

Wheezing, a significant clinical phenotype of COPD: experience from the Taiwan Obstructive Lung Disease Study

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Background: COPD is an important public health challenge with significant heterogeneity of clinical presentation and disease progression. Clinicians have been trying to find phenotypes that may be linked to distinct prognoses and different therapeutic choices. Not all patients with COPD present with wheezing, a possible clinical phenotype that can help differentiate patient subgroups.

Methods: The Taiwan Obstructive Lung Disease study was a retrospective, multicenter research study to investigate the treatment patterns of COPD after the implementation of the Global Initiative for Chronic Obstructive Lung Disease 2011 guidelines. Between November 2012 and August 2013, medical records were retrieved from patients with COPD aged ≥ 40 years; patients diagnosed with asthma were excluded. Demographic data, lung function, symptom scores, and acute exacerbation were recorded and analyzed, and the differences between patients with and without wheezing were evaluated.

Results: Of the 1,096 patients with COPD, 424 (38.7%) had the wheezing phenotype. The wheezing group had significantly higher COPD Assessment Test scores (12.4 ± 7.8 versus 10.5 ± 6.7 , $P < 0.001$), higher modified Medical Research Council grade (2.0 ± 1.0 versus 1.7 ± 0.9 , $P < 0.001$), and more acute exacerbations within the past year (0.9 ± 1.3 versus 0.4 ± 0.9 , $P < 0.001$) than the nonwheezing group. The postbronchodilator forced expiratory volume in 1 second was lower in wheezing patients (1.2 ± 0.5 L versus 1.5 ± 0.6 L, $P < 0.001$). Even in patients with maintenance treatment fitting the Global Initiative for Chronic Obstructive Lung Disease 2011 guidelines, the wheezing group still had worse symptom scores and more exacerbations.

Conclusion: Wheezing is an important phenotype in patients with COPD. Patients with COPD having the wheezing phenotype are associated with worse symptoms, more exacerbations, and worse lung function.

Keywords: chronic obstructive pulmonary disease, acute exacerbation, wheezing phenotype

Introduction

COPD is a leading cause of morbidity and mortality worldwide and its burden is both substantial and increasing.¹ Previous studies have shown heterogeneity of clinical phenotypes in patients with COPD, which may correlate with treatment response and disease progression.²⁻⁵ Identification of these phenotypes can help determine treatment choices to achieve better disease control.^{6,7}

Wheezing is a feature of small airway narrowing that frequently occurs in patients with asthma; some clinicians used wheezing as a diagnostic criterion for asthma and asthma-COPD overlap syndrome (ACOS) if the patients had fixed airway obstruction.⁸ Previous studies showed that patients with ACOS are more likely to have wheezing and a higher risk of exacerbations.⁹⁻¹² Notably, acute exacerbation (AE) is positively

correlated with increased respiratory failure, hospitalizations, emergency department visits, and deaths in patients with COPD.^{13,14}

Patients with COPD alone may also have wheezing; however, not all of them present with wheezing. The significance of wheezing and its correlation with clinical parameters in patients with COPD have not yet been identified.

In this study, we conducted a retrospective analysis of the Taiwan Obstructive Lung Disease (TOLD) cohort. The primary end point of this study was to investigate the prevalence of patients with COPD having the wheezing phenotype in Taiwan. The secondary end point was to analyze the clinical symptoms and the risk factors in patients with COPD with and without the wheezing phenotype.

Materials and methods

Study design and study subjects

In this study, we examined the data of participants enrolled in the TOLD study. Twelve hospitals across Taiwan participated in this study to investigate the relevant comorbidities and evaluate the implementation of the Global Initiative for Chronic Obstructive Lung Disease (GOLD) management strategy in patients with COPD. Data were abstracted from medical charts, including demographic characteristics, presence of wheezing, COPD severity, smoking history, pulmonary function test, and pharmacological therapy for the previous year.

Between November 2012 and August 2013, the participating physicians screened patients for entry into the study. Eligible patients were ≥ 40 years old with diagnosis of COPD based on the GOLD 2011 guidelines. Patients with a history of asthma were excluded. Demographic characteristics, symptom scores, presence of wheezing, AE, and pharmacological therapy were recorded and analyzed.

Data collection

Interviews were conducted by trained staff in charge of COPD case management who used a well-established questionnaire to collect the demographic information of the study participants, including date of birth, sex, smoking status, height, weight, and personal medical history. Body weight, height, and blood pressure were measured for each participant. Presence of wheezing was identified if the physicians of the participants recorded a positive result for wheezing in the medical charts. The questionnaire tools, including the modified Medical Research Council (mMRC) grade and COPD assessment test (CAT) score, were obtained to evaluate each patient's severity of symptoms. An AE was

defined as a worsening of symptoms that required antibiotics or steroids, emergency room visits, or hospitalizations. Frequent exacerbators referred to patients with two or more exacerbations within past 1 year. Postbronchodilator forced expiratory volume in 1 second (FEV₁) criteria were assessed using the patients' latest postbronchodilator FEV₁. FEV₁ within 1 year prior to the enrollment or the latest prebronchodilator FEV₁ was substituted for the latest postbronchodilator FEV₁ if it was not retrievable. Patients were classified into four grades, A, B, C, or D, by their COPD symptoms and risk of exacerbation according to the GOLD 2011 report.

Prescriptions of pharmacological therapy for COPD up to 1 year prior to the enrollment were collected. Inhaled bronchodilators or inhaled corticosteroids (ICSs) prescribed ≥ 6 months were regarded as the use of maintenance inhalers. Inhaled medications were evaluated according to the GOLD 2011 recommended pharmacological model. Overmedication was defined as overprescribed medication, despite GOLD 2011 recommendations.

Differences in basic demographics, pharmacological therapy, and pulmonary function tests were compared between patients with and without wheezing. Clinical symptoms and exacerbations were also assessed.

The study protocol was reviewed and approved by institutional review boards of all the hospitals involved.

Statistical analysis

Data were analyzed using SAS statistical software for Windows, version 9.3 (SAS Institute Inc., Cary, NC, USA). Continuous data were expressed as mean \pm standard deviation. Student's *t*-test was used when the data were normally distributed; otherwise, the nonparametric Mann–Whitney *U*-test was used. Categorical data were compared using the chi-square test if the observed numbers in all categories were larger than 5; otherwise, Fisher's exact test was used.

Results

Of the 1,096 participants, 424 patients (38.7%) had wheezing. There was no significant difference in age, sex, body mass index, and smoking history between patients with COPD with and without the wheezing phenotype. Table 1 shows that the wheezing group had significantly higher CAT (12.4 \pm 7.8 versus 10.5 \pm 6.7, $P < 0.001$) and mMRC scores (2.0 \pm 1.0 versus 1.7 \pm 0.9, $P < 0.001$) than the nonwheezing group. Notably, the wheezing group had significantly more episodes of AE within the past 1 year (0.9 \pm 1.3 versus 0.4 \pm 0.9, $P < 0.001$) and a higher risk of developing the frequent exacerbator phenotype (23.3% versus 8.2%, $P < 0.001$) than the nonwheezing group.

Table 1 Demographic data of all enrolled patients with COPD with and without wheezing phenotype

Characteristics	Wheezing		P-value
	Yes (n=424)	No (n=672)	
Age (years)	73.3±9.6	73.7±9.9	0.403
Median	74	75	
95% CI	(72.4–74.2)	(72.9–74.4)	
Male sex (%)	400 (94.3)	633 (94.2)	0.921
BMI (kg/m ²)	23.3±3.7	23.5±3.8	0.303
Median	23	23.2	
95% CI	(23.0–23.7)	(23.2–23.8)	
Smoking history			
Never	43 (10.4)	62 (9.6)	0.909
Exsmoker	36 (57.0)	372 (57.4)	
Number of pack-years	51.9±29.9	45.5±32.3	
Currently smoking	135 (32.6)	214 (33.0)	
Number of pack-years	49.8±28.2	50.0±30.0	
CAT score	12.4±7.8	10.5±6.7	<0.001
Median	12	9	
95% CI	(11.7–13.2)	(10.0–11.0)	
mMRC grade	2.0±1.0	1.7±0.9	<0.001
Median	2	2	
95% CI	(1.9–2.1)	(1.6–1.8)	
Acute exacerbation within past 1 year	0.9±1.3	0.4±0.9	<0.001
Median	0	0	
95% CI	(0.8–1.0)	(0.4–0.5)	
Frequent exacerbator	99 (23.3)	55 (8.2)	<0.001

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CI, confidence interval; mMRC, modified Medical Research Council.

Table 2 shows the spirometry data of the study population. Postbronchodilator FEV₁ and forced vital capacity were significantly lower in patients with the wheezing phenotype (1.2±0.5 L versus 1.5±0.6 L and 2.2±0.7 L versus 2.5±0.7 L, both $P<0.001$) compared with patients without the wheezing phenotype. However, in terms of reversibility of FEV₁ after bronchodilator, no statistical difference was found.

Among patients who received long-term maintenance treatment fitting the GOLD 2011 guidelines (470/1,096; 42.9%), patients with the wheezing phenotype (183/470; 38.8%) also had significantly higher CAT (12.6±8.1 versus 9.9±6.5, $P<0.001$) and mMRC scores (2.1±1.1 versus 1.7±0.8, $P<0.001$) compared with patients without the wheezing phenotype. Additionally, a significantly higher percentage of AE was also found in the wheezing group than in the nonwheezing group (1.1±1.4 versus 0.5±1.1, $P<0.001$; Table 3).

Table 4 shows that patients with wheezing history in GOLD groups A and B had significantly higher percentages of ICS usage than patients without wheezing history (43.2% versus 23.4% in GOLD group A, $P=0.0088$; 45.6% versus 29.8% in GOLD group B, $P=0.0017$). In addition, high rates

Table 2 Pulmonary function in patients with COPD with and without wheezing phenotype

Pulmonary function tests	Wheezing		P-value
	Yes	No	
Postbronchodilator			
FEV ₁			
Number	399	602	
Mean ± SD	1.2±0.5	1.4±0.5	<0.001
Median	1.1	1.4	
95% CI	(1.2–1.3)	(1.4–1.5)	
FVC			
Number	397	604	
Mean ± SD	2.2±0.7	2.5±0.7	<0.001
Median	2.1	2.4	
95% CI	(2.1–2.2)	(2.4–2.5)	
Change in FEV ₁			
Number	399	602	
Mean ± SD	0.1±0.1	0.1±0.2	0.987
Median	0.1	0.1	
95% CI	(0.1–0.1)	(0.1–0.1)	
Change in FVC			
Number	397	604	
Mean ± SD	0.2±0.2	0.1±0.2	0.039
Median	0.1	0.1	
95% CI	(0.1–0.2)	(0.1–0.2)	

Abbreviations: CI, confidence interval; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation.

of overmedication were also found in patients with wheezing history.

Discussion

This study shows the prevalence of wheezing in a nationwide COPD cohort. Patients with the wheezing phenotype had worse clinical symptoms and lower levels of spirometry results. Wheezing also correlated with a higher possibility of AE. Even among those who were treated according to the GOLD 2011 guidelines, patients with wheezing still had worse symptom scores and more exacerbations.

Table 3 Severity of symptoms in patients with COPD with and without wheezing phenotype

Characteristics	Wheezing		P-value
	Yes (n=183)	No (n=287)	
CAT score	12.6±8.1	9.9±6.5	<0.001
Median	12	8	
95% CI	(11.4–13.8)	(9.2–10.7)	
mMRC grade	2.1±1.1	1.7±0.8	<0.001
Median	2	2	
95% CI	(2.0–2.3)	(1.6–1.8)	
Acute exacerbation within past 1 year	1.1±1.4	0.5±1.1	<0.001
Median	1	0	
95% CI	(0.9–1.3)	(0.4–0.6)	

Abbreviations: CI, confidence interval; CAT, COPD assessment test; mMRC, modified Medical Research Council.

Table 4 Maintenance treatment for patients with COPD with and without wheezing phenotype in GOLD groups A and B

Patient number	Group A		P-value	Group B		P-value
	Wheezing	No wheezing		Wheezing	No wheezing	
	n=51	n=128		n=136	n=262	
Inhaler						
SABA	17 (33.3%)	12 (9.4%)	<0.0001	48 (35.3%)	42 (16.0%)	<0.0001
SAMA	0 (0.0%)	4 (3.1%)	0.5159	1 (0.7%)	0 (0.0%)	0.6834
LABA	1 (2.0%)	7 (5.5%)	0.5605	6 (4.4%)	29 (11.1%)	0.0261
LAMA	14 (27.5%)	37 (28.9%)	0.8456	32 (23.5%)	61 (23.3%)	0.9560
LABA/LAMA	0 (0.0%)	4 (3.1%)	0.5159	3 (2.2%)	16 (6.1%)	0.0834
ICS in combination with bronchodilator	22 (43.2%)	30 (23.4%)	0.0088	62 (45.6%)	78 (29.8%)	0.0017
Overmedication	22 (43.1%)	34 (26.6%)	0.0309	62 (45.6%)	78 (29.8%)	0.0017

Note: The groups were categorized according to GOLD 2011 report.

Abbreviations: GOLD, Global Initiative for Chronic Obstructive Lung Disease; ICS, inhaled corticosteroid; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist; SAMA, short-acting muscarinic antagonist.

Wheezing can be detected in all mechanisms causing airway narrowing, especially COPD and asthma. In addition, patients with COPD do not always present with wheezes.¹⁵ Godfrey et al indicated that only 70% of severe airflow obstruction patients presented with wheezing.¹⁶ Notably, Kulich et al used electronic diaries to identify the relevant symptoms, including wheezing, and degree of bother due to symptoms in moderate-to-severe patients with COPD;¹⁷ their results indicated that only “shortness of breath” showed a significant association with “bother” and “difficulty with activities”.¹⁷ However, to date, little is known regarding whether or not wheezing present in patients with COPD is associated with other clinical conditions. In this study, we confirmed that wheezes in patients with COPD had a significantly higher frequency of AE and worse clinical symptoms than patients without wheezes. Similar results were observed in patients with COPD having adequate maintenance therapy according to GOLD 2011 guidelines. Therefore, wheezing should be identified as a phenotype of COPD, which we would suggest a definition as audible wheezing breathing sounds identified by clinicians in a patient with COPD.

ACOS has been discussed extensively as a phenotype of COPD. Patients with ACOS had a significantly higher risk of frequent exacerbations than patients with COPD.^{9,11,12,18} Additionally, Kauppi et al reported that patients with ACOS had significantly worse quality of life than patients with COPD alone.¹⁰ The Spanish guideline reported by Miravittles et al was the first guideline that clearly described the multidimensional basis of recognition of clinical phenotypes, severity of rating scales, and specific therapeutic approach in patients with ACOS and/or COPD.¹⁹ However, accurate diagnosis of ACOS is still difficult for clinicians to obtain. Nevertheless, patients with a history of asthma were excluded from our cohort. Moreover, the airway responsiveness, the change in FEV₁ after administration of an inhaled short-acting

bronchodilator, was not different between patients with and without wheezing phenotypes. Therefore, the patients enrolled in our cohort should have COPD alone. This suggests that the presence of wheezing is a phenotype of COPD that is associated with poor patient-rated symptom scores and more frequent exacerbations, instead of a characteristic of ACOS.

According to the GOLD 2011 guidelines, ICSs are not a recommended therapy for patients with COPD in the GOLD A and GOLD B groups. Our results revealed that patients with the wheezing phenotype in both GOLD groups had a significantly higher frequency of ICS use and ratio of overmedication than patients without the wheezing phenotype. This observation was possible due to the concern of ACOS by clinicians, for which an ICS is suggested in the treatment regimen.^{20,21} Since the possibility of ACOS in our cohort was actually low, the observation warrants the necessity of better diagnosis to achieve better discrimination between COPD alone and ACOS.

In the study of Sanchez Morillo et al, computerized analysis of respiratory sounds identified two possible phenotypes of COPD exacerbation.²² The patients who belonged to the first phenotype were characterized by higher values of FEV₁ and absence of abnormal sounds. The other phenotype included patients who presented with pronounced adventitious breathing sounds. The result, alone with our findings and previous reports, suggests that wheezes can be absent in patients with COPD and that COPD may actually include heterogeneous patient groups who have different clinical and prognostic characteristics.^{2,7} More studies about breathing sounds evolution in patients with COPD are warranted to validate this idea and to connect clinical features with underlying pathophysiology and etiology. The consistency in breathing sounds evaluation between clinicians and computerized analysis should also be researched.

Previous studies reported higher risk of wheezing in current smokers, and female smokers had even greater risk than male smokers.^{23,24} In this study, the percentage of current smoking did not show statistical significance between patients with wheezing and without wheezing. However, our cohort included only patients with COPD and consisted of mainly male patients, which may explain the inconsistent findings between our study and previous reports. Further studies are necessary to identify the influence of smoking habit on the risk of wheezing in patients with COPD.

Researches regarding phenotypes of childhood wheezing disorders have been available in the past few decades.^{25,26} Spycher et al recently reviewed the definitions of those phenotypes and their prospective validation.²⁷ The authors also suggested multidimensional approaches to define phenotypes that can help with genetic research and our understanding about underlying pathophysiological pathways. Similarly, phenotypes of COPD, in addition to ACOS, need to be validated more carefully so that we can identify risk factors, prognostic, and distinct treatment plans.

The study was limited by its retrospective data collection. Although the presence of wheezing was associated with poor symptoms and more exacerbations, whether or not patients were treated according to widely accepted guidelines, the prediction of wheezing phenotype for quality of life, and risk of exacerbation in the future is not known. Further prospective study is necessary to confirm its clinical relevance as a phenotype of COPD.

Another limitation of this study was the possibility of ACOS in our cohort. There is currently no consensus regarding the diagnosis of ACOS, which brings difficulties for study design. We excluded patients with history of asthma so that the diagnosis of ACOS should be unlikely for our patients. Furthermore, there were only 31 patients (2.8%) who had a postbronchodilator increase in FEV₁ >12% and 400 mL, a spirometric feature of ACOS proposed by Global Initiative for Asthma (GINA) and GOLD.²⁰ Nevertheless, the accuracy would be even better if more parameters were used, for example, blood eosinophils, sputum samples, and more detailed past history and family history.

Conclusion

In conclusion, wheezing is a clinical significant phenotype of COPD. Patients with COPD having the wheezing phenotype are associated with worse quality of life, more exacerbations, and a lower level of pulmonary function test performance. Even among those patients who were treated according to the GOLD 2011 guidelines, patients with wheezing still had

worse symptom scores and more exacerbations. More studies are needed to further validate its clinical relevance; adjustment in treatment suggestions for patients with wheezing may also be necessary.

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Disclosure

The authors report no conflicts of interest in this work.

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