
Chee-Shee Chai	2019	Malaysia	English	Cross-sectional observation study	25/75	70.0 ± 13.1 70.7 ± 9.2	$FEV_1\%$, pack-years, CAT, mMRC, exacerbations in previous year
Corlateanu, A	2017	Moldova	English	Cross-sectional observation study	33/138	–	FVC%, $FEV_1\%$, FEV_1/FVC, CAT
Cosio, BG	2016	Spain	English	Cross-sectional observation study	125/99	66.5 ± 8.7 69.5 ± 8.1	BMI, CAT, $FEV_1\%$, FVC%, FEV_1/FVC, pack-years, exacerbations in previous year
Golpe, R	2018	Spain	English	Cross-sectional observation study	75/194	68.0 ± 9.0 72.7 ± 8.9	$FEV_1\%$, FVC%, FEV_1/FVC, BMI, BODEx
Koblizek, V	2017	Czech	English	Cross-sectional observation study	231/687	62.3 ± 10.2 66.6 ± 8.3	$FEV_1\%$, BMI, CAT, FVC%, mMRC, exacerbations in previous year
Miravitlles, M	2015	Germany	English	Cross-sectional observation study	496/602	64.6 ± 9.4 69.3 ± 9.2	BMI, pack-years, $FEV_1\%$, FVC%, FEV_1, FVC, FEV_1/FVC, mMRC, exacerbations in previous year, BODEx
Pan Qing	2016	China	Chinese	Cross-sectional observation study	102/267	–	FEV_1, $FEV_1\%$

ACOS = asthma-COPD overlap syndrome, BMI = body mass index, BODEx = BMI, obstruction, dyspnea, exacerbations, CAT = COPD assessment test, FE-CB = frequent exacerbators with chronic bronchitis, $FEV_1\%pred$ = forced expiratory volume in 1 second percent predicted, FEV_1 = forced expiratory volume in 1 second, FVC%pred = forced vital capacity percent predicted, FVC = forced vital capacity, mMRC = modified British Medical Research Council dyspnea scale.

Table 2

Methodological quality evaluation of studies included.

| Study ID	1	2	3	4	5	6	7	8	9	10	11	Total
Alcázar-Navarrete, B 2016	+	+	−	−	+	+	−	+	−	−	−	5
Arkhipov, V 2017	+	+	+	−	+	+	+	+	−	+	−	8
Calle Rubio, M 2017	+	+	+	−	+	+	−	+	−	−	−	6
Chee-Shee Chai 2019	+	+	+	−	+	+	+	−	−	−	−	6
Corlateanu, A 2017	+	+	−	−	+	+	−	+	−	−	−	5
Cosio, BG 2016	+	+	+	−	+	+	+	+	−	−	+	8
Golpe, R 2018	+	+	+	−	+	+	+	+	−	−	+	8
Koblizek, V 2017	+	+	+	−	+	+	+	+	−	−	−	7
Miravitlles, M 2015	+	+	−	−	+	+	+	+	−	−	−	6
Pan Qing 2016	+	+	+	−	+	+	−	+	−	−	−	6

1. Define the source of information (survey, record review); 2. List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications; 3. Indicate time period used for identifying patients; 4. Indicate whether subjects were consecutive, if not population-based; 5. Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants; 6. Describe any assessments undertaken for quality assurance purposes (eg, test/retest of primary outcome measurements); 7. Explain any patient exclusions from analysis; 8. Describe how confounding was assessed and/or controlled; 9. If applicable, explain how missing data were handled in the analysis; 10. Summarize patient response rates and completeness of data collection; 11. Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained.
+ = Yes, − = No, 0 = not clear.
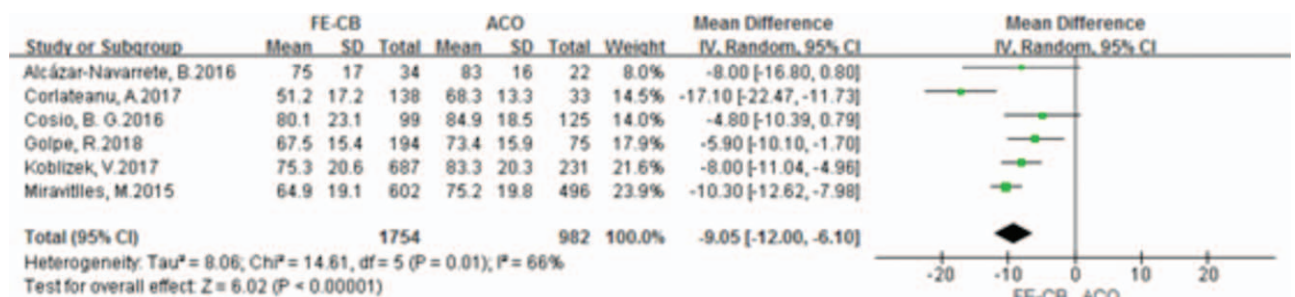
Figure 2. Difference of FVC%pred between the FE-CB and the ACO phenotypes. ACO = asthma-COPD overlap syndrome, FE-CB = frequent exacerbators with chronic bronchitis, FVC%pred = forced vital capacity percent predicted.
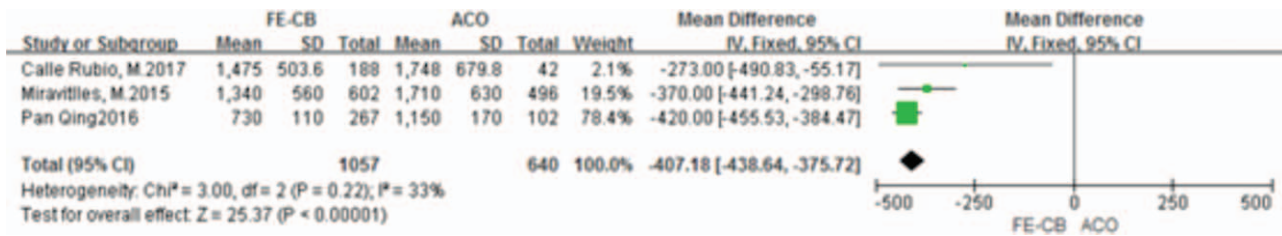
Figure 3. Difference of FEV$_1$ between the FE-CB and the ACO phenotypes. ACO = asthma-COPD overlap syndrome, FE-CB = frequent exacerbators with chronic bronchitis, FEV$_1$ = forced expiratory volume in 1 second.
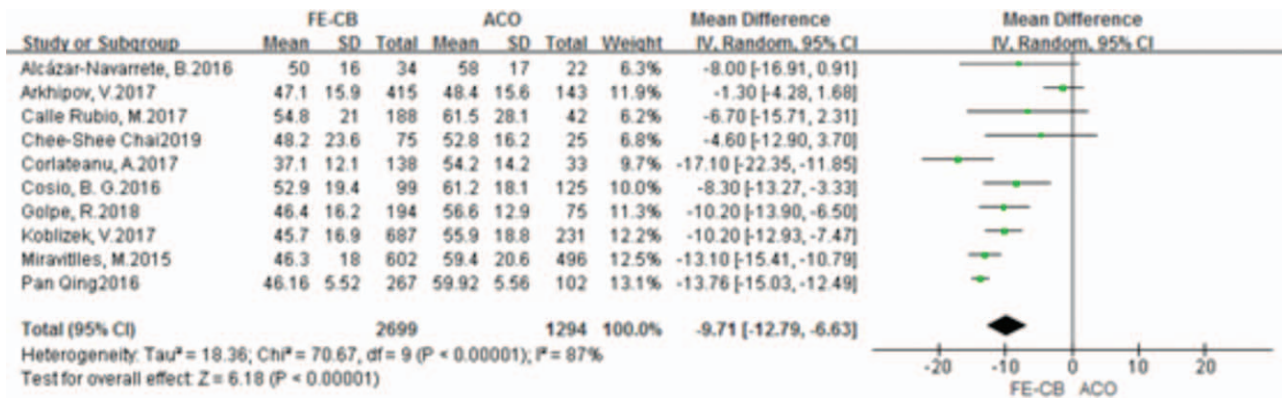

Figure 4. Difference of FEV$_1$%pred between the FE-CB and ACO phenotypes. ACO = asthma-COPD overlap syndrome, FE-CB = frequent exacerbators with chronic bronchitis, FVC%pred = forced vital capacity percent predicted.

the ACO phenotype. CAT score, smoking index, number of acute exacerbations, mMRC score, and BODEx were higher in the former.

Several studies have shown that COPD patients with different phenotypes show different disease characteristics in terms of gender, age, smoking habits, severity of symptoms (measured by CAT and mMRC scores), severity of airflow restriction, and number of complications.[9,13]

Pulmonary function tests are essential for the diagnosis of COPD; however, these do not provide in-depth characterization

COPD. Therefore, use of these indices for guiding individualized diagnosis and treatment of COPD has some limitations.[25] In clinical practice, the FEV$_1$ of some COPD patients varies greatly during the course of the disease. Moreover, COPD patients with similar FEV$_1$ may have different clinical manifestations, imaging findings, varying degrees of airway inflammation and systemic inflammation, and different disease prognosis. Phenotype can better reflect these characteristics of COPD patients.[26] However, the lung function indices of patients with different phenotypes are not well characterized. This study found that lung function of
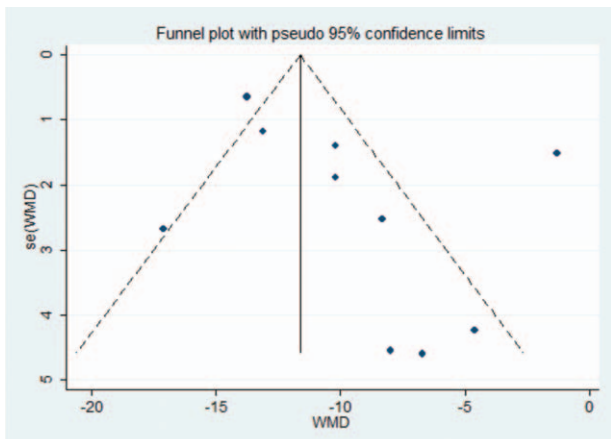
Figure 5. Funnel plot of FEV$_1$%. FEV$_1$ = forced expiratory volume in 1 second.
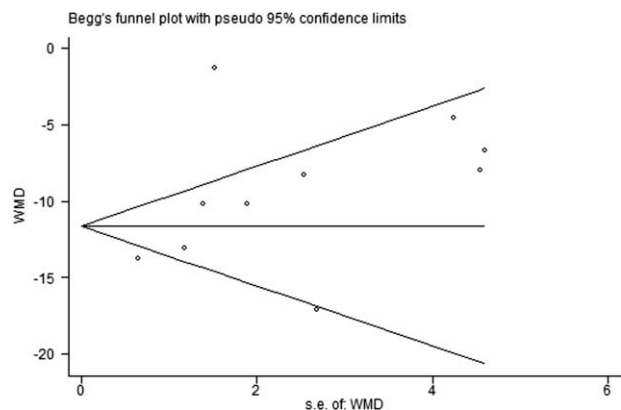
Figure 6. Begg funnel plot of FEV$_1$%. FEV$_1$ = forced expiratory volume in 1 second.
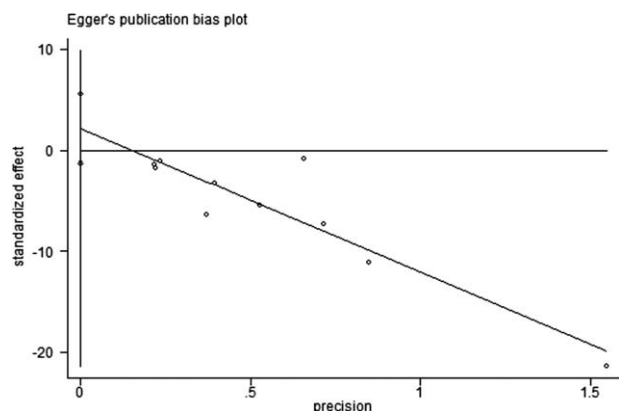
Figure 7. Egger publication bias plot of FEV$_1$%. FEV$_1$ =forced expiratory volume in 1 second.

patients with the FE-CB phenotype was worse than that of patients with the ACO phenotype. The reason may be related to the higher frequency of acute exacerbations in patients with the FE-CB phenotype and impaired pulmonary function. The heterogeneity between the studies was large, which may be related to the selected samples on the 1 hand and the variability of FEV$_1$ itself on the other hand.

Smoking is one of the main risk factors of COPD. The prevalence of COPD is proportional to the length of smoking time and smoking index.[27] In addition, it is also related to the type and mode of smoking.[25] Cigarette smokers are 3 times more likely to develop COPD than cigar smokers and pipe smokers. This meta-analysis included 6 studies[11,16–18,20,23] that reported smoking index; in 2 studies,[17,23] the smoking index of patients with FE-CB phenotype was significantly higher than that of ACO phenotype, while opposite results were obtained in the other 4 studies.[11,16,18,20] Owing to significant heterogeneity between the samples, the random effect model was used for analysis. On meta-analysis, the smoking index of the FE-CB phenotype was higher than that of the ACO phenotype (MD 6.45, 95% CI [1.82, 11.09], $P < .001$, $I^2 = 73\%$). Sensitivity analysis suggested that heterogeneity was mainly derived from the study by Miravitlles et al.[23] After exclusion of the results of this study, smoking index of FE-CB phenotype was higher than that of ACO phenotype (MD 5.07, 95% CI [2.14, 8.01], $P < .001$, $I^2 = 0$). According to the "Global Tobacco Epidemic Report 2017" published by the World Health Organization,[28] Europe has a relatively high smoking rate. In addition, there are differences in smoking types such as cigarettes and cigars, which may have a certain impact on the conclusions of this study. In addition, the potential correlation between smoking index and phenotype should be investigated in future studies.

Studies have shown that COPD patients with the FE-CB phenotype have higher CAT scores and lower motor ability compared with other phenotypes, while patients with the ACO phenotype have better lung function and fewer symptoms, as assessed by CAT. The conclusion is similar to this study. In this meta-analysis, 8 studies[11,16–20,22,23] reported CAT findings. In 7 studies,[11,17–20,23] the smoking index of patients with the FE-CB phenotype was significantly higher than that of patients with the ACO phenotype; however, another study[16] found no difference in this respect. There was no heterogeneity among the samples. Fixed-effect model was used for analysis. Meta-analysis showed that smoking index of patients with the FE-CB phenotype was higher than that of patients with the ACO phenotype (MD 4.04, 95% CI [3.46, 4.61], $P < .001$, $I^2 = 0$).
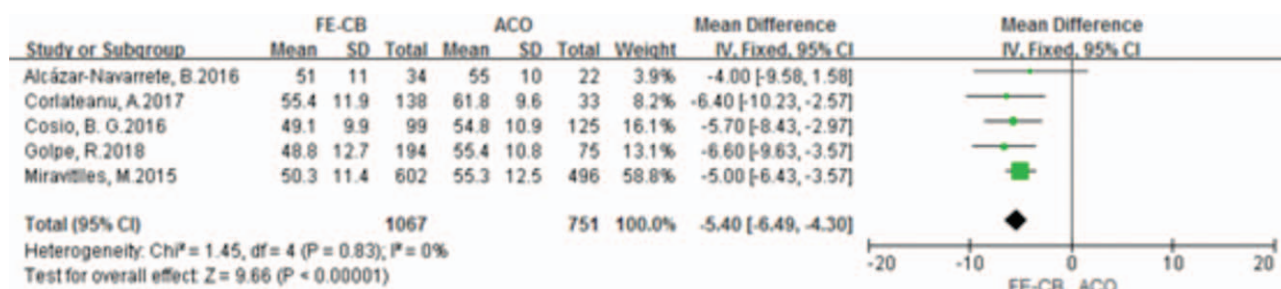
Figure 8. Difference of FEV$_1$/FVC between the FE-CB and ACO phenotypes. ACO = asthma-COPD overlap syndrome, FEV$_1$ =forced expiratory volume in 1 second, FE-CB=frequent exacerbators with chronic bronchitis.

Table 3

Difference of other indexes between the FE-CB and ACO phenotypes.

Secondary outcomes	Included studies	MD	95% CI	P	I^2, P
Quantity of cigarettes smoked (pack-years)	6 studies	6.45	(1.82,11.09)	<.001	73%, .001
CAT	9 studies	4.04	(3.46,4.61)	<.001	0, .78
mMRC	4 studies	0.54	(0.46,0.62)	<.001	34%, .21
Exacerbations in previous year	4 studies	1.34	(0.98,1.71)	<.001	68%, .02
BMI	7 studies	−0.81	(−1.18, −0.45)	<.001	44%, .10
BODEx	3 studies	1.59	(1.00,2.18)	<.001	86%, <.001

BMI=body mass index, BODEx=BMI, obstruction, dyspnea, exacerbations, CAT=COPD assessment test score, CI = confidence interval, MD = mean difference, mMRC=modified Medical British Research Council.

Previous studies on BMI in different phenotypes of COPD mainly focused on emphysema and bronchitis. Studies have shown that COPD patients with emphysema have lower BMI, lesser sputum expectoration, severe dyspnea, and lower diffusion function as compared to those with the chronic bronchial phenotype. However, the difference of BMI between the ACO phenotype and the FE-CB phenotype is controversial. In this meta-analysis, 7 studies[16–18,20–23] reported data pertaining to BMI. In 2 studies,[21,22] BMI of COPD patients with the FE-CB phenotype was significantly higher than that of patients with the ACO phenotype; however, the other 5 studies[16–18,20,23] found no significant difference between the 2 in this respect. There was no heterogeneity among the samples. Fixed-effect model was used for analysis. Meta-analysis showed that BMI of FE-CB phenotype was higher than that of ACO phenotype (MD −0.81, 95% CI [−1.18, −0.45], $P < .001$, $I^2 = 44\%$).

mMRC can be used for symptom assessment in patients with COPD. In clinic, mMRC ≥2 is generally regarded as the threshold for the severity of dyspnea. However, mMRC may not provide a comprehensive assessment of symptoms in COPD patients. It is suggested that more complex assessment scales, such as CAT and clinical COPD questionnaire, should be used for comprehensive assessment.[29] The reason may be that mMRC is insensitive to change in status.[30] In this meta-analysis, 4 studies[11,18,22,23] reported mMRC. In 3 studies,[18,22,23] the mMRC score of FE-CB phenotype was significantly higher than that of the ACO phenotype, while 1 study[11] showed opposite results. There was no heterogeneity among the samples. Fixed-effect model was used for analysis. Meta-analysis showed that the mMRC score of FE-CB phenotype was higher than that of ACO phenotype (MD 0.54, 95% CI [0.46, 0.62], $P < .001$, $I^2 = 34\%$). The reason may be related to the fact that the number of acute exacerbations in COPD patients with the FE-CB phenotype is higher than that in patients with the ACO phenotype. In this meta-analysis, 4 studies[11,18,22,23] reported exacerbations in previous year. In all 4 studies, the exacerbations in previous year of FE-CB phenotype was significantly higher than that of the ACO phenotype. Owing to significant heterogeneity between the samples, the random effect model was used for analysis. Meta-analysis showed that the exacerbations in previous year of the FE-CB phenotype was higher than that of the ACO phenotype (MD 1.34, 95% CI [0.98, 1.71], $P < .001$, $I^2 = 68\%$). Sensitivity analysis suggested that the heterogeneity was mainly derived from the studies by Calle Rubio et al.[18] After excluding the results of these studies, the exacerbations in previous year of FE-CB phenotype was still higher than that of the ACO phenotype (MD 1.55, 95% CI [1.42, 1.68], $P < .001$, $I^2 = 0\%$).

We also found that the BODEx of COPD patients with the FE-CB phenotype was higher than that of patients with the ACO phenotype; however, owing to the small sample size of the study, no definitive conclusions could be drawn in this respect.

5. Study limitations

In this study, we discussed the clinical characteristics of COPD patients with the FE-CB and the ACO phenotypes. However, we did not include several variables in the analysis such as gender, age, main symptoms (cough, sputum, wheezing), other smoking conditions (past smoking, current smoking, smoking rate, active smoking, passive smoking), complications ([ischemic heart disease, heart failure, atrial fibrillation, hypertension], bronchiectasis, osteoporosis, anxiety/depression and cognitive

impairment, lung cancer, severe infection, diabetes), different GOLD comprehensive assessment grades (A, B, C, D), mMRC stratification (mMRC ≥2, mMRC <2), acute aggravation stratification (acute aggravation times 1, acute aggravation times ≥2).

Due to the geographical application of the Spanish guidelines, most of the studies included in this meta-analysis were conducted in Europe (8 studies), while only 2 studies were conducted in Asia. However, the various phenotypes can only be fully characterized after inclusion of studies conducted in Africa, America, and Oceania. In addition, phenotypes in different races have not been reported yet, and need to be studied in the future.

There may be some limitations with respect to the selected cases. Nine of the 10 papers reported the cases of FE-CB phenotype more than ACO phenotype, while another multi-center prospective cohort study from Spain (Clinic Trials.gov Identifier: NCT01122758) reported fewer cases of FE-CB phenotype than ACO phenotype[20] The potential selection bias may have impacted the results of this study.

The effect of genetic factors on COPD susceptibility had been confirmed in previous family studies.[31] So far, more than 20 loci had been associated with the development of COPD, and some loci were associated with COPD-related phenotypes such as emphysema, chronic bronchitis and hypoxia.[31] However, due to the complexity and heterogeneity of COPD, the effect of a single gene locus was still small. Therefore, Genetic Epidemiology of COPD (COPDGene) researchers attempted to determine the genetic factors that contribute to the clinical manifestations of COPD by examining the genetic association with COPD-related phenotypes such as pulmonary function phenotype and image phenotype.[31] A meta-analysis of COPDGene-Non-Hispanic white subjects and ECLIPSE evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints and Genetics of Chronic Obstructive Lung Disease study subjects had revealed that most of the Genome-wide association studies results for FEV_1 and FEV_1/FVC were located at 15q25 locus, 4q22 chromosome near fam13A and 4q31 chromosome near hedgehog interacting protein.[32] Patients with different phenotypes of COPD showed different characteristics of lung function, which led to the hypothesis that there are also differences in genetic loci in patients with different phenotypes of COPD. However, due to the limitation of conditions, this study has not been discussed in this regard, and needs to be studied in a larger sample size.

6. Summary

Among patients with COPD, those with the FE-CB phenotype had poorer pulmonary function, lower BMI, and higher CAT score, smoking index, frequency of acute exacerbation, mMRC score, and BODEx as compared to those with the ACO phenotype.

Author contributions

Conceptualization: Jian-Jun Wu, Liang-Duo Jiang, Cheng-Xiang Wang, Han Mei.
Supervision: Jian-Jun Wu, Hui-Yong Yu.
Visualization: Jian-Jun Wu, Yi-Xuan Li.
Writing – original draft: Jian-Jun Wu, Hong-Ri Xu, Ying-Xue Zhang.
Writing – review and editing: Jian-Jun Wu, Hui-Yong Yu.

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