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Original Article

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Risk Factors of FEV_1/FVC Decline in COPD Patients

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ABSTRACT

Background: Factors influencing the decline in forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) for chronic obstructive pulmonary disease (COPD) progression remain uncertain. We aimed to identify risk factors associated with rapid FEV_1/FVC decline in patients with COPD.

Methods: This multi-center observational study was conducted from January 2012 to December 2022. Eligible patients were monitored with symptoms, spirometric tests, and treatment patterns over 3 years. Rapid FEV_1/FVC decliners were defined as the quartile of patients exhibiting the highest annualized percentage decline in FEV_1/FVC.

Results: Among 1,725 patients, 435 exhibited rapid FEV_1/FVC decline, with an annual change of −2.5%p (interquartile range, −3.5 to −2.0). Rapid FEV_1/FVC decliners exhibited lower body mass index (BMI), higher smoking rates, elevated post-bronchodilator (BD) FEV_1, higher post-BD FEV_1/FVC, and a lower prevalence of Staging of Airflow Obstruction by Ratio (STAR) stage IV. Rapid FEV_1/FVC decline was not linked to the annual exacerbation rate, but there was an association with symptom deterioration and FEV_1 decline. In multivariable analyses, low BMI, current smoking, increased modified Medical Research Council dyspnoea score, low post-BD FEV_1, low STAR stage, high forced mid-expiratory flow ($FEF_{25-75\%}$), accelerated FEV_1 decline, and not initiating dual BD therapy were identified as independent risk factors for rapid FEV_1/FVC decline.

Conclusion: We identified the risk factors for rapid FEV_1/FVC decline, including BMI, smoking, symptoms deterioration, FEV_1 decline, and adherence to standard inhaler treatment. Our findings underscore the potential benefits of maintaining consistent use of long-acting beta-agonist/long-acting muscarinic antagonist even in the presence of worsening symptoms, in attenuating FEV_1/FVC decline.

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Disclosure
The authors have no potential conflicts of interest to disclose.

Data Availability Statement
The data that support the findings of this study are available from the KOrea COpd Subgroup Study (KOCOSS) team but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the KOCOSS team.

Author Contributions
Conceptualization: Lee HW. Data curation: Kim NY, Lee HW. Formal analysis: Kim NY, Lee HW. Funding acquisition: Yoo KH. Methodology: Kim NY, Lee HW. Supervision: Kim DK, Park S, Hwang YI, Seo H, Park D, Park SJ, Lee JH, Yoo KH, Lee HW. Visualization: Lee HW. Writing - original draft: Kim NY, Lee HW. Writing - review & editing: Kim DK, Park S, Hwang YI, Seo H, Park D, Park SJ, Lee JH, Yoo KH, Lee HW.

Keywords: Chronic Obstructive Pulmonary Disease; Cohort Studies; Forced Expiratory Volume; Forced Vital Capacity; Respiratory Function Tests; Risk Factors

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous airway disease characterized by irreversible airflow limitation.[1] Airflow obstruction has been typically measured by the forced expiratory volume in one second (FEV_1)/forced vital capacity (FVC) ratio. In addition, the severity of COPD is usually evaluated using post-bronchodilator (BD) percentage predicted of FEV_1 ($ppFEV_1$), which has significant correlations with symptoms,[2,3] acute exacerbations,[4] and mortality.[5] The $ppFEV_1$ can be estimated by age, height, and gender-adjusted reference values.[6] However, the use of $ppFEV_1$ has limitations due to factors like obesity,[7] genetics,[8] and lung volume variations.[9] Therefore, alternative approaches for assessing the severity of airway obstruction such as the FEV_1/FVC ratio, have been proposed for COPD patients.[10,11] In the COPDgene study, the Staging of Airflow Obstruction by Ratio (STAR) stage, based on the FEV_1/FVC ratio, demonstrated an enhanced performance for predicting mortality, especially in mild COPD patients, compared to conventional FEV_1 severity assessments.[11]

Physiological decline in lung function begins in early adulthood and progresses with aging; however, COPD patients experience faster and more heterogenous lung function decline compared to the general population.[12] It is well known that a rapid decline in lung function is associated with an increased risk of COPD-related hospitalization[13] and death.[14] Recently, the clinical significance of the annual FEV_1/FVC decline rate has been evaluated in the general population.[15] This study suggested that a rapid FEV_1/FVC decline in the general population is linked to the development of obstructive lung disease and higher mortality rates.[15] Certain studies showed that occupational dust exposure[16] and narcotic use[17] were associated with a decrease in FEV_1/FVC. However, previous studies were conducted in the general population, and there has been a scarcity of studies examining the association between FEV_1/FVC decline specifically in COPD patients.

The identification of risk factors for COPD progression stands as a pivotal role in the strategic landscape of COPD management. Most studies on the risk factors for COPD progression have predominantly focused on changes in FEV_1, leaving the investigation of rapid declines in FEV_1/FVC relatively underexplored. Hence, our study aimed to identify independent risk factors associated with a rapid decline in post-BD FEV_1/FVC (%p/year).

METHODS

Our study adhered to the guidelines outlined in the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.[18]

Study design and eligibility criteria

Our nested case-control study used database of the Korea COPD Subgroup Study (KOCOSS) cohort (NCT02800499), which prospectively enrolled individuals diagnosed with COPD from January 2012 to December 2022 at 54 medical institutions in South Korea. Detailed information on study design and methodology is available in a prior study.[19] In KOCOSS

cohort, COPD patients ≥ 40 years and post-BD FEV_1/FVC ratio < 0.7 were included.[20] In our study, inclusion criteria required patients to have baseline and at least one follow-up post-BD spirometric assessment over the 3-year follow-up period. Regarding exclusion criteria, patients with statistically significant outliers in annual changes of post-BD FEV_1/FVC were excluded, given that their spirometric assessments were considered unreliable, unrepeatable, or non-predictable.

Baseline variables

In the baseline assessment, we compiled demographic details from eligible patients, covering age, sex, body mass index (BMI), smoking habits, respiratory and non-respiratory comorbidities, as well as a history of previous exacerbations. We acquired information on baseline symptoms, including the modified Medical Research Council (mMRC) dyspnoea scale, the COPD assessment test (CAT) score, and St. George's Respiratory Questionnaire for COPD Patients (SGRQ-C) score. Additionally, we checked the current inhaled therapies and oral medications being prescribed at the baseline.

Baseline spirometric data included post-BD FEV_1, FVC, FEV_1/FVC, diffusing capacity for carbon monoxide (DL_{CO}), DL_{CO}/alveolar volume (VA), and total lung capacity. Evaluation of exercise capacity involved the assessment of the 6-minute walking distance (6MWD). For laboratory analysis, the information on complete blood cells with differential counts was collected. Radiological assessment entailed an exploration of structural abnormalities, including emphysema, bronchiectasis, and tuberculosis-induced destructed lung, based on chest computed tomography (CT) scans.

Dynamically changing variables

We investigated dynamically changing variables over a 3-year period, including moderate-to-severe or severe exacerbation rates, mMRC change, CAT score change, SGRQ-C score change, 6MWD change, annual FEV_1 change, annual FVC change, and inhaled therapy treatment patterns, to investigate their association with a rapid decline in FEV_1/FVC. The analyses for dynamically changing variables were conducted with available data, excluding cases with missing values. Annual FEV_1 change (mL/yr), annual FVC change (mL/yr), and annual FEV_1/FVC change (%p/yr) were estimated for each patient by dividing the difference between baseline lung function and the last follow-up lung function values by the duration of the follow-up period.

Definition of rapid decliners

We employed the definition of rapid FEV_1/FVC decline based on quartiles of the annual changes in FEV_1/FVC, as introduced in a previous study.[15] Patients with the most negative change in FEV_1/FVC (1st quartile) were categorized as rapid FEV_1/FVC decliners, while patients with the remaining quartiles (2nd, 3rd, and 4th quartiles) were designated as non-rapid FEV_1/FVC decliners.

Statistical analysis

We used Student's *t*-test for the comparison of continuous variables and the χ^2 test for categorical variables between rapid and non-rapid FEV_1/FVC decliners. Univariable and multivariable logistic regression analyses were performed to identify significant risk factors associated with rapid FEV_1/FVC decliners. Significant covariates identified from the univariable analysis as risk factors for rapid FEV_1/FVC decline were included in the multivariable analysis. We assessed significant multicollinearity with a variance inflation

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factor > 4.0. Variables exhibiting multicollinearity were analyzed in separate logistic regression models. For multivariable analyses, handling missing values included the use of the 'mice' R package, leveraging associations with other variables for imputation. We thoroughly checked the similarity in data distribution and representative values before and after the imputation process. Statistical significance was determined at a $P < 0.05$. R statistical software, version 4.3.2 (R Core Team [2021], Vienna, Austria), was employed for all statistical analyses.

Ethics statement

The study protocol received approval from the Institutional Review Board (IRB) at each hospital (Seoul Metropolitan Government-Seoul National University Boramae Medical Center, IRB No. 06-2012-36). All participants provided written informed consent at the time of enrollment. This study adhered to the principles outlined in the Declaration of Helsinki.

RESULTS

Among the 3,477 patients with COPD, 1,992 underwent both baseline and follow-up pulmonary function tests over a 3-year observation period (**Fig. 1**). We included the remaining eligible 1,725 patients with a reliably estimated post-BD FEV_1/FVC decline rate. The median annual post-BD FEV_1/FVC change rate was 0%p/year (−1.3 to 1.5) (**Supplementary Fig. 1**). The patients were categorized according to the quartiles of the annual post-BD FEV_1/FVC change rate. The 1st quartile, representing the fastest FEV_1/FVC decline, was defined as the rapid FEV_1/FVC decliners (n = 435, 25.2%). The median change of FEV_1/FVC in rapid decliner was −2.5 (interquartile range [IQR], −3.5 to −2.0) (**Supplementary Fig. 2**).

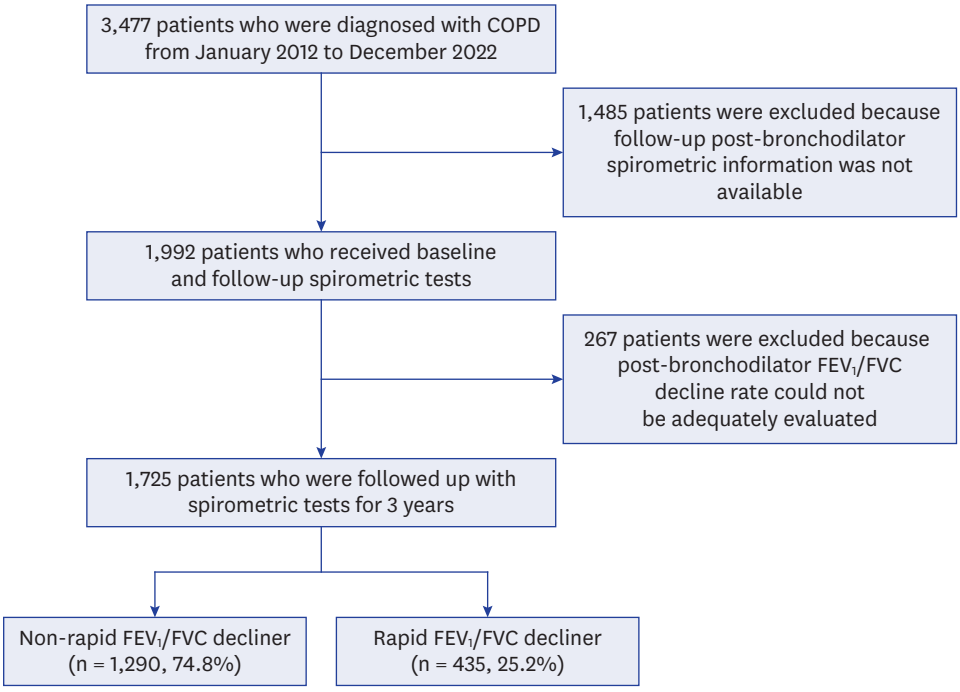

Fig. 1. Flow diagram for the inclusion of patients.
COPD = chronic obstructive pulmonary disease, FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity.

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Demographic and clinical features

Rapid FEV_1/FVC decliners had lower BMI and exhibited a higher proportion of current smokers (**Table 1**). There were no significant differences in terms of comorbidities, exacerbations, symptoms, or treatments between the rapid and non-rapid FEV_1/FVC decliners. In the baseline spirometric assessment, rapid FEV_1/FVC decliners showed higher values in post-BD FEV_1 (%), post-BD FEV_1/FVC (%), and forced mid-expiratory flow ($FEF_{25-75\%}$),

Table 1. Baseline characteristics according to FEV_1/FVC decline rate

Characteristics	Non-rapid decliner (n = 1,290)	Rapid decliner (n = 435)	*P* value
Age, yr	68.1 ± 7.8	68.6 ± 8.0	0.217
Female	100 (7.8)	28 (6.4)	0.424
BMI, kg/m^2	23.4 ± 3.4	22.7 ± 3.2	< 0.001
Smoking status			0.002
Never smoker	125 (9.7)	31 (7.1)	
Ex-smoker	860 (66.7)	265 (60.9)	
Current smoker	305 (23.7)	139 (32.0)	
Ever smokers, pack/yr	40.5 ± 25.2	40.5 ± 24.9	0.971
Respiratory comorbidity			
Asthma	97 (7.5)	27 (6.2)	0.418
History of pulmonary tuberculosis	325 (25.3)	98 (22.6)	0.303
Comorbidity			
MI	59 (4.6)	13 (3.0)	0.199
HF	51 (4.0)	8 (1.8)	0.052
HTN	497 (38.5)	155 (35.7)	0.323
DM	215 (16.6)	74 (17.1)	0.917
Chronic liver disease	13 (1.8)	1 (0.4)	0.224
Chronic kidney disease	9 (1.2)	2 (0.8)	0.817
GERD	115 (8.9)	30 (6.9)	0.232
Malignancy	23 (3.2)	8 (3.4)	1.000
Previous history of exacerbation			
Moderate-to-severe exacerbation	171 (19.2)	49 (17.6)	0.615
Moderate exacerbation	158 (17.8)	44 (15.8)	0.516
Severe exacerbation	68 (7.6)	23 (8.3)	0.829
Symptoms			
Cough	293 (22.7)	81 (18.8)	0.085
Sputum	381 (29.6)	131 (30.5)	0.866
mMRC score	1.3 ± 0.9	1.3 ± 0.9	0.075
CAT score	14.2 ± 7.9	13.8 ± 7.4	0.401
SGRQ-C score	30.7 ± 20.5	28.8 ± 19.3	0.094
Inhaled therapy			
No treatment	34 (2.6)	8 (1.8)	0.351
LABA	68 (5.3)	25 (5.7)	0.704
LAMA	341 (26.4)	110 (25.3)	0.638
LABA/LAMA	337 (26.1)	97 (22.2)	0.112
ICS/LABA	182 (14.1)	77 (17.8)	0.070
ICS/LABA/LAMA	328 (25.4)	118 (27.1)	0.484
Oral medication			
Methylxanthine	261 (20.2)	95 (21.8)	0.517
PDE4 inhibitor	78 (6.0)	32 (7.4)	0.393
LTRA	63 (4.9)	31 (7.1)	0.097
Erdosteine	41 (3.2)	20 (4.6)	0.216
Acetylcysteine	10 (0.8)	1 (0.2)	0.375
Macrolide	6 (0.5)	2 (0.5)	1.000

Data are expressed as mean ± standard deviation or number (percentage).
FEV_1 = forced expiratory volume in one second, FVC = forced vital capacity, BMI = body mass index, MI = myocardial infarction, HF = heart failure, HTN = hypertension, DM = diabetes mellitus, GERD = gastroesophageal reflux disease, mMRC = modified Medical Research Council, COPD = chronic obstructive pulmonary disease, CAT = COPD assessment test, SGRQ-C = St. George's Respiratory Questionnaire for COPD Patients, LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist, ICS = inhaled corticosteroid, PDE-4 = phosphodiesterase-4, LTRA = leukotriene receptor agonist.

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and there was a significantly lower prevalence of STAR stage IV (**Table 2**). The percentage of blood eosinophil counts (BECs) exceeding 300 /uL did not show a significant association with a rapid FEV_1/FVC decline. Additionally, radiologic findings in CT showed no significant differences between the two groups.

Table 2. Lung function, laboratory, and radiological findings according to FEV_1/FVC decline rate

Variables	Non-rapid decliner (n = 1,290)	Rapid decliner (n = 435)	*P* value
Lung function tests			
Post-BD FEV_1, L	1.7 ± 0.6	1.7 ± 0.6	0.134
Post-BD FEV_1, %	57.9 ± 18.2	60.1 ± 17.8	0.026
GOLD stage I (FEV_1 ≥ 80%)	165 (12.9)	59 (13.7)	0.732
GOLD stage II (80% > FEV_1 ≥ 50%)	689 (53.8)	254 (58.9)	0.074
GOLD stage III (50% > FEV_1 ≥ 30%)	357 (27.9)	102 (23.7)	0.099
GOLD stage IV (30% > FEV_1)	69 (5.4)	16 (3.7)	0.208
Post-BD FVC, L	3.3 ± 0.8	3.3 ± 0.8	0.949
Post-BD FVC, %	81.0 ± 16.1	81.4 ± 15.8	0.701
Post-BD FEV_1/FVC, %	50.8 ± 12.5	52.6 ± 12.0	0.009
STAR stage I (70% > FEV_1/FVC ≥ 60%)	383 (29.7)	141 (32.4)	0.314
STAR stage II (60% > FEV_1/FVC ≥ 50%)	332 (25.7)	120 (27.6)	0.487
STAR stage III (50% > FEV_1/FVC ≥ 40%)	302 (23.4)	112 (25.7)	0.357
STAR stage IV (40% > FEV_1/FVC)	273 (21.2)	62 (14.3)	0.002
Post-BD $FEF_{25-75\%}$, L	0.7 ± 0.4	0.8 ± 0.4	0.012
Post-BD $FEF_{25-75\%}$, %	27.9 ± 15.6	30.7 ± 16.6	0.001
DL_{CO}, mL/min/mmHg	13.3 ± 4.6	13.2 ± 4.5	0.632
DL_{CO}, %	64.7 ± 20.2	64.7 ± 20.5	0.980
DL_{CO}/VA, mL/min/mmHg	3.2 ± 1.0	3.1 ± 1.0	0.181
DL_{CO}/VA, %	76.5 ± 22.6	75.5 ± 22.6	0.445
TLC, L[a]	5.9 ± 1.15	5.92 ± 1.22	0.426
TLC, %[a]	98.0 ± 17.8	98.4 ± 19.6	0.658
RV, L[a]	2.6 ± 1.1	2.6 ± 1.1	0.400
RV, %[a]	107.5 ± 44.2	108.5 ± 48.6	0.683
RV/TLC, %[a]	43.0 ± 12.0	43.2 ± 11.5	0.771
6MWD, m	389 ± 116	399 ± 105	0.138
Laboratory tests			
WBC, /uL	7,352 ± 2,376	7,387 ± 2,494	0.790
Neutrophil, /uL	3,280 ± 2,024	4,470 ± 2,221	0.433
Lymphocyte, /uL	2,078 ± 780	2,034 ± 753	0.306
Eosinophil, /uL	239 ± 280	232 ± 246	0.645
> 300 /uL	303 (23.5)	106 (24.4)	0.758
Hemoglobin, mg/dL	14.4 ± 1.5	14.4 ± 1.4	0.358
Radiologic findings on chest CT scan[b]			
Emphysema	452 (55.2)	144 (54.5)	0.911
Old TB sequalae	163 (23.4)	57 (24.3)	0.847
Bronchiectasis	145 (17.7)	38 (14.4)	0.249
TB destroyed lung	33 (4.0)	9 (3.4)	0.787
Lung fibrosis	15 (2.3)	3 (1.3)	0.543
No abnormality	197 (24.1)	76 (28.8)	0.145

Data are expressed as mean ± standard deviation or number (percentage).
FEV_1 = forced expiratory volume in 1 second, FVC = force volume capacity, BD = bronchodilator, GOLD = Global Initiative for Chronic Obstructive Lung Disease, STAR = Staging of Airflow Obstruction by Ratio, $FEF_{25-75\%}$ = forced mid-expiratory flow, DLco = diffusing capacity for carbon dioxide, VA = alveolar volume, TLC = total lung capacity, RV = residual volume, 6MWD = 6-minute walking distance, WBC = white blood cell, CT = computed tomography, TB = tuberculosis.
[a]Lung volume measurements were underwent in 872 (67.6%) of non-rapid decliners and 279 (64.1%) of rapid decliners.
[b]Chest CT scans were underwent in 819 (63.5%) of non-rapid decliners and 264 (60.7%) of rapid decliners.

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FEV_1/FVC decline and change of clinical features

The annual change was −2.5%p (IQR, −3.5 to −2.0) in rapid FEV_1/FVC decliners, while it increased by 0.6%p (IQR, −0.3 to 2.0) annually in non-rapid FEV_1/FVC decliners (**Supplementary Fig. 3**). Rapid FEV_1/FVC decline was not associated with the annual exacerbation rate, but was associated with the worsening of symptoms and FEV_1 decline (**Table 3**). A significant increase in the deterioration of patient reported outcomes (PROs) beyond the minimum clinically important difference (MCID), including mMRC, CAT score, and SGRQ-C, was observed in rapid FEV_1/FVC decliners during the 3-year follow-up. In addition, the annual change in FEV_1 for rapid FEV_1/FVC decliners was −71.0 mL/yr (IQR, −122.5 to −12.5), which deteriorated at a faster rate compared to non-rapid FEV_1/FVC decliners with −7.0 mL/yr (IQR, −71.75 to 46.75). A higher proportion of rapid FEV_1/FVC decliners experienced a decline in FEV_1 ≥ 60 mL/yr or 100 mL/yr. However, 20% of rapid FEV_1/FVC decliners had an annual FEV_1 decline rate slower than the median value of −10 mL/yr, and notably, these patients commonly showed an increasing trend in annual FVC (**Supplementary Fig. 4**).

FEV_1/FVC decline and treatment change

At the baseline, the rapid FEV_1/FVC decliners predominantly were treated with triple therapy, with no significant differences in treatment compared to the non-rapid FEV_1/FVC decliners. Over the 3-year tracking period of inhaler therapy usage, it was observed that the use of long-acting beta-agonist (LABA)/long-acting muscarinic antagonist (LAMA) in the non-rapid FEV_1/FVC decliners increased over time, and the difference compared to the rapid FEV_1/FVC decliners became more pronounced ($P < 0.05$) (**Fig. 2**, **Supplementary Fig. 5**). There was a tendency for more inhaled corticosteroid (ICS)/LABA use in the rapid FEV_1/FVC decliners over the 3-year period, although a consistent statistical significance was not observed. Additionally, in the patients with BEC < 100 /uL, there was a significantly higher proportion of rapid FEV_1/FVC decliners using ICS-containing medications at the 1-year follow-up. (**Supplementary Fig. 6**).

Table 3. Comparison of dynamic changes in clinical parameters according to FEV_1/FVC decline rate

Variables	Non-rapid decliner		Rapid decliner		*P* value
	Mean ± SD or median (IQR)	No. (%)	Mean ± SD or median (IQR)	No. (%)	
Annual moderate-to-severe exacerbation rate, /yr	0.98 ± 1.12		1.08 ± 1.12		0.120
Annual severe exacerbation rate, /yr	0.16 ± 0.30		0.14 ± 0.24		0.300
Change of mMRC grade for 3 yr	0.04 ± 1.13		0.26 ± 1.19		< 0.001
mMRC change ≥ 1		402 (31.2)		162 (37.2)	0.023
mMRC change ≤ −1		381 (29.5)		101 (23.2)	0.013
Change of CAT score for 3 yr	−1.30 ± 9.42		−0.17 ± 9.42		0.030
CAT change ≥ 2		452 (35.0)		192 (44.1)	0.001
CAT change ≤ −2		612 (47.4)		188 (43.2)	0.141
Change of SGRQ-C for 3 yr	−2.60 ± 23.90		2.39 ± 23.27		< 0.001
SGRQ-C change ≥ 4		462 (35.8)		180 (41.4)	0.043
SGRQ-C change ≤ −4		597 (46.3)		169 (38.9)	0.008
Change of 6MWD for 3 yr, m	4.43 ± 142.44		−9.69 ± 136.89		0.071
6MWD change ≥ 30 m		531 (41.2)		163 (37.5)	0.193
6MWD change ≤ −30 m		491 (38.1)		172 (39.5)	0.623
Annual FEV_1 change, mL/yr	−7.0 (−71.75 to 46.75)		−71.0 (−122.5 to −12.5)		< 0.001
Annual FEV_1 change ≤ −60 mL/yr		262 (20.3)		272 (62.5)	< 0.001
Annual FEV_1 change ≤ −100 mL/yr		135 (10.5)		186 (42.8)	< 0.001
Annual FVC change, mL/yr	−30.5 (−138.0 to 70.0)		−40.0 (−144.5 to 47.0)		0.243

The total number of patients analyzed for each variable is described, listed in the order of non-rapid decliners and rapid decliners within bracket.
FEV_1 = forced expiratory volume in 1 second, FVC = force volume capacity, SD = standard deviation, IQR = interquartile range, COPD = chronic obstructive pulmonary disease, mMRC = modified Medical Research Council, CAT = COPD assessment test, SGRQ-C = St. George's Respiratory Questionnaire for COPD Patients, 6MWD = 6-minute walking distance.

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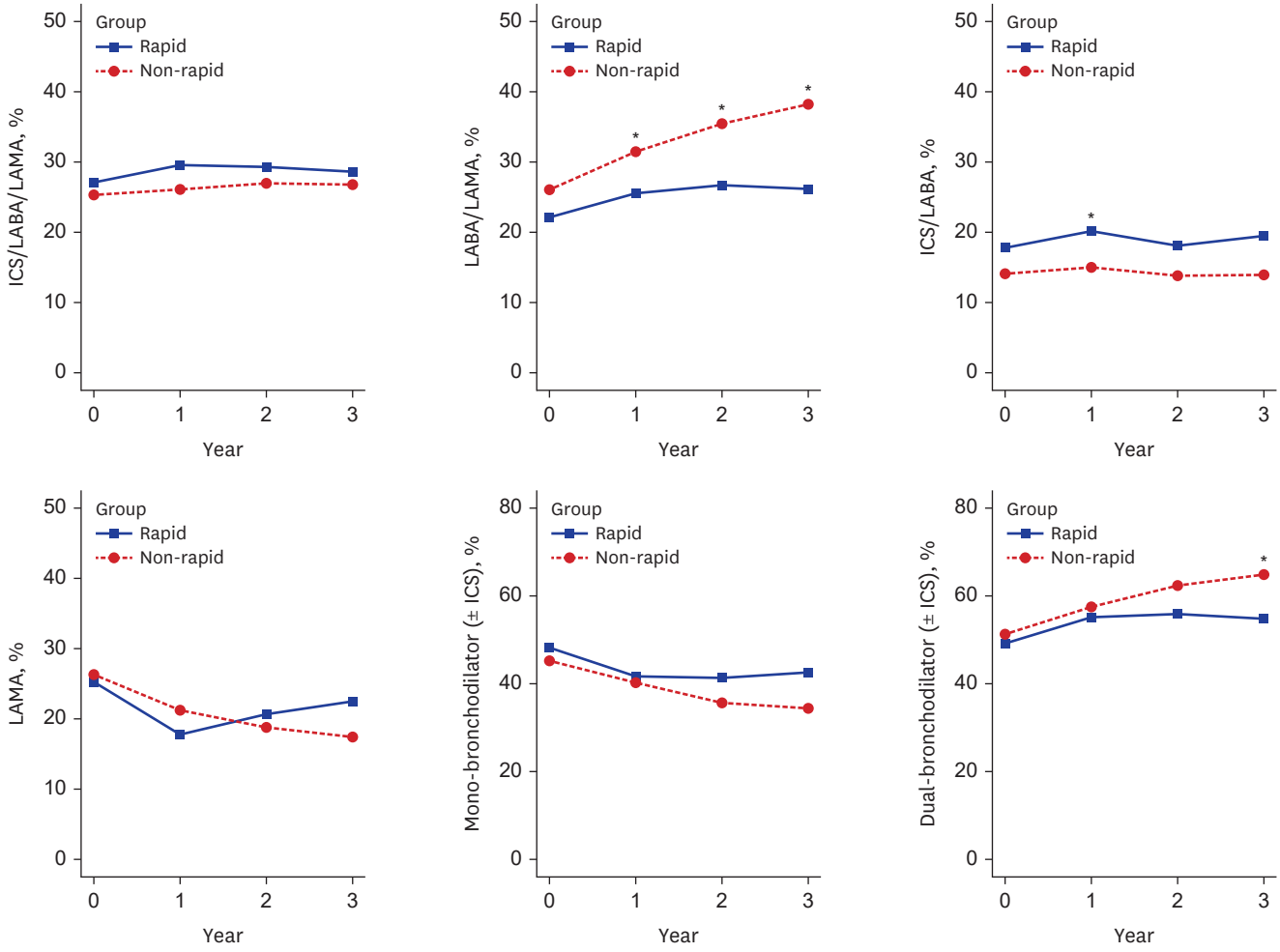

Fig. 2. Dynamic treatment changes in rapid and non-rapid FEV_1/FVC decliners. For the evaluation of dynamic treatment changes, a total of 662 patients were analyzed, comprising 514 in the non-rapid FEV_1/FVC group and 148 in the rapid FEV_1/FVC group.
FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, LABA = long-acting beta-agonist, LAMA = long-acting muscarinic antagonist, ICS = inhaled corticosteroid.
*$P < 0.05$.

Risk factors related to rapid FEV_1/FVC decline

In univariable logistic regression analysis, BMI, current smoker status, cardiovascular disease, post-BD FEV_1 (%), STAR stage IV, $FEF_{25-75\%}$, and annual FEV_1 change were significantly associated with rapid FEV_1/FVC decline. Change of PROs (mMRC, CAT score, and SGRQ-C) and change to dual-BD were also found to be factors associated with the rapid FEV_1/FVC decline (**Table 4**). In multivariable analyses, model 1 showed low BMI (adjusted odds ratio [aOR], 0.946; 95% confidence interval [CI], 0.909–0.984), current smoking (aOR, 1.850; 95% CI, 1.118–3.062), increased mMRC (aOR, 1.155; 95% CI, 1.037–1.286) over 3 years, low post-BD FEV_1 (%) (aOR, 0.972; 95% CI, 0.959–0.985), low STAR stage (STAR stage IV: aOR, 0.361; 95% CI, 0.204–0.639), high $FEF_{25-75\%}$ (%) (aOR, 1.021; 95% CI, 1.006–1.037), accelerated FEV_1 decline (mL/yr) (aOR, 0.992; 95% CI, 0.991–0.993), not initiating dual BD therapy (aOR, 0.526; 95% CI, 0.322–0.859) were identified as independent risk factors for rapid FEV_1/FVC decline. In Model 2, CAT score was included instead of mMRC, showing no significant association with rapid FEV_1/FVC decline. In Model 3, SGRQ-C was included, revealing a significant association with rapid FEV_1/FVC decline (aOR, 1.006; 95% CI,

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Table 4. Risk factors for rapid FEV_1/FVC decline

Variables	Univariable analysis		Multivariable analysis					
	OR (95% CI)	*P* value	Model 1		Model 2		Model 3	
			OR (95% CI)	*P* value	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Body mass index	0.936 (0.905–0.968)	< 0.001	0.946 (0.909–0.984)	0.006	0.944 (0.908–0.983)	0.005	0.947 (0.91–0.986)	0.008
Smoking status (reference: never smoker)								
Ex-smoker	1.323 (0.862–2.030)	0.201	1.403 (0.875–2.249)	0.160	1.428 (0.890–2.29)	0.139	1.413 (0.881–2.265)	0.152
Current smoker	1.944 (1.235–3.060)	0.004	1.850 (1.118–3.062)	0.017	1.860 (1.123–3.079)	0.016	1.833 (1.107–3.034)	0.019
Cardiovascular disease	0.565 (0.345–0.926)	0.023	0.643 (0.375–1.101)	0.108	0.652 (0.381–1.117)	0.119	0.648 (0.378–1.112)	0.116
Change of mMRC grade for 3 yr	1.183 (1.074–1.303)	< 0.001	1.155 (1.037–1.286)	0.009	-	-	-	-
Change of CAT score for 3 yr	1.014 (1.002–1.026)	0.022	-	-	1.008 (0.995–1.021)	0.246	-	-
Change of SGRQ-C for 3 yr	1.009 (1.004–1.014)	< 0.001	-	-	-	-	1.006 (1.001–1.012)	0.015
Post-BD FEV_1	1.007 (1.001–1.013)	0.032	0.972 (0.959–0.985)	< 0.001	0.972 (0.959–0.985)	< 0.001	0.972 (0.959–0.985)	< 0.001
STAR stage (reference: stage I)								
Stage II	0.961 (0.719–1.285)	0.788	0.998 (0.678–1.468)	0.990	0.985 (0.670–1.450)	0.940	0.997 (0.677–1.469)	0.988
Stage II	1.039 (0.775–1.393)	0.799	0.757 (0.481–1.194)	0.231	0.743 (0.472–1.170)	0.200	0.754 (0.478–1.189)	0.225
Stage IV	0.628 (0.447–0.882)	0.007	0.361 (0.204–0.639)	< 0.001	0.350 (0.198–0.618)	< 0.001	0.359 (0.203–0.635)	< 0.001
$FEF_{25-75\%}$	1.010 (1.004–1.017)	0.002	1.021 (1.006–1.037)	0.007	1.020 (1.005–1.036)	0.011	1.020 (1.005–1.036)	0.011
Annual FEV_1 change	0.992 (0.991–0.993)	< 0.001	0.992 (0.991–0.993)	< 0.001	0.992 (0.991–0.993)	< 0.001	0.992 (0.991–0.993)	< 0.001
Initiating dual-BD therapy	0.452 (0.284–0.720)	< 0.001	0.526 (0.322–0.859)	0.010	0.532 (0.327–0.868)	0.012	0.532 (0.326–0.868)	0.016
Addition of ICS	1.250 (1.000–1.562)	0.050	1.109 (0.857–1.437)	0.431	1.106 (0.855–1.431)	0.443	1.106 (0.854–1.432)	0.445

FEV_1 = forced expiratory volume in 1 second, FVC = force volume capacity, OR = odds ratio, CI = confidence interval, mMRC = modified Medical Research Council, COPD = chronic obstructive pulmonary disease, CAT = COPD assessment test, SGRQ-C = St. George's Respiratory Questionnaire for COPD Patients, BD = bronchodilator, STAR = Staging of Airflow Obstruction by Ratio, $FEF_{25-75\%}$ = forced mid-expiratory flow, ICS = inhaled corticosteroid.

Table 5. Risk factors for rapid FEV_1/FVC decline in subgroups with deterioration beyond minimal clinically important difference in mMRC, CAT, or SGRQ-C

Variables	Multivariable analysis			
	Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Body mass index	0.955 (0.919–0.993)	0.019	0.944 (0.907–0.982)	0.004
Smoking status (reference: never smoker)				
Ex-smoker	1.320 (0.827–2.108)	0.245	1.426 (0.890–2.283)	0.140
Current smoker	1.755 (1.064–2.895)	0.028	1.871 (1.132–3.095)	0.015
Cardiovascular disease	0.661 (0.388–1.128)	0.129	0.628 (0.366–1.077)	0.091
Post-BD FEV_1	0.983 (0.971–0.995)	0.006	0.972 (0.959–0.985)	< 0.001
STAR stage (reference: stage I)				
Stage II	0.976 (0.664–1.434)	0.900	0.977 (0.665–1.437)	0.908
Stage III	0.741 (0.471–1.165)	0.194	0.738 (0.469–1.161)	0.189
Stage IV	0.344 (0.195–0.606)	< 0.001	0.348 (0.197–0.615)	< 0.001
$FEF_{25-75\%}$	1.023 (1.010–1.037)	< 0.001	1.020 (1.005–1.035)	0.011
Annual FEV_1 change	0.992 (0.991–0.994)	< 0.001	0.992 (0.991–0.993)	< 0.001
Continued use of dual-BD (reference: no initiation of treatment with dual-BD or discontinuation of dual-BD during the follow-up)	0.708 (0.508–0.987)	0.042	-	-
Discontinued use of dual-BD (reference: no initiation of treatment with dual-BD or continued use of dual-BD during the follow-up)	-	-	1.526 (1.191–1.955)	< 0.001
Addition of ICS	1.120 (0.870–1.443)	0.379	1.144 (0.885–1.479)	0.303

FEV_1 = forced expiratory volume in 1 second, FVC = forced vital capacity, mMRC = modified Medical Research Council, COPD = chronic obstructive pulmonary disease, CAT = COPD assessment test, SGRQ-C = St. George's Respiratory Questionnaire for COPD Patients, BD = bronchodilator, STAR = Staging of Airflow Obstruction by Ratio, $FEF_{25-75\%}$ = forced mid-expiratory flow, ICS = inhaled corticosteroid.

1.001–1.012). Especially, in the subgroup patients who showed mMRC, CAT score, or SGRQ-C deterioration beyond the MCID over 3 years, the patients who continued using dual BDs exhibited a lower risk of rapid FEV_1/FVC decline (aOR, 0.708; 95% CI, 0.508–0.987), while those who discontinued using dual BDs showed a higher risk of rapid FEV_1/FVC decline (aOR, 1.526; 95% CI, 1.191–1.955) (**Table 5**).

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DISCUSSION

In this observational study, we identified the risk factors associated with rapid FEV_1/FVC decline in COPD patients. Our study showed that annual change of FEV_1/FVC in COPD patients was 0%p/year, which was attenuated compared to −0.3%p/year in the general population.[15] However, rapid FEV_1/FVC decliners (1st quartile) in COPD patients exhibited a greater decline of −2.5%p/year compared to those in general population, which showed −0.8%p/year.[15] Rapid FEV_1/FVC decline was associated with worsening symptoms and accelerated FEV_1 decline. The risk factors for rapid FEV_1/FVC decline included low BMI, current smoking status, increased mMRC score, low post-BD FEV_1, low STAR stage, high $FEF_{25-75\%}$, accelerated FEV_1 decline, and not initiating dual BD therapy. Our study found that rapid FEV_1/FVC decline was not associated with annual rate of acute exacerbation. This may be because if an exacerbation causes a reduction in both FEV_1 and FVC, the patient would be classified as a non-rapid decliner.[21] As a result, there would be no significant difference in exacerbation rates between rapid and non-rapid decliners. There was a significantly lower usage of LABA/LAMA in the rapid FEV_1/FVC decliners during follow-up period, while there was no meaningful correlation with ICS usage.

The concept of pre-disease stages such as prediabetes and precancer has emerged in COPD to identify and intervene early-stage patients for disease modification, giving rise to the concepts of pre-COPD including preserved ratio impaired spirometry.[22] Given that the decline in lung function is faster in early-stage disease than in severe cases,[23] it is crucial to recognize high-risk groups prone to the rapid lung function deterioration at the pre-COPD or mild COPD stage. Similarly, in our study, rapid declines in FEV_1/FVC were more frequently observed in less advanced stages of COPD, characterized by higher $ppFEV_1$ and FEV_1/FVC ratios. Interestingly, both in COPD patients and the general population, rapid FEV_1/FVC decliners had higher baseline FEV_1/FVC ratios and $FEF_{25-75\%}$ values.[15] This finding suggests that rapid FEV_1/FVC decline may occur before the onset or progression of small airway disease. Therefore, identifying risk factors associated with rapid lung function decline before significant impairment occurs holds significant value. In a similar population, male sex, current smoking, BEC < 150 /μL, and high FVC were associated with an increased risk of rapid FEV_1 decline.[24] Among these risk factors, current smoking is a common modifiable factor for both rapid FEV_1/FVC and FEV_1 decline. Cigarette smoking significantly contributes to the development and progression of COPD.[25,26] Therefore, smoking cessation can have benefits in preserving FEV_1/FVC decline rate and preventing the progression of COPD.

Recently, the COPDgene group introduced a new severity stage for COPD.[11] In our study, the proportion of COPD patients classified as severe grade according to STAR stage (IV, FEV_1/FVC < 40%) was unexpectedly lower among rapid FEV_1/FVC decliners, suggesting a reduced risk of rapid FEV_1/FVC decline in STAR stage IV. In COPDgene cohort findings,[11] the greatest decline in FEV_1 occurred in Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2 and STAR 3, with even less decline in stage 4 of both severity categories. Other recent cohort studies suggest that individuals with mild airflow obstruction experience a faster decline in FEV_1 compared to those with more severe disease.[23,27] This phenomenon is explained by the idea that individuals with relatively preserved lung function have a greater potential for decline.

Reduced lung function is significantly associated with symptoms, quality of life, and exercise capacity in COPD patients.[2] Rapid FEV_1 decline and rapid FVC decline are associated with respiratory symptoms and an increased risk of acute exacerbations, garnering attention as

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prognostic factors for COPD progression.[28-31] However, a single indicator such as FEV_1 or FVC may be impacted by several factors such as lung volume and restrictive lung disease,[7,9] beyond lung function, thereby leading to limitations. In addition, the decline in FEV_1 can be influenced by a decrease in FVC. Previous studies have shown that FEV_1 decline can be influenced by FVC (L) in COPD patients[24,32] and general population.[33] On the other hand, our study and another previous study showed that FEV_1/FVC decline rate was not affected by FVC (L) in COPD patients and in general population.[15] Therefore, FEV_1/FVC decline rate may provide a more reliable clinical indicator for assessing disease progression in COPD patients, particularly when FVC is impaired. Indeed, in a previous study, the decline in FEV_1/FVC was more prominent in the emphysema-predominant group, while the decline in FEV_1 and FVC in pre-COPD or GOLD 1 stage COPD was more pronounced in the airway-predominant group.[34] Therefore, FEV_1/FVC decline rate may serve as an indicator of the progression of parenchymal destruction in COPD patients. Considering the association of STAR stage with the prognosis of COPD patients,[11] the decline in FEV_1/FVC can be considered as an important indicator of COPD progression.

The previous Swedish general population study demonstrated a continuous decrease in the odds of any respiratory symptoms with an increase in FEV_1/FVC.[35] Similarly, SGRQ and mMRC deteriorated with the progression of STAR stage in COPDgene cohort.[11] We also observed a significant increase in mMRC, CAT score, and SGRQ-C beyond MCID in rapid FEV_1/FVC decliners. In addition to PROs, we observed a progressive disparity in the proportion of LABA/LAMA usage between rapid and non-rapid FEV_1/FVC decliners throughout the 3-year observation period. There was a gradual and significant increase in LABA/LAMA usage among non-rapid FEV_1/FVC decliners, and a transition to dual bronchodilators was associated with a potentially reduced risk of rapid FEV_1/FVC decline. This suggests that dual bronchodilation, compared to monotherapy, significantly improves FEV_1[36] and lowers the risk of FEV_1/FVC decline. On the other hand, the impact of ICS on the annual change in FEV_1/FVC was not clear. The proposed criteria for recommending ICS use, such as previous exacerbation history and an elevated BEC,[37] did not differ between the two groups in baseline characteristics. However, within the BEC <100 group, there was a higher usage of ICS among rapid FEV_1/FVC decliners. Therefore, it is speculated that both transitioning to dual bronchodilators and inappropriate use of ICS significantly contribute to the notable differences in FEV_1/FVC decline rate. Our findings underscores the role of appropriate inhaled medication selection and adherence in attenuating the lung function decline.

Our study has several limitations. First, air trapping and emphysema can reduce FVC, potentially leading to changes in the FEV_1/FVC ratio.[38] Because of lack of longitudinal information for progression of small airway disease and parenchymal destruction, and therefore, we could not assess the impact of these structural changes on lung function decline. Second, there is a lack of information on comorbid lung disease[39] and environmental[40] or occupational exposures[41] that may influence FEV_1 or FVC, and these factors were not included in the analysis as potential risk factors. Third, some patients were excluded from the present analysis due to markedly aberrant changes observed in their FEV_1/FVC ratios, which were considered statistically as outliers. Within the cohort dataset, the causes for these abrupt fluctuations could not be clarified. These outliers were likely attributed to various factors, such as suboptimal patient conditions during measurement, procedural errors during pulmonary function testing, or inaccuracies in data entry. Regardless of the underlying cause, the extreme variability in these measurements rendered them unreliable for inclusion in the analysis. Fourth, our cohort consisted of patients

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recruited from teaching hospitals, which might have led to a higher likelihood of enrolling high-risk patients compared to the general COPD population.

In conclusion, our study identified a significant correlation between rapid decline in post-BD FEV_1/FVC and specific baseline characteristics, such as low BMI and current smoking, as well as dynamic changes in clinical parameters, including worsened symptoms, accelerated FEV_1 decline, and non-compliance with dual BD therapy in COPD patients. Particularly, noteworthy is the observation that individuals who failed to consistently use LABA/LAMA despite experiencing worsening symptoms were more prevalent among rapid FEV_1/FVC decliners.

SUPPLEMENTARY MATERIALS

Supplementary Fig. 1
Distribution of annual change of FEV_1/FVC.

Supplementary Fig. 2
Quartile classification based on annual change in FEV_1/FVC.

Supplementary Fig. 3
Difference in annual change in FEV_1/FVC between rapid and non-rapid FEV_1/FVC decliners.

Supplementary Fig. 4
Annual FEV_1 and FVC changes in rapid and non-rapid FEV_1/FVC decliners.

Supplementary Fig. 5
Disparities in treatment patterns at baseline and 3-year follow-up between rapid and non-rapid FEV_1/FVC decliners.

Supplementary Fig. 6
Differences in patterns of inhaled corticosteroid usage based on blood eosinophil counts in rapid and non-rapid FEV_1/FVC decliners.

REFERENCES

1. Celli B, Fabbri L, Criner G, Martinez FJ, Mannino D, Vogelmeier C, et al. Definition and nomenclature of chronic obstructive pulmonary disease: time for its revision. *Am J Respir Crit Care Med* 2022;206(11):1317-25. PUBMED | CROSSREF
2. Lee HW, Lee JK, Hwang YI, Seo H, Ahn JH, Kim SR, et al. Spirometric interpretation and clinical relevance according to different reference equations. *J Korean Med Sci* 2024;39(4):e20. PUBMED | CROSSREF
3. Jakeways N, McKeever T, Lewis SA, Weiss ST, Britton J. Relationship between FEV1 reduction and respiratory symptoms in the general population. *Eur Respir J* 2003;21(4):658-63. PUBMED | CROSSREF
4. Han MK, Muellerova H, Curran-Everett D, Dransfield MT, Washko GR, Regan EA, et al. GOLD 2011 disease severity classification in COPDGene: a prospective cohort study. *Lancet Respir Med* 2013;1(1):43-50. PUBMED | CROSSREF
5. Bikov A, Lange P, Anderson JA, Brook RD, Calverley PM, Celli BR, et al. FEV_1 is a stronger mortality predictor than FVC in patients with moderate COPD and with an increased risk for cardiovascular disease. *Int J Chron Obstruct Pulmon Dis* 2020;15:1135-42. PUBMED | CROSSREF
6. Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, et al. Interpretative strategies for lung function tests. *Eur Respir J* 2005;26(5):948-68. PUBMED | CROSSREF

7. Doherty DE. A review of the role of FEV1 in the COPD paradigm. *COPD* 2008;5(5):310-8. PUBMED | CROSSREF
8. Kumar R, Seibold MA, Aldrich MC, Williams LK, Reiner AP, Colangelo L, et al. Genetic ancestry in lung-function predictions. *N Engl J Med* 2010;363(4):321-30. PUBMED | CROSSREF
9. Gardner ZS, Ruppel GL, Kaminsky DA. Grading the severity of obstruction in mixed obstructive-restrictive lung disease. *Chest* 2011;140(3):598-603. PUBMED | CROSSREF
10. Hegewald MJ, Collingridge DS, DeCato TW, Jensen RL, Morris AH. Airflow obstruction categorization methods and mortality. *Ann Am Thorac Soc* 2018;15(8):920-5. PUBMED | CROSSREF
11. Bhatt SP, Nakhmani A, Fortis S, Strand MJ, Silverman EK, Sciurba FC, et al. FEV1/FVC severity stages for chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2023;208(6):676-84. PUBMED | CROSSREF
12. Sin DD. The importance of early chronic obstructive pulmonary disease: a lecture from 2022 Asian Pacific Society of Respirology. *Tuberc Respir Dis (Seoul)* 2023;86(2):71-81. PUBMED | CROSSREF
13. Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. *Thorax* 2006;61(6):472-7. PUBMED | CROSSREF
14. Mannino DM, Reichert MM, Davis KJ. Lung function decline and outcomes in an adult population. *Am J Respir Crit Care Med* 2006;173(9):985-90. PUBMED | CROSSREF
15. Choi KY, Lee HJ, Lee JK, Park TY, Heo EY, Kim DK, et al. Rapid FEV1/FVC decline is related with incidence of obstructive lung disease and mortality in general population. *J Korean Med Sci* 2023;38(1):e4. PUBMED | CROSSREF
16. Liao SY, Lin X, Christiani DC. Occupational exposures and longitudinal lung function decline. *Am J Ind Med* 2015;58(1):14-20. PUBMED | CROSSREF
17. Taylor DR, Fergusson DM, Milne BJ, Horwood LJ, Moffitt TE, Sears MR, et al. A longitudinal study of the effects of tobacco and cannabis exposure on lung function in young adults. *Addiction* 2002;97(8):1055-61. PUBMED | CROSSREF
18. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370(9596):1453-7. PUBMED | CROSSREF
19. Lee JY, Chon GR, Rhee CK, Kim DK, Yoon HK, Lee JH, et al. Characteristics of patients with chronic obstructive pulmonary disease at the first visit to a pulmonary medical center in Korea: the KOrea COpd Subgroup Study team cohort. *J Korean Med Sci* 2016;31(4):553-60. PUBMED | CROSSREF
20. Global Initiative for Chronic Obstructive Lung Disease (GOLD). *Global Strategy for Prevention, Diagnosis and Management of COPD: 2024 Report*. Bethesda, MD, USA: GOLD; 2024.
21. Halpin DM, Decramer M, Celli BR, Mueller A, Metzdorf N, Tashkin DP. Effect of a single exacerbation on decline in lung function in COPD. *Respir Med* 2017;128:85-91. PUBMED | CROSSREF
22. Agustí A, Celli BR, Criner GJ, Halpin D, Anzueto A, Barnes P, et al. Global Initiative for Chronic Obstructive Lung Disease 2023 Report: GOLD executive summary. *Eur Respir J* 2023;61(4):2300239. PUBMED | CROSSREF
23. Bhatt SP, Soler X, Wang X, Murray S, Anzueto AR, Beaty TH, et al. Association between functional small airway disease and FEV1 decline in chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016;194(2):178-84. PUBMED | CROSSREF
24. Lee HW, Lee JK, Lee MG, Shin KC, Ra SW, Kim TH, et al. Risk factors of rapid FEV1 decline in a real-world chronic obstructive pulmonary disease cohort. *Respiration* 2022;101(12):1078-87. PUBMED | CROSSREF
25. Løkke A, Lange P, Scharling H, Fabricius P, Vestbo J. Developing COPD: a 25 year follow up study of the general population. *Thorax* 2006;61(11):935-9. PUBMED | CROSSREF
26. Vogelmeier CF, Criner GJ, Martinez FJ, Anzueto A, Barnes PJ, Bourbeau J, et al. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Lung Disease 2017 Report. GOLD executive summary. *Am J Respir Crit Care Med* 2017;195(5):557-82. PUBMED | CROSSREF
27. Kim J, Yoon HI, Oh YM, Lim SY, Lee JH, Kim TH, et al. Lung function decline rates according to GOLD group in patients with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2015;10:1819-27. PUBMED | CROSSREF
28. Bae J, Lee HJ, Choi KY, Lee JK, Park TY, Heo EY, et al. Risk factors of acute exacerbation and disease progression in young patients with COPD. *BMJ Open Respir Res* 2024;11(1):e001740. PUBMED | CROSSREF
29. Whittaker HR, Pimenta JM, Jarvis D, Kiddle SJ, Quint JK. Characteristics associated with accelerated lung function decline in a primary care population with chronic obstructive pulmonary disease. *Int J Chron Obstruct Pulmon Dis* 2020;15:3079-91. PUBMED | CROSSREF
30. An TJ, Rhee CK, Park YB, Yoo KH, Yoon HK. FVC, but not FEV1, is associated with clinical outcomes of asthma-COPD overlap. *Sci Rep* 2022;12(1):13820. PUBMED | CROSSREF

31. Cukic V, Lovre V, Ustamujic A. The changes of pulmonary function in COPD during four-year period. *Mater Sociomed* 2013;25(2):88-92. PUBMED | CROSSREF

32. Lee HW, Lee JK, Kim Y, Jang AS, Hwang YI, Lee JH, et al. Differential decline of lung function in COPD patients according to structural abnormality in chest CT. *Heliyon (Lond)* 2024;10(7):e27683. PUBMED | CROSSREF

33. Lee HW, Lee HJ, Lee JK, Park TY, Heo EY, Kim DK. Rapid FEV1 decline and lung cancer incidence in South Korea. *Chest* 2022;162(2):466-74. PUBMED | CROSSREF

34. Young KA, Strand M, Ragland MF, Kinney GL, Austin EE, Regan EA, et al. Pulmonary subtypes exhibit differential Global Initiative for Chronic Obstructive Lung Disease spirometry stage progression: the COPDGene® study. *Chronic Obstr Pulm Dis (Miami)* 2019;6(5):414-29. PUBMED | CROSSREF

35. Torén K, Schiöler L, Lindberg A, Andersson A, Behndig AF, Bergström G, et al. The ratio FEV1/FVC and its association to respiratory symptoms-a Swedish general population study. *Clin Physiol Funct Imaging* 2021;41(2):181-91. PUBMED | CROSSREF

36. Rodrigo GJ, Price D, Anzueto A, Singh D, Altman P, Bader G, et al. LABA/LAMA combinations versus LAMA monotherapy or LABA/ICS in COPD: a systematic review and meta-analysis. *Int J Chron Obstruct Pulmon Dis* 2017;12:907-22. PUBMED | CROSSREF

37. Agusti A, Fabbri LM, Singh D, Vestbo J, Celli B, Franssen FM, et al. Inhaled corticosteroids in COPD: friend or foe? *Eur Respir J* 2018;52(6):1801219. PUBMED | CROSSREF

38. Gildea TR, McCarthy K. Pulmonary function testing. In: Cleveland Clinic, editors. *Current Clinical Medicine*. 2nd ed. Cleveland, OH, USA: Saunders; 2010, 1084-1095.e1.

39. Johannson KA, Chaudhuri N, Adegunsoye A, Wolters PJ. Treatment of fibrotic interstitial lung disease: current approaches and future directions. *Lancet* 2021;398(10309):1450-60. PUBMED | CROSSREF

40. Bush A. Impact of early life exposures on respiratory disease. *Paediatr Respir Rev* 2021;40:24-32. PUBMED | CROSSREF

41. Ramírez-Venegas A, Sansores RH, Quintana-Carrillo RH, Velázquez-Uncal M, Hernandez-Zenteno RJ, Sánchez-Romero C, et al. FEV1 decline in patients with chronic obstructive pulmonary disease associated with biomass exposure. *Am J Respir Crit Care Med* 2014;190(9):996-1002. PUBMED | CROSSREF