ORIGINAL RESEARCH

Clinical characteristics of chronic bronchitic, emphysematous and ACOS phenotypes in COPD patients with frequent exacerbations

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Purpose: Chronic bronchitis (CB), emphysematous (EM) and asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) phenotypes in COPD are well recognized. This study aimed to investigate distinguishing characteristics of these phenotypes in COPD patients with frequent exacerbations (FE).

Patients and methods: A retrospective study was carried out. COPD patients with acute exacerbations were consecutively reviewed from November 2015 to October 2016. Patients were divided into FE and infrequent exacerbations (iFE) subgroups.

Results: A total of 142 eligible COPD subjects were reviewed. In the CB phenotype subgroup, age, body mass index, forced expiratory volume in 1 second (FEV_1) % predicted, COPD assessment test (CAT), modified Medical Research Council breathlessness measurement (mMRC) dyspnea scale, emphysema scores and arterial carbon dioxide pressure ($PaCO_2$) were significantly different in subjects with FE when compared to those in subjects with iFE of CB. In the EM phenotype subgroup, age, CAT, mMRC scores and history of COPD were different in subjects with FE when compared to those in CB subjects with iFE. Multivariate analysis indicated that FEV_1% predicted (odds ratio [OR] =0.90, P=0.04) and $PaCO_2$ (OR =1.22, P=0.02) were independent risk factors for FE in COPD with CB phenotype, and CAT (OR =2.601, P=0.001) was the independent risk factor for FE in COPD with EM phenotype. No significant differences in characteristics were observed in ACOS phenotype subgroups with FE or iFE.

Conclusion: In CB or EM phenotypes, COPD patients with FE present several differential clinical characteristics compared to patients with iFE, while the characteristics of ACOS phenotype in patients with FE need more investigation.

Keywords: chronic bronchitis, emphysema, ACOS, COPD, frequent exacerbations

Introduction

Chronic obstructive pulmonary disease (COPD) is a common and heterogeneous respiratory disease involving different pathophysiological changes and is a major cause of morbidity and mortality worldwide.[1] Incompletely reversible airflow obstruction, the hallmark of COPD, presents as diverse clinical manifestations. Clinical phenotypes of COPD are differentiated by severity of systemic inflammation, quality of life, the degree of airway obstruction and the response of available medications.[2] Chronic bronchitis (CB), emphysematous (EM) and asthma–COPD overlap syndrome (ACOS) are the three generally accepted clinical phenotypes.[3–6] In an observational and multicenter study, it was reported that CB accounted for 44.7% of COPD patients, EM was 43.2% and ACOS was only 12.1%.[6] COPD patients with CB showed greater chronic dyspnea and activity restriction than patients without CB.[7] Compared to CB or ACOS phenotype,

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COPD patients with EM phenotype present with poorer pulmonary function and greater dyspnea.[6] Notably, COPD patients with ACOS phenotype suffer more from obesity and atopic diseases, compared to COPD patients without ACOS phenotype.[8] However, a subgroup of COPD patients experience frequent exacerbations (FE), which was clearly described in the ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints) study and was associated with accelerated deterioration of lung function, high economic burden and increased mortality.[9,10]

Around 16% of FE patients are of the EM phenotype.[11] COPD patients with FE in the CB phenotype are the only patient group that benefits from treatment with phosphodiesterase-4 inhibitors.[12] The ACOS phenotype is reported to be a predictor for FE in patients with COPD.[13] Only limited prior work has been undertaken to evaluate these typical phenotypes in COPD patients with FE. The purpose of this study was to investigate differential characteristics of these phenotypes in COPD patients with FE, compared to those patients with infrequent exacerbations (iFE).

Patients and methods
Study subjects

This was a retrospective study which was approved by the Institutional Ethics Committee of Wan Nan Medical College. Due to the retrospective nature of the study all patient data were strictly confidential and the committee waived the need for written informed consent from the subjects. COPD subjects with acute exacerbations, admitted to the Department of Respiratory Medicine, Yijishan Hospital of Wannan Medical College, were reviewed from November 2015 to October 2016. Patients with CB, EM or ACOS phenotype were included. Patients with comorbidities of pulmonary tuberculosis, pulmonary fibrosis, bronchiectasis, lung cancer, pulmonary embolism or other organ failures were excluded. The definition of acute exacerbations of COPD followed the guideline of Global Initiative for Chronic Obstructive Lung Disease (GOLD). FE was defined by the presence of at least two exacerbations (an increase in, or new onset of, ≥ 2 respiratory symptoms, such as cough, sputum, dyspnea, wheezing and chest tightness, with ≥ 1 symptom lasting for ≥ 3 days and requiring treatment with antibiotics and/or systemic steroids or hospitalization) in the previous year and separated by at least 4 weeks (or 6 weeks from the previous exacerbation that did not receive treatment). Others were categorized into the iFE group.[14] The definition of CB was chronic phlegm alone for most days, 3 months a year, for 2 years. EM was defined as no chronic cough and sputum, but having typical clinical and radiologic manifestations of EM. The ACOS definition was based on dyspnea at rest and wheezing episodes, with post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) <0.7 and bronchodilator responsiveness (increase in FEV_1 $\geq 12\%$ and ≥ 200 mL increase over baseline value).[15]

Clinical parameters

All clinical parameters were collected and appraised during 24 hours after patients' admission. Demographic and clinical data including age, gender, body mass index (BMI), smoking index and medical history were collected from medical databases in our hospital. Pulmonary function tests and results of routine hematological examination (white blood cell counts, neutrophils, neutrophil-to-lymphocyte ratio [NLR], C-reactive protein and arterial blood gas) were also collected. The COPD assessment test (CAT) and the modified Medical Research Council breathlessness measurement (mMRC) dyspnea scale were assessed as previously described. Thoracic high-resolution computed tomography (HRCT) was performed with a Philips Brilliance 16-slice spiral CT scanner. Sequential scanning was performed continuously from the apex to the diaphragm at maximal inspiration with a slice thickness of 1 mm and a layer distance of 10 mm. HRCT images were visualized on coronal and sagittal planes to assess the heterogeneity of emphysema by two independent pulmonologists blinded to the patients' clinical information. The distribution of emphysema was qualitatively assessed by a modified 5-point visual scoring system as follows: a score of 1 indicated obvious predominance of emphysema in upper lung; 2, somewhat predominance of emphysema in upper lung; 3, equal extent of emphysema in upper and lower lung; 4, somewhat predominance of emphysema in lower lung and 5, obvious predominance of emphysema in lower lung.[16] A simplified CT scoring system was used to assess bronchial wall thickening for each patient: 0= absent; 1= mild (air wall thickness equal to adjacent vessel); 2= moderate (air wall thickness > adjacent vessel, but $\leq 2\times$ the diameter of adjacent vessel), and 3= severe (airway wall thickening $>2\times$ diameter of adjacent vessel).[17]

Statistical analysis

Data were expressed as mean ± standard deviation or number (n). Categorical variables were compared between groups using chi-square testing. Continuous variables were evaluated by Student's *t*-test. Multivariate analysis was used to assess risk factors for FE in different phenotypes. Odds ratios (OR) and 95% CIs were presented. A *P*-value <0.05

was considered statistically significant. Statistical analyses were done using SPSS 17.0.

Results

Baseline characteristics of COPD patients with FE or iFE

A total of 142 eligible COPD subjects were reviewed: 60 subjects were categorized as FE and 82 with iFE. As shown in Table 1 – which summarizes clinical data without subphenotyping – subjects with FE were on average substantially older than those with iFE (P=0.001). Subjects with FE had longer history of COPD than subjects with iFE (P=0.001). Smoking index, pulmonary function testing, CAT score, mMRC, bronchial thickening score and $PaCO_2$ in subjects with FE shared significant differences with those in subjects with iFE. However, the proportion of CB,

Table 1 Characteristics of all COPD patients with FE or iFE

Variables	Subjects with FE	Subjects with iFE	P-value
Total subjects (N)	60	82	
Male (n)	47	62	0.841
Age (years)	72.1±8.24	66.72±10.97	**0.001**
History of COPD (years)	15.43±9.35	10.4±7.47	**0.001**
Smoking index (pack × years)	53.46±52.95	38.31±21.45	**0.040**
BMI (kg/m²)	20.51±4.19	21.34±3.07	0.192
FEV₁ (% predicted)	42.22±17.19	48.93±16.91	**0.022**
FEV₁/FVC (%)	50.72±10.7	57.74±9.31	**0.000**
CAT score	29.53±3.9	23.77±6.26	**0.000**
mMRC	3.08±0.74	2.13±0.94	**0.000**
Emphysema score	2.3±1.43	2.02±1.52	0.275
Bronchial thickening score	1.25±0.68	0.95±0.7	**0.012**
Leukocyte (×10⁹)	7.48±2.79	7.87±3.09	0.449
NLR	8.98±12.61	5.72±4.7	0.079
CRP (mg/L)	56.35±67.4	44.3±67.31	0.429
pH value	7.41±0.05	7.42±0.04	0.079
PaO₂ (mmHg)	86.79±27.35	78.35±20.34	0.070
PaCO₂ (mmHg)	45.69±12.4	41.19±8.88	**0.040**
Phenotypes of COPD			0.119
Chronic bronchitis (n)	30	27	
Emphysema (n)	20	38	
ACOS (n)	10	17	
Medical history			
Systemic hypertension (n)	16	13	0.141
Coronary heart disease (n)	7	2	**0.036**
Diabetes mellitus (n)	9	2	**0.009**

Notes: Data are presented as mean ± standard deviation, number (n), or percentage. *P*-value <0.05 was considered statistically significant: data shown in bold.
Abbreviations: ACOS, asthma–COPD overlap syndrome; BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FE, frequent exacerbations; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, the ratio of FEV₁ and forced vital capacity; iFE, infrequent exacerbations; mMRC, modified British Medical Research Council breathlessness measurement; NLR, neutrophil lymphocyte ratio in whole blood; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure.

Table 2 Characteristics of the chronic bronchitis phenotype in COPD patients with FE vs iFE

Variables	Subjects with FE	Subjects with iFE	P-value
Total subjects (N)	30	27	
Male (n)	24	17	0.238
Age (years)	73±6.4	64.37±12.5	**0.003**
History of COPD (years)	14.17±9.5	10.44±8.45	0.124
Smoking (pack × years)	64.05±70.1	43.33±28.77	0.158
BMI (kg/m²)	19.82±3.62	22.07±3.11	**0.016**
FEV₁ (% predicted)	40±13.61	51.74±16.13	**0.004**
FEV₁/FVC (%)	51.17±10.78	57.47±10.18	**0.028**
CAT score	29.4±3.94	23.41±6.98	**0.000**
mMRC	3.1±0.711	2.15±1.1	**0.000**
Emphysema score	1.97±1.56	0.63±1.15	**0.001**
Bronchial thickening score	1.43±0.68	1.19±0.4	0.095
Leukocytes (×10⁹)	8.29±3.14	8.7±3.78	0.656
NLR	11.42±6.35	17.03±5.3	0.144
CRP (mg/L)	53.38±54.72	42.26±54.89	0.557
pH value	7.41±0.05	7.43±0.05	0.272
PaO₂ (mmHg)	83.23±30.75	76.21±20.55	0.400
PaCO₂ (mmHg)	49.42±13.21	37.54±4.77	**0.000**

Notes: Data are presented as mean ± standard deviation, number (n), or percentage. *P*-value <0.05 was considered statistically significant: data shown in bold.
Abbreviations: BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FE, frequent exacerbations; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, the ratio of FEV₁ and forced vital capacity; iFE, infrequent exacerbations; mMRC, modified British Medical Research Council breathlessness measurement; NLR, neutrophil lymphocyte ratio in whole blood; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure.

emphysema and ACOS phenotypes, and other characteristics in subjects with FE did not differ from those in subjects with iFE (Table 1).

Characteristics of the CB phenotype in COPD patients with FE

As indicated in Table 2, CB phenotype COPD subjects with FE were significantly older than subjects with iFE (P=0.003). BMI, FEV₁% predicted, FEV₁/FVC (%), CAT, mMRC, emphysema scores and $PaCO_2$ in CB phenotype subjects with FE shared significant differences with those in subjects with iFE. By multivariate analysis, we found that FEV₁% predicted (OR =0.899, P=0.044) and $PaCO_2$ (OR =1.215, P=0.017) were two independent risk factors for CB phenotype subjects with FE (Table 3).

Table 3 Independent risk factors for FE in COPD patients with chronic bronchitis phenotype by multivariate analysis

Variables	OR	95% CI	P-value
FEV₁	0.899	0.81–0.997	0.044
PaCO₂	1.215	1.035–1.426	0.017

Note: *P*-value <0.05 was considered statistically significant.
Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; FE, frequent exacerbations; FEV₁, forced expiratory volume in 1 second; OR, odds ratios; PaCO₂, arterial carbon dioxide pressure.

Table 4 Characteristics of emphysema phenotype in COPD patients with FE vs iFE

Variables	Subjects with FE	Subjects with iFE	*P*-value
Total subjects (N)	20	38	
Male (n)	16	32	0.475
Age (years)	74±6.6	67.5±10.16	**0.012**
History of COPD (years)	19.85±9.05	10.66±7.28	**0.000**
Smoking (pack × years)	39.08±15.91	36.76±18.07	0.631
BMI (kg/m²)	21.66±4.95	20.87±2.78	0.515
FEV₁ (% predicted)	37.71±12.06	44.07±16.83	0.140
FEV₁/FVC (%)	50.5±10.99	58.45±9.32	**0.005**
CAT score	31.1±1.71	23.87±5.98	**0.000**
mMRC	3.35±0.49	2.16±0.79	**0.000**
Emphysema score	2.75±1.12	2.87±0.88	0.658
Bronchial thickening score	1.43±0.68	1.19±0.4	0.151
Leukocytes (×10⁹)	6.76±2.24	7.16±2.4	0.545
NLR	7.36±10.32	5.63±4.81	0.387
CRP (mg/L)	63.6±83.56	47.64±79.44	0.547
pH value	7.41±0.06	7.42±0.05	0.504
PaO₂ (mmHg)	87.95±20.97	79.57±22.79	0.245
PaCO₂ (mmHg)	43.87±10.86	44.69±10.71	0.812

Notes: Data are indicated as mean ± standard deviation, number (n), or percentage. *P*-value <0.05 was considered statistically significant: data shown in bold.
Abbreviations: BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FE, frequent exacerbations; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, the ratio of FEV₁ and forced vital capacity; iFE, infrequent exacerbations; mMRC, modified British Medical Research Council breathlessness measurement; NLR, neutrophil lymphocyte ratio in whole blood; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure.

Characteristics of the emphysema phenotype in COPD patients with FE

As shown in Table 4, the age of EM phenotype subjects with FE was greater than subjects with iFE (*P*=0.012). A longer history of COPD was observed in EM phenotype subjects with FE than in subjects with iFE. Similar to CB phenotype subjects, lower FEV₁/FVC (%) and higher CAT and mMRC scores were found in EM phenotype subjects with FE. However, there was no statistical difference in other variables, including BMI, FEV₁% predicted and arterial blood PaCO₂. Using multivariate analysis, CAT (OR =2.601, *P*=0.001) proved to be an independent risk factor for FE in COPD patients with the EM phenotype (Table 5).

Table 5 Independent risk factor for FE in COPD patients with emphysema phenotype by multivariate analysis

Variable	OR	95% CI	*P*-value
CAT	2.601	1.442–4.691	0.001

Note: *P*-value <0.05 was considered statistically significant.
Abbreviations: CAT, COPD assessment test; CI, confidence interval; COPD, chronic obstructive pulmonary disease; FE, frequent exacerbations; OR, odds ratio.

Table 6 Comparison of characteristics of ACOS phenotype in COPD patients with FE vs iFE

Variables	Subjects with FE	Subjects with iFE	*P*-value
Total subjects (N)	10	17	
Male (n)	7	13	1.000
Age (years)	65.6±12.77	68.71±10.05	0.489
History of COPD (years)	10.4±5.72	9.76±6.57	0.802
Smoking (pack × years)	50.5±34.19	33.79±12.64	0.167
BMI (kg/m²)	20.24±4.06	21.24±3.57	0.509
FEV₁ (% predicted)	57.88±26.46	55.32±16.03	0.786
FEV₁/FVC (%)	49.81±10.91	56.59±8.16	0.077
CAT score	26.8±5.47	24.12±6.0	0.258
mMRC	2.5±0.97	2.06±1.03	0.283
Emphysema score	2.4±1.43	2.35±1.62	0.940
Bronchial thickening score	0.7±0.67	0.59±0.62	0.665
Leukocyte (×10⁹)	6.51±2.03	8.13±3.07	0.151
NLR	4.9±3.17	4.89±3.26	0.993
CRP (mg/L)	24.36±29.71	30.09±22.99	0.821
pH value	7.4±0.03	7.42±0.03	**0.032**
PaO₂ (mmHg)	94.84±29.0	78.83±15.35	0.103
PaCO₂ (mmHg)	38.39±9.53	39.14±6.65	0.829

Notes: Data are indicated as mean ± standard deviation, number (n), or percentage. *P*-value <0.05 was considered statistically significant: data shown in bold.
Abbreviations: ACOS, asthma–COPD overlap syndrome; BMI, body mass index; CAT, COPD assessment test; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; FE, frequent exacerbations; FEV₁, forced expiratory volume in 1 second; FEV₁/FVC, the ratio of FEV₁ and forced vital capacity; iFE, infrequent exacerbations; mMRC, modified British Medical Research Council breathlessness measurement; NLR, neutrophil lymphocyte ratio in whole blood; PaCO₂, arterial carbon dioxide pressure; PaO₂, arterial oxygen pressure.

Characteristics of the ACOS phenotype in COPD patients with FE

As shown in Table 6, arterial pH value was somewhat lower in the ACOS phenotype of COPD with FE than in the iFE subgroup (7.40±0.03 vs 7.42±0.03; *P*=0.032). However, there were no statistically significant differences in other characteristics between ACOS phenotype COPD subjects with FE and subjects with iFE.

Discussion

In line with previous reports,[4,18–22] we revealed that COPD patients with FE showed significantly older age, longer history of disease, greater smoking index, worse lung function (FEV₁% predicted, FEV₁/FVC%), higher CAT, mMRC and bronchial thickening score, PaCO₂ and more comorbidities (coronary heart disease and diabetes) than COPD patients with iFE. Higher bronchial thickening score is also associated with COPD patients with FE.[20,23]

Previous studies suggested that NLR (examining together the influences of neutrophilia and lymphopenia) reflected systemic inflammatory status in COPD, which was one of the independent predictors of future exacerbations.[24,25] However, we found that NLR did not associate with FE in COPD in our study.

Compared to CB phenotype COPD subjects with iFE, clinical characteristics of subjects with FE were older age, lower BMI, more severe airway obstruction (lower $FEV_1\%$ predicted, FEV_1/FVC), increases of CAT and mMRC score, elevated $PaCO_2$ in arterial blood and higher emphysema scores, compared to subjects with iFE. Low BMI is recognized as a marker for predicting future exacerbations among patients with COPD.[26,27] Mucus hypersecretion in CB subjects causes distal airway collapse and air trapping, leading to increased residual volume and hyperinflation-emphysema. The ECLIPSE study has identified emphysema as a strong predictor for physiological decline in patients with COPD.[1] We found that $FEV_1\%$ predicted and $PaCO_2$ were two independent risk factors for CB phenotype COPD presenting with FE. The association between $FEV_1\%$ predicted and CB phenotype with FE has been well documented.[28,29] CB phenotype COPD patients with FE present with increased sputum production and bronchial mucosal edema leading to bronchial obstruction, decreased pulmonary ventilation and, consequently, increased arterial $PaCO_2$.[30] Similar to the CB phenotype, FE patients with EM phenotype also were older, had a longer history of COPD, lower FEV_1/FVC (%), higher CAT and mMRC scores, compared to iFE subjects. Consistent with previous reports, $FEV_1\%$ predicted in EM subjects with FE did not differ from iFE subjects, supporting that $FEV_1\%$ predicted is a poor clinical predictor for FE.[31] Indeed, a group of COPD patients with high $FEV_1\%$ predicted commonly experience FE.[32] Clearly, $FEV_1\%$ predicted does not reflect the complexity of COPD, nor alone adequately assess treatment effect in patients with COPD.[33,34] Thus, other factors in COPD patients, such as clinical variables, biological indicators and history of exacerbations, need to be evaluated. The associations between emphysema and FE in patients with COPD were inconsistent in previous publications, though we pointed out that emphysema score shared no difference between FE and iFE.[20,23,35] Using multivariate analysis, we identified CAT score was an independent risk factor for FE in EM phenotype COPD. This is consistent with previous studies.[36,37] The CAT score – which includes 8 questions with scores ranging from 0 to 40 for evaluating symptoms of patients with COPD – is able to more comprehensively capture the impact of COPD symptoms on the daily life and physical and mental health of patients. Clinical symptoms of COPD may provide important information, which should be comprehensively considered for predicting future COPD exacerbations.[38,39]

Unlike in CB or EM phenotypes, clinical characteristics in ACOS phenotype subjects with FE were not particularly distinguishable from those with iFE. Other factors relating to the asthma, such as atopy, environmental exposures and airway inflammation, may help to identify contributors to FE in the ACOS phenotype.

Some limitations exist in the present study. First, this was a retrospective study and the sample size was small. Second, other phenotypes or endotypes were not appraised in this study. Finally, the underlying mechanisms resulting in differences between the FE risks among the phenotypes were not clarified.

Conclusion

Our study identified differential clinical characteristics in the CB, EM and ACOS phenotypes of COPD patients with FE, compared with patients with iFE. We demonstrated related risk factors for the existence of FE in patients with CB or EM phenotype. An understanding of FE in ACOS phenotype patients will require more investigation.

Acknowledgments

Author contributions

All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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