

Mixed Phenotype of Emphysema and Airway Wall Thickening Is Associated with Frequent Exacerbation in Chronic Obstructive Pulmonary Disease Patients

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Objective: The presence of both emphysema and airway wall thickening determined via volumetric computed tomography (CT) is defined as mixed phenotype. The long-term clinical course of this phenotype has not been studied in depth. This study compared the mixed phenotype to other phenotypes of chronic obstructive pulmonary disease (COPD) patients.

Methods: COPD patients enrolled in the Korean Obstructive Lung Disease (KOLD) study from June 2005 to October 2015 were evaluated. The emphysema index and the percentage of bronchial mean wall area were calculated from volumetric CT scans. Patients with COPD were classified into four phenotypes using two cutoffs: emphysema index of 15% and median value of mean wall area (MWA%).

Results: Of 435 patients with COPD, 99 (22.8%) were defined as CT-normal type, 119 (27.4%) as emphysema-dominant type, 113 (26.0%) as airway-dominant type, and 104 (23.9%) as mixed type. The mixed phenotype showed the highest baseline total COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ) scores. Moreover, it had the highest proportion of patients experiencing exacerbation of COPD (50.0%), and had the lowest baseline FEV1. Lower BMI, GOLD stages III–IV, and mixed phenotype were significant factors associated with severe exacerbation frequency in univariate analyses. Multivariate analyses showed that lower BMI and CT phenotype were significant factors associated with severe exacerbation frequency. Compared to the CT-normal phenotype, the mixed phenotype was significantly associated with more frequent severe exacerbation (IRR 4.134, 95% CI: 1.135–15.057, $P=0.031$).

Conclusion: Patients with mixed phenotype are more symptomatic, have poorer pulmonary function, and are associated with more frequent severe exacerbation.

Keywords: COPD, emphysema, computed tomography, mixed phenotype

Plain Language Summary

Patients with mixed phenotype of emphysema and airway wall thickening are more symptomatic, have poorer pulmonary function, and are associated with more frequent severe exacerbation.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease entity with different clinical presentation, disease progression, and concurrent lung lesions.¹ There has been a great deal of research regarding COPD phenotypes to allow more individualized clinical approaches for patients with COPD.

However, when only spirometry and clinical presentations are used, phenotyping of patients with COPD could be inaccurate.² Quantitative computed tomography (CT), a noninvasive imaging technique, has recently been used to evaluate patients with COPD. This diagnostic modality can be used to find the structural abnormalities of the lungs in patients with COPD, which could influence the clinical outcomes.¹ Furthermore, the American Thoracic Society and American College of Chest Physicians recommend using thoracic CT as an aid for phenotyping COPD.³ The combination of spirometry and quantitative CT enables more accurate phenotyping of COPD and will eventually contribute to more individualized treatment.

Among the various phenotyping attempts, defining emphysema-dominant versus airway-dominant groups has been an issue of clinical interest, because the two groups of COPD patients show distinct clinical characteristics.⁴ In previous studies, several CT parameters were found to have significant associations with each phenotype. In emphysema-dominant COPD, the extent of the emphysema is associated with the percentage of volume of low attenuation (LAV%) calculated from volumetric chest CT.⁵ On the other hand, increased airway wall thickness has been reported to be associated with chronic bronchitis in COPD.⁶ The clinical characteristics of these two phenotypes and their associations with quantitative CT parameters have been demonstrated in previous studies.^{5,6}

In addition to emphysema-dominant and airway-dominant phenotypes, the mixed phenotype is defined as the presence of both emphysema and airway wall thickening.^{7,8} There have been a number of attempts to phenotype patients with mixed phenotype COPD using both quantitative CT and spirometry, and their clinical characteristics were initially described by Lee et al.⁷ A subsequent study demonstrated that the CT-defined mixed phenotype requires more hospitalizations and is more symptomatic compared to other CT-based phenotypes.⁹ Furthermore, the European Respiratory Society group has defined “emphysematous,” “airway-dominant,” “mixed,” and “mild” COPD groups based on standardized quantitative CT (QCT) indices.¹⁰ In a previous study, the mixed phenotype was characterized as the coexistence of upper lung predominant emphysema and airway wall thickening, and a group with such radiological characteristics was associated with more frequent exacerbations and hospitalizations.¹¹

Nevertheless, the longitudinal clinical outcomes of patients with mixed phenotype COPD have not been evaluated

in depth. Moreover, further research is necessary to define this phenotype before applying to the management of patients with COPD. This study compared baseline clinical characteristics and the longitudinal clinical course of the mixed phenotype to other CT-based phenotypes of COPD patients.

Materials and Methods

Patients

Patients with COPD enrolled in the Korean Obstructive Lung Disease study cohort recruited from pulmonary clinics from 16 hospitals in South Korea from June 2005 to October 2015 were evaluated. Patients with postbronchodilator forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) <0.7 and with a smoking history of a minimum of 10 pack-years were diagnosed with COPD. Patients with evident lung parenchymal destruction or large lung mass from chest radiograph were excluded. In initial and follow-up evaluations, pulmonary function tests (PFTs) and CT scans were performed on the same day.

Written informed consent was obtained from each patient. The institutional review boards of the participating hospitals approved use of the clinical and imaging data for evaluation (i.e., Asan Medical Center, Bundang CHA Hospital, Ewha Womans University Mokdong Hospital, Korea University Anam Hospital, Hanyang University Guri Hospital, Inje University Ilsan Paik Hospital, Kangbuk Samsung Hospital, Hallym University Kangnam Sacred Heart Hospital, Kangwon National University Hospital, Seoul National University Hospital, Seoul National University Bundang Hospital, Ajou University Hospital, Konkuk University Hospital, The Catholic University of Korea Yeouido St Mary's Hospital, The Catholic University of Korea Seoul St Mary's Hospital, and the National Medical Center).

Clinical Parameters

Patient sex, age at enrollment, and baseline total COPD Assessment Test (CAT) and St. George's Respiratory Questionnaire (SGRQ) scores were included in the analyses. COPD-related visits to the hospital and admissions were also longitudinally recorded during the cohort observation period. FEV₁, FVC, and FEV₁/FVC were evaluated from the results of the initial PFT. The diffusion capacity of the lungs for carbon monoxide (DL_{co}) and 6 min walking distance (6MWD) at baseline were also evaluated.

Computed Tomography

Volumetric CT scans of all patients were performed at full inspiration and expiration using a 16-MDCT scanner (Somatom Sensation; Siemens Healthineers, Erlangen, Germany). The scans were performed craniocaudally with the patient in the supine position, and no intravenous contrast medium was used. Scan parameters included 0.75 mm collimation, 100 eff. mAs, and 140 kVp with a pitch of 1.0. The scale of attenuation coefficients ranged from -1024 to 3072 Hounsfield units (HUs). Using the soft kernel (B30f; Siemens Medical Systems), the images were reconstructed from the thoracic inlet to the lung base, and extracted automatically. Using in-house software, whole lung images were extracted, and the attenuation coefficient of each pixel was measured and calculated.^{12,13} Airway dimensions were measured at the site near the origin of four segmental bronchi (RB1, LB1 + 2, LB10, and RB10). In accordance with previous studies, the cut-off level dividing normal lung density and area of low attenuation was -950 HU.¹³⁻¹⁵

A modified sharpening filter with a 3×9×3 kernel size was used for more accurate airway measurement. The validation process using polyacrylic tubes was performed beforehand, and the software discriminated the airway lumen and the inner and outer boundaries of the airway wall automatically by the full-width-maximum method.¹⁴⁻¹⁶ Wall area (WA) percentage, which was defined as $WA/(WA + \text{lumen area (LA)}) \times 100$, was measured in each segmental bronchus. The mean value of each dimension value was used for statistical analyses.

COPD Phenotyping Based on CT

The mean bronchial wall area and emphysema index (EI) were calculated from the volumetric CT images. Patients with COPD were classified into four phenotypes using two cutoffs: emphysema index of 15% and mean wall area percentage (MWA%).^{17,18} The median value of MWA% was 66.5% and was used as a cutoff for phenotyping. Patients with an EI lower than 15% and MWA% lower than the median value were categorized into the CT-normal phenotype group. Patients with an EI higher than 15% and MWA% lower than the median value were categorized into the emphysema-dominant phenotype. Patients with an EI lower than 15% and MWA% higher than the median value were categorized into the airway-dominant phenotype. Patients with an EI higher than 15% and MWA%

% higher than the median value were categorized into the mixed phenotype.

Overall Survival

Overall survival was defined as time duration between the date of cohort enrollment and the date of death. The last survival status of each patient was checked on April 26, 2018.

COPD Exacerbation

Severe COPD exacerbations, defined as exacerbations requiring emergency room visit or admission, were analyzed. COPD patients with exacerbation were defined as those who experienced at least one COPD exacerbation during the first observation year from the cohort enrollment. Only exacerbations during the first post-enrollment year were evaluated. Exacerbation analyses were performed using exacerbation data from the first year after enrollment, which were collected prospectively. Patients with a follow-up period of less than 1 year were excluded. We also evaluated clinical parameters at enrollment to determine the association with rate of severe exacerbations during the first year.

Statistical Analyses

All statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL). Data of continuous variables are presented as mean ±SD. The chi-square test was used to compare categorical parameters. Continuous variables were analyzed using one-way analysis of variance (ANOVA). Patients' overall survival was evaluated via Kaplan-Meier analyses and compared statistically between CT-defined phenotypes using the log rank test.

Binary logistic regression analyses were performed to assess the associations between risk factors and the occurrence of severe COPD exacerbations. Factors that were significant in univariate analyses were entered into multivariate analyses.

To evaluate factors associated with the rate of severe exacerbation, we used negative binomial regression to estimate the incidence rate ratios (IRRs), as there were a substantial number of patients without exacerbations. Significant risk factors from the unadjusted model were entered into multivariate analyses. In all analyses, $P < 0.05$ was taken to indicate statistical significance.

Ethics Statement

This study was conducted in accordance with the Declaration of Helsinki.

Results

Clinical Characteristics

Table 1 shows the baseline clinical characteristics of the four CT-defined phenotypes. Of the 435 patients, 99 (22.8%) were defined as CT-normal type, 119 (27.4%) were defined as an emphysema-dominant type, 113 (26.0%) were defined as airway-dominant type, and 104 (23.9%) were defined as mixed type.

There were no significant differences in mean age between groups. The airway-dominant phenotype showed the highest proportion of female patients (13.3%). Nearly all of the patients with mixed and emphysema-dominant phenotypes had significant smoking histories (97.1% and 97.5%, respectively). The mean BMI was lower in the

mixed phenotype group than in the CT-normal and airway-dominant groups ($P<0.001$). The mixed phenotype group had significantly higher baseline total CAT and SGRQ scores than the other phenotypes (15.6 ± 7.6 , $P=0.014$; and 37.6 ± 17.6 , $P<0.001$, respectively). That group also had the highest mortality rate (21.2%, $P<0.001$), the highest proportion of patients experiencing COPD exacerbation (50.0%, $P=0.013$), and the highest proportion of patients experiencing severe COPD exacerbation requiring admission (15.4%, $P<0.001$).

The patients in the mixed phenotype group had the lowest FEV1, both in absolute value and percentage. The mixed phenotype group also had the lowest FEV1/FVC, DLco (absolute value), and DLco (% predicted) (all $P<0.001$). RV/TLC,

Table 1 Comparisons of Characteristics Among Four Computed Tomography-Based Phenotypes in 435 Patients with Chronic Obstructive Pulmonary Disease

	CT-Normal (N=99)	Emphysema- Dominant (N=119)	Airway-Dominant (N=113)	Mixed (N=104)	P-value
Mean age (years, mean, SD)	67.0±8.5	68.3±7.2	65.9±8.7	68.2±7.4	0.091
Sex					0.003 ^{ad}
Female	8 (8.1%)	1 (0.8%)	15 (13.3%)	7 (6.7%)	
Male	91 (91.9%)	118 (99.2%)	98 (86.7%)	97 (93.3%)	
Smoking					
Ever smoker (n, %)	87 (87.9%)	116 (97.5%)	99 (87.6%)	101 (97.1%)	0.002 ^{acdf}
Pack-years (mean, SD)	38.2±29.7	47.0±29.6	38.5±30.2	42.9±22.7	0.066
Body mass index (mean, SD)	23.8±2.8	22.0±3.0	24.5±3.0	22.1±3.0	<0.001 ^{acdf}
CAT Total score (mean, SD)	10.5±7.0	12.5±7.8	11.9±7.6	15.6±7.6	0.014 ^c
SGRQ, Total (mean, SD)	24.0±16.0	31.1±17.9	26.1±17.6	37.6±17.6	<0.001 ^{acef}
Deaths during observation (n,%)	6 (6.1%)	16 (13.4%)	4 (3.5%)	22 (21.2%)	<0.001 ^{acdf}
Patients who experienced exacerbation during 1st year (n,%)	32 (32.3%)	57 (47.9%)	39 (34.5%)	52 (50.0%)	0.013 ^c
Patients admitted due to exacerbation during 1st year (n,%)	3 (3.0%)	9 (7.6%)	1 (0.9%)	16 (15.4%)	<0.001 ^{cdf}
FEV1 (absolute, L)	2.0±0.5	1.6±0.5	1.8±0.6	1.4±0.5	<0.001 ^{abcdef}
FEV1 (percentage predicted)	66.4±13.6	53.0±15.5	62.5±15.0	46.7±14.3	<0.001 ^{acdef}
FVC (absolute value, L)	3.6±0.7	3.6±0.8	3.3±0.8	3.4±0.8	0.005 ^b
FVC (percentage predicted)	88.9±13.3	92.0±17.7	86.6±14.9	89.1±18.6	0.105
FEV1/FVC (percentage)	56.0±9.0	44.5±10.2	55.4±10.2	40.5±9.4	<0.001 ^{acdef}
DLCO, absolute	16.9±4.4	12.7±4.6	17.0±5.2	11.2±4.3	<0.001 ^{acdf}
DLCO, percentage predicted	81.1±18.4	62.4±20.5	85.2±18.5	58.5±18.6	<0.001 ^{acdf}
RV/TLC,%	31.4±10.7	44.0±13.5	40.4±13.5	48.8±12.9	<0.001 ^{abcdf}
6MW (distance, meter)	419.9±84.8	425.8±82.8	433.5±77.1	406.6±87.3	0.137
Mean wall area (%)	62.5±3.0	62.5±2.8	70.8±3.0	69.8±3.0	<0.001 ^{bcde}
Emphysema index, inspiratory	8.0±4.4	30.2±11.4	7.3±4.5	30.7±11.0	<0.001 ^{acdf}

Notes: ^{a-f}Significant statistical difference between a) CT normal and emphysema dominant, b) CT normal and airway dominant, c) CT normal and mixed phenotype, d) emphysema dominant and airway dominant, e) emphysema dominant and mixed phenotype, and f) airway dominant and mixed phenotype.

Abbreviations: 6MW, 6-mins walk test; BMI, body mass index; CAT, COPD assessment test; DLCO, diffuse capacity of the lungs for carbon monoxide; EI, emphysema index; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; RV, residual volume; SD, standard; SGRQ-C, St George's Respiratory Questionnaire; TLC, total lung capacity.

an index of air trapping, was highest in the mixed phenotype group ($P<0.001$).

Survival

Overall survival was compared between the four CT-defined phenotypes. The mean follow-up time of the overall patient population was 75.1 months (95% CI: 71.1–79.1 months). Kaplan–Meier curve analyses indicated a significant difference in overall survival among the groups (Figure 1). The mixed phenotype had the shortest mean overall survival (121.5 months, 95% CI: 112.2–130.9 months), while the airway-dominant phenotype had the longest (150.9 months, 95% CI: 145.7–156.2 months). The mixed type showed a statistically significant difference in overall survival when compared to the CT normal and the airway-dominant type. The airway-dominant type showed a significant difference when compared to the emphysema-dominant type, however, did not show significant difference when compared to the CT-normal type (Table 2). Multivariate analyses were performed for overall survival, but no significant associations were observed between shorter survival and CT-defined phenotypes.

Severe Exacerbation Frequency

Table 3 shows the results of analyses of factors associated with exacerbation frequency. Age, sex, GOLD stages, BMI, total CAT score, and CT-defined phenotypes were included in univariate analyses. Lower BMI, poor pulmonary function measured using GOLD stage, and mixed phenotype were significant factors associated with more frequent severe exacerbation of COPD. Significant factors in the unadjusted model were entered into multivariate analyses. Lower BMI

was independently associated with more frequent severe exacerbation (IRR 0.843 per 1 kg/m² increase, 95% CI: 0.744–0.954, $P=0.007$). Compared to the CT-normal phenotype, the mixed phenotype was associated with more frequent severe exacerbation (IRR 4.134, 95% CI: 1.135–15.057, $P=0.031$).

Discussion

COPD patients with the mixed phenotype are more symptomatic, have poorer quality of life, and exhibit reduced pulmonary function compared to other phenotypes. Furthermore, the mixed phenotype was associated with more frequent severe COPD exacerbation.

With the lowest values of FEV1 and DLco, COPD patients with the mixed phenotype showed poorer pulmonary function. These results are consistent with a previous study that compared different COPD phenotypes.⁹ The clinical characteristics of the mixed phenotype in our study were similar to those of COPD patients with chronic bronchitis and low DLco. We previously found that patients with chronic bronchitis symptoms and low DLco are more symptomatic and are at higher risk for acute exacerbations than patients without CB or decreased DLco.¹⁹ A previous study that compared different COPD phenotypes demonstrated that FEV1, DLco, and BMI were significantly lower in a severe mixed phenotype than in other phenotypes.⁷ In line with these findings, we observed higher CAT scores and higher RV/TLC in the mixed phenotype in the present study.

We assumed that increased air trapping, chronic bronchitis, and small airway disease contributed to the poorer longitudinal clinical outcome and pulmonary functions in patients with mixed phenotype COPD compared to the emphysema-dominant phenotype. Patients with mixed phenotype had significantly lower FEV1 and higher RV/TLC than the emphysema-dominant phenotype. Increased RV/TLC is associated with small airway disease, frequent exacerbations of COPD, and increased mortality in patients with COPD.^{20–23} In addition, we assumed that the component of bronchial wall thickening was added to the emphysema component, which eventually contributed to poor outcome. Chronic bronchitis patients with COPD are characterized by airway wall thickening as detected via thoracic CT.^{6,14} Such patients are often more symptomatic and show more frequent exacerbations compared to patients without chronic bronchitis.^{24–27} Furthermore, MWA% is also correlated with small airway disease,¹⁰ and it may also have had a detrimental effect on COPD patients with mixed phenotype. We found that frequent

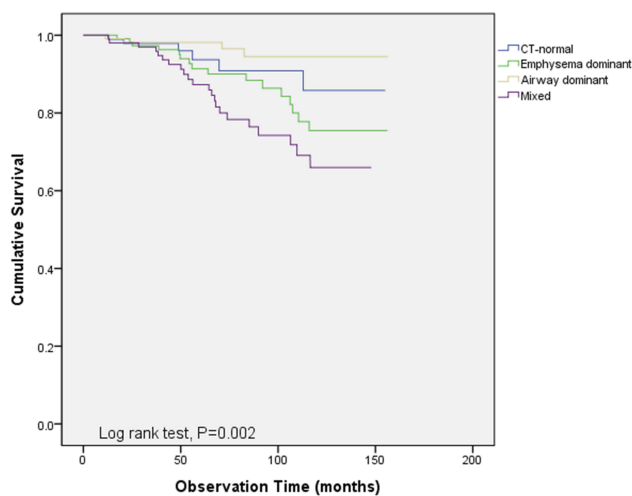


Figure 1 Overall survival was compared between the four CT-defined phenotypes. Kaplan–Meier curve analyses indicated significant differences among groups ($P=0.002$).

Table 2 Comparison of Mortality Risk Between the Different Types (Log Rank Test)

CT Phenotype	CT Normal		Emphysema Dominant		Airway Dominant		Mixed Phenotype	
	Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value	Hazard Ratio	P-value
CT normal	–	–	0.963	0.326	1.481	0.224	5.724	0.030
Emphysema dominant	0.963	0.326	–	–	5.638	0.018	2.219	0.136
Airway dominant	1.481	0.224	5.638	0.018	–	–	13.379	<0.001
Mixed phenotype	4.724	0.030	2.219	0.136	13.379	<0.001	–	–

Abbreviation: CT, computed tomography.

Table 3 Association of Patient Factors with Severe Exacerbations Frequency During 1st Post-enrolment Year

Baseline Characteristics	Exacerbations During 1 Year			
	IRR (95% CI) Unadjusted	P-value	IRR (95% CI) Adjusted	P-value
Age (≤65/>65)	1.019 (0.493–2.105)	0.959	–	–
Male sex	2.609 (0.345–19.703)	0.353	–	–
BMI*	0.782 (0.697–0.876)	<0.001	0.843 (0.744–0.954)	0.007
GOLD 12vs34	3.043 (1.502–6.164)	0.002	1.374 (0.626–3.017)	0.428
Total CAT score*	1.012 (0.940–1.089)	0.754	–	–
CT phenotypes				
CT normal	1	–	1	–
Emphysema dominant	2.773 (0.743–10.355)	0.129	1.695 (0.433–6.634)	0.448
Airway dominant	0.292 (0.30–2.853)	0.290	0.314 (0.032–3.089)	0.320
Mixed	6.663 (1.927–23.041)	0.003	4.134 (1.135–15.057)	0.031

Note: *Indicate risk associated with 1-unit increase.

Abbreviations: BMI, body mass index; CAT, COPD assessment test; CI, confidence interval; CT, computed tomography; GOLD, Global Initiative for Chronic Obstructive Lung Disease; IRR, incidence rate ratio.

exacerbations in the mixed phenotype may have led to increased mortality, consistent with previous studies.^{9,28}

The definition of mixed phenotype in COPD can be variable. We applied EI for phenotyping the emphysema-dominant subgroup, and the MWA% for phenotyping the airway-dominant subgroup. Van Tho et al used the percentage of low attenuation area (%LAA) and internal perimeter of 10 mm (Pi10) for phenotyping subgroups,⁹ while Loh et al phenotyped patients using EI and postbronchodilator FEV1.⁸ Grouping mixed phenotype using quantitative CT usually involves the combination of CT parameters correlated with emphysema and chronic bronchitis in COPD. While LAA is associated with emphysema in COPD, airway wall thickening, manifested as Pi10 or MWA, is associated with chronic bronchitis.^{6,9,10}

The strength of our study is the long observation time (median observation time 75 months). Due to the long study period, we could compare overall survival between the CT-based phenotypes. In the near future, when the observation time is extended, we will observe how the survival difference between the CT-based phenotype changes.

This study had some limitations. First, MWA% was used as a cutoff for phenotyping COPD patients, and application of this cutoff to other COPD populations is limited. However, there is as yet no clear cutoff for defining bronchial wall thickening, and MWA% was used for phenotyping the airway-dominant phenotype in a previous study.¹⁰ Furthermore, for airway wall thickness evaluation, only segmental bronchi were measured, and it is possible that severity of small airway disease was not reflected while phenotyping the study patients. Second, only severe COPD exacerbations were evaluated. Lastly, clinical features associated with chronic bronchitis were not evaluated comprehensively in this study, and should be discussed in a future study.

Conclusion

Patients with volumetric CT-defined mixed phenotype have poor pulmonary function and shorter overall survival as well as more frequent severe exacerbation than other phenotypes. The mixed phenotype is a subgroup of COPD with distinct clinical characteristics and prognosis. Various

criteria should be applied to define the mixed phenotype in COPD.

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Disclosure

Authors have no conflicts of interest in this work.

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