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Rapid FEV$_1$/FVC Decline Is Related With Incidence of Obstructive Lung Disease and Mortality in General Population

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ABSTRACT

Background: Forced expiratory volume in 1 second (FEV$_1$)/forced vital capacity (FVC) naturally decreases with age; however, an excessive decline may be related with increased morbidity and mortality. This study aimed to evaluate the FEV$_1$/FVC decline rate in the Korean general population and to identify whether rapid FEV$_1$/FVC decline is a risk factor for obstructive lung disease (OLD) and all-cause and respiratory mortality.
Methods: We evaluated individuals aged 40–69 years who underwent baseline and biannual follow-up spirometric assessments for up to 18 years, excluding those with airflow limitations at baseline. Based on the quartiles of the annual FEV$_1$/FVC decline rate, the most negative FEV$_1$/FVC change (1st quartile of annual FEV$_1$/FVC decline rate) was classified as rapid FEV$_1$/FVC decline. We investigated the risk of progression to OLD and all-cause and respiratory mortality in individuals with rapid FEV$_1$/FVC decline.
Results: The annual FEV$_1$/FVC decline rate in the eligible 7,768 patients was 0.32 percentage point/year. The incidence rate of OLD was significantly higher in patients with rapid FEV$_1$/FVC decline than in those with non-rapid FEV$_1$/FVC decline (adjusted incidence rate, 2.119; 95% confidence interval [CI], 1.932–2.324). Rapid FEV$_1$/FVC decline was an independent risk factor for all-cause mortality (adjusted hazard [HR], 1.374; 95% CI, 1.105–1.709) and respiratory mortality (adjusted HR, 1.353; 95% CI, 1.089–1.680).
Conclusion: The annual FEV$_1$/FVC decline rate was 0.32%p in the general population in Korea. The incidence rate of OLD and the hazards of all-cause and respiratory mortality were increased in rapid FEV$_1$/FVC decliners.

Keywords: Cohort Studies; Forced Expiratory Volume; Forced Vital Capacity; Respiratory Function Tests; Mortality; Risk Factors

INTRODUCTION

Obstructive lung disease (OLD) is a chronic respiratory condition characterized by airflow limitation. Airflow limitation is commonly defined as a reduced ratio of forced expiratory

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volume in 1 second (FEV$_1$) to forced vital capacity (FVC). Most airflow limitations are caused by chronic obstructive pulmonary disease (COPD) or asthma, although a broad spectrum of other chronic airway diseases also contribute to airflow limitation.[1] The prevalence of airflow limitation has increased globally,[2] influenced by cigarette smoke and air pollution.[3,4] Airflow limitation is related to increased mortality in not only chronic airway disease such as COPD[5] and asthma,[6] but in lung cancer,[7] chronic infectious disease,[8] chronic non-specific lung disease,[9] and heart failure,[10] and even in general population.[6]

Screening for airflow limitation by spirometric examination has been tried for early detection of OLD.[11] Among the spirometric tests, peak expiratory flow (PEF) and FEV$_1$/FVC have been evaluated as an index for screening of COPD.[12] The AU-ROC of pre-bronchodilator PEF to detect COPD in general population was 0.66 (low-risk subgroup) and 0.76 (high-risk subgroup), which are considered suboptimal for clinical applications.[13] Pre-bronchodilator FEV$_1$/FVC showed a good performance with AU-ROC of 0.84–0.85 for COPD screening only in ever-smokers.[14,15] Most studies for COPD screening cross-sectionally evaluated the accuracy of pre-bronchodilator spirometric indexes, but did not predict the long-term future occurrence of COPD in general population. In addition, there has been a lack of evidence on whether screening for OLD with pre-bronchodilator spirometry affects health-related quality of life or mortality.

In the general population, FEV$_1$/FVC is not a fixed value; it decreases with age.[16] Different decline rates of FEV$_1$/FVC have been reported according to different clinical characteristics. Current or former smokers show a faster FEV$_1$/FVC decline rate than those who have never smoked.[17] An excessive decline in FEV$_1$/FVC has been reportedly related to biologic changes such as airway smooth muscle contraction, hypersecretion, and destruction or remodeling of small airways.[18] Therefore, even if the current state of lung function lies within the normal range, OLD can develop in people with an accelerated decline rate of FEV$_1$/FVC during their lifetime. In addition, a reduced FEV$_1$/FVC was related to a higher risk of all-cause mortality in a multivariable analysis.[19] However, the association between the FEV$_1$/FVC decline rate and all-cause mortality or respiratory mortality has not been sufficiently studied in general population.

In this context, we aimed to evaluate the FEV$_1$/FVC decline rate in the Korean general population and compare the incidence rate of OLD and the risk of all-cause and respiratory mortality between participants with rapid and non-rapid FEV$_1$/FVC decline.

METHODS

Our study has been structured according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[20]

Study design and eligibility criteria

We conducted an observational longitudinal study to evaluate the general population between 40 and 69 years of age with biannual follow-up from 2001 to 2018. We analyzed epidemiologic data and lung function information of two prospective population-based studies (the rural Ansung and urban Ansan cohorts) as sub-cohorts of the Korean Genome Epidemiology Study (KoGES). Detailed information on the study design for the two cohorts has been described in a previous cohort profile report.[21] The eligibility criteria for this study were as follows: 1) presence of spirometric information at baseline examination, and 2)

subsequent follow-up with spirometric evaluation. We excluded the subjects with existing airflow limitation (FEV$_1$/FVC < 0.7) at baseline examination.

Variables and outcomes

For baseline sociodemographic and anthropometric information, we evaluated age, sex, body mass index (BMI), waist circumference, history of cigarette smoking, cigarette pack-years, history of physical exercise, school year, and income. For baseline medical information, underlying comorbid disease and medication history were acquired through protocolized and systematic questionnaires. For baseline lung function information, we evaluated pre-bronchodilator FEV$_1$, FVC, FEV$_1$/FVC (%), and forced expiratory flow between 25% and 75% of vital capacity (FEF$_{25-75}$). A proportion of preserved ratio impaired spirometry (PRISM) was checked. For baseline general medical conditions, we evaluated the results of a complete blood count test and blood laboratory test. The development of OLD was defined using the spirometric criterion for airflow limitation of pre-bronchodilator FEV$_1$/FVC < 0.7. We obtained information on all-cause mortality and specific causes of death from Statistics Korea.

Spirometric data

We calculated the annual FEV$_1$/FVC decline percentage point (%p) for each participant using the Spirometry Longitudinal Data Analysis (SPIROLA) Software (Centers for Disease Control and Prevention, MorganTown, WV, USA).[22] A linear regression slope, which is the beta-coefficient, for each individual was estimated using all available spirometric information from baseline examination to the last follow-up. Follow-up was terminated by death or censoring. We estimated missing FEV$_1$/FVC values by linear interpolation or extrapolation to figure out the year in which FEV$_1$/FVC was expected to decrease to below 0.7.

Definition of rapid decline

As an appropriate definition for rapid FEV$_1$/FVC decline was not found through systematic review, we made an operational definition for rapid FEV$_1$/FVC decline based on the quartiles of the annual FEV$_1$/FVC decline rate. This approach was also used to define rapid FEV$_1$ decline in previous studies.[23-25] The most negative change in FEV$_1$/FVC (1st quartile) was defined as rapid FEV$_1$/FVC decline. The other quartiles (2nd, 3rd, and 4th quartiles) were defined as non-rapid FEV$_1$/FVC decline. The participant with rapid FEV$_1$/FVC decline was referred to as a rapid FEV$_1$/FVC decliner, while the participant with non-rapid FEV$_1$/FVC decline was referred to as a non-rapid FEV$_1$/FVC decliner.

Statistical analysis

We used Student's *t*-test or the Wilcoxon rank-sum test to analyze continuous variables and the chi-square test or Fisher's exact test to analyze categorical variables. A multivariable linear mixed effect model was used to evaluate the clinical factors related to annual FEV$_1$/FVC change. Repeatedly measured lung function was considered as a random effect variable and other variables as fixed effect variables in our linear mixed effect model. We performed a multivariate Poisson regression analysis to compare the incidence rate ratio (IRR) of OLD between the rapid and non-rapid FEV$_1$/FVC decliners. The Cochran–Armitage test for trend was conducted to evaluate the incidence of all-cause mortality across deciles. Kaplan–Meier survival analysis with log-rank test was conducted for all-cause mortality and respiratory mortality. Univariate and multivariate Cox proportional regression analyses were performed to determine whether rapid FEV$_1$/FVC decline is an independent risk factor for all-cause mortality and respiratory mortality. The stepwise variable selection method was applied for the multivariable Poisson regression model or Cox proportional regression model using the R package 'My.stepwise'. The stepwise

variable selection method initially selected variables with $P < 0.05$ in univariable analyses and excluded variables with $P \geq 0.05$ by performing multivariable analysis whenever variables were added one by one. For multivariable Cox regression analyses, adjustment variables including age, sex, BMI, waist circumference, smoking history, income, congestive heart failure, and platelet were used to evaluate all-cause mortality and those including age, sex, smoking history, income, congestive heart failure, total cholesterol were used to evaluate respiratory mortality. $P < 0.05$ was considered statistically significant. The variance inflation factor for significant multicollinearity was > 4.0. R statistical software, version 4.1.0 (R Core Team [2020], Vienna, Austria), was used for all statistical analyses.

Ethics statement

The Institutional Review Board (IRB) Committee of Seoul National University-Seoul Metropolitan Government (SNU-SMG) Boramae Medical Center approved the study protocol (IRB No. 07-2022-10). Our study followed the ethical guidelines of the Declaration of Helsinki in 1975. The Korean Centers for Disease Control and Prevention obtained written informed consent from all patients included in the study.

RESULTS

Among the 10,030 participants, baseline FEV$_1$/FVC was measured in 9,791 and follow-up FEV$_1$/FVC was measured in 8,554. Among the eligible 8,554 participants, we excluded 786 with FEV$_1$/FVC < 0.7 at baseline. Eventually, we included 7,768 participants in this study (**Supplementary Fig. 1**). During the study period, the median number of times that FEV$_1$/FVC was measured was 6 (interquartile range = 3–7) for each patient, and the median annual FEV$_1$/FVC decline rate was 0.32 (interquartile range [IQR] = 0.14–0.54) %p/year (**Supplementary Fig. 2**). Among the eligible 7,768 patients, 1,941 (25.0%) were described as rapid FEV$_1$/FVC decliners, and the remaining 5,827 (75.0%) were described as non-rapid FEV$_1$/FVC decliners.

Demographic and clinical features

Rapid FEV$_1$/FVC decliners were predominantly male, older, and had a lower BMI, a smaller waist circumference, and more cigarette smoking exposure (**Table 1**). Rapid FEV$_1$/FVC decliners also exercised lesser, had a shorter school year, and had less income. We found no significant difference in underlying comorbidities and medication history between the non-rapid and rapid FEV$_1$/FVC decliners. In the baseline spirometric assessment, rapid FEV$_1$/FVC decliners showed a lower FEV$_1$ (%) or FVC (%) but a higher FEV$_1$/FVC than the non-rapid FEV$_1$/FVC decliners (**Table 2**). In the laboratory findings, inflammatory markers such as white blood cell (WBC) count and high-sensitivity C-reactive protein (hs-CRP) levels were higher in the rapid FEV$_1$/FVC decliners.

FEV$_1$/FVC decline and OLD

FEV$_1$/FVC was reduced annually by 0.76 (IQR = 0.63–1.05) %p in rapid FEV$_1$/FVC decliners and 0.24 (IQR = 0.06–0.37) %p in non-rapid FEV$_1$/FVC decliners (**Supplementary Fig. 3**). We found that FEV$_1$ (%) decline rate was faster in rapid FEV$_1$/FVC decliners, while FVC (%) decline rate was similar between rapid and non-rapid FEV$_1$/FVC decliners. Clinical factors related to the annual decline rate of FEV$_1$/FVC are described in **Supplementary Table 1**. Annual FEV$_1$/FVC decline rate was faster with variables including older age, female sex, lower BMI, ex- or current smoker, previous history of chronic lung disease, history of treatment for asthma, higher FEV$_1$ (L), higher FVC (L), lower FEV$_1$/FVC (%), lower FEF$_{25-75}$ (L), higher WBC,

Table 1. Baseline characteristics of non-rapid and rapid FEV$_1$/FVC decliner

Variables	Non-rapid FEV$_1$/FVC decliner (n = 5,827)	Rapid FEV$_1$/FVC decliner (n = 1,941)	P
Age	50.95 ± 8.43	52.60 (9.03)	< 0.001
Male	2,452 (42.1)	1,107 (57.0)	< 0.001
Body mass index, kg/cm^2	25.00 ± 3.02	23.94 ± 3.16	< 0.001
Waist circumference, cm	83.11 ± 8.69	81.78 ± 8.98	< 0.001
Smoking history			
Never smoker	3,808 (65.4)	976 (50.3)	< 0.001
Ex-smoker	889 (15.3)	332 (17.1)	0.057
Current smoker	1,130 (19.4)	633 (32.6)	< 0.001
Pack years			
< 10	4,374 (75.1)	1,188 (61.2)	< 0.001
≥ 10 and < 30	962 (16.5)	465 (24.0)	< 0.001
≥ 30	491 (8.4)	288 (14.8)	< 0.001
Physical exercise ≥ 2/wk	1,806 (31.0)	547 (28.2)	< 0.021
School year ≥ 6 yr	4,701 (69.9)	1,271 (65.5)	< 0.001
Income[a]			
< 873 dollars/mon	1,751 (30.0)	704 (36.3)	< 0.001
873–1,745 dollars/mon	1,750 (30.0)	544 (28.0)	0.099
≥ 1,746 dollars/mon	2,234 (38.3)	665 (34.3)	0.001
Underlying comorbid disease			
Chronic lung disease	113 (1.9)	42 (2.2)	0.604
Cardiovascular disease	73 (1.3)	26 (1.3)	0.859
Congestive heart failure	14 (0.2)	7 (0.4)	0.526
Hypertension	988 (17.0)	328 (16.9)	0.982
Diabetes	1,612 (27.7)	520 (26.8)	0.473
Dyslipidemia	1,728 (29.7)	574 (29.6)	0.981
Cerebrovascular disease	54 (0.9)	13 (0.7)	0.360
Medication history			
Oral corticosteroid	19 (0.3)	1 (0.1)	0.070
Treatment for asthma	27 (0.5)	13 (0.7)	0.359

Data are expressed as mean ± standard deviation or number (percentage).
FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity.
[a]1,000 won is converted into 0.873 dollar.

higher hs-CRP, higher total protein, and lower albumin. Risk factors related to rapid FEV$_1$/FVC decliner were summarized in **Supplementary Tables 2** and **3**. In addition to the effect of cigarette smoking, other risk factors related to rapid FEV$_1$/FVC decliner were older age, male sex, lower BMI, higher baseline FEV$_1$/FVC, higher total protein, and higher HDL cholesterol in the total and never-smoker patients. During the follow-up period, the cumulative incidence of OLD was significantly higher in rapid FEV$_1$/FVC decliners than in non-rapid FEV$_1$/FVC decliners (35.0% vs. 8.5%, $P < 0.001$, **Fig. 1**). Incidence of OLD increased with worsening annual FEV$_1$/FVC decline (Cochran−Armitage test for trend, $P < 0.001$). Adjusted IRR for OLD was significantly increased in rapid FEV$_1$/FVC decliners compared to non-rapid FEV$_1$/FVC decliners (adjusted IRR, 2.118; 95% CI, 1.932–2.324; **Supplementary Table 4**).

All-cause mortality

Rapid FEV$_1$/FVC decliners showed higher all-cause mortality than non-rapid FEV$_1$/FVC decliners (8.0% vs. 3.9%, $P < 0.001$). All-cause mortality increased with worsening annual FEV$_1$/FVC decline (Cochran−Armitage test for trend, $P < 0.001$, **Supplementary Fig. 4**). In the Kaplan−Meier curve, the probability of all-cause mortality was significantly higher in rapid FEV$_1$/FVC decliners (log-rank test $P < 0.001$, **Fig. 2A**). We summarized the unadjusted hazard ratios (HRs) for all-cause mortality according to various clinical variables (**Supplementary Tables 5** and **6**). In the multivariable Cox-regression model using the clinical variables with statistical significance,
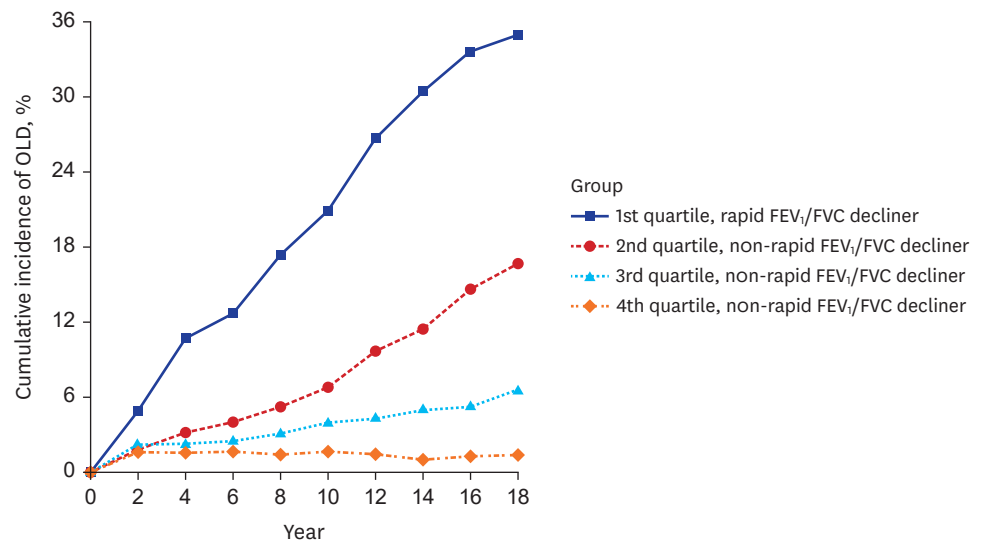
Fig. 1. Cumulative incidence of OLD according to quartiles of FEV$_1$/FVC decline rate measured at two-year intervals. Cumulative incidence of OLD for 18 years was 35.03% in 1st quartile group, 16.67% in 2nd quartile group, 6.59% in 3rd quartile group, and 1.39% in 4th quartile group. There was a linear trend of cumulative incidence of OLD according to quartiles of FEV$_1$/FVC decline rate (P = 0.034).
FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, OLD = obstructive lung disease.

Table 2. Spirometric and laboratory findings at initial assessment

Tests	Non-rapid FEV$_1$/FVC decliner (n = 5,827)	Rapid FEV$_1$/FVC decliner (n = 1,941)	P
Spirometry			
FEV$_1$, L	2.95 ± 0.67	2.99 ± 0.74	0.020
FEV$_1$, % of the predicted value	114.58 ± 16.01	112.28 ± 16.92	< 0.001
FEV$_1$, < 80% of the predicted value	59 (1.0)	45 (2.3)	< 0.001
FVC, L	3.65 ± 0.88	3.64 ± 0.94	0.899
FVC, % of the predicted value	106.15 ± 13.83	101.61 ± 15.04	< 0.001
FEV$_1$/FVC, %	81.12 ± 5.06	82.57 ± 6.58	< 0.001
FEF$_{25-75}$, L	3.17 ± 1.01	3.28 ± 1.13	< 0.001
FEF$_{25-75}$, %	107.56 ± 28.90	110.33 ± 32.27	< 0.001
Blood test			
White blood cells, /uL	6.44 ± 1.74	6.62 ± 1.89	< 0.001
Hemoglobin, g/dL	13.49 ± 1.61	13.81 ± 1.52	< 0.001
Platelet, 10^3/uL	266.32 ± 62.60	265.11 ± 63.63	0.462
hs-CRP, mg/L	0.13 (0.07–0.24)	0.14 (0.06–0.25)	0.017
AST, IU/L	24.6 (20.7–30.0)	25.0 (21.0–30.6)	< 0.001
ALT, IU/L	21.4 (16.1–30.0)	22.0 (16.1–29.9)	0.957
GGT, IU/L	19.0 (13.0–35.0)	21.0 (13.1–38.0)	< 0.001
Total protein, g/dL	6.06 ± 1.39	6.25 ± 1.39	< 0.001
Albumin, g/dL	4.34 ± 0.35	4.38 ± 0.36	< 0.001
BUN, mg/dL	14.14 ± 3.59	14.16 ± 3.64	0.816
Creatinine, mg/dL	0.82 ± 0.19	0.86 ± 0.22	< 0.001
Total cholesterol, mg/dL	194.84 ± 35.12	194.05 ± 36.98	0.397
HDL cholesterol, mg/dL	45.80 ± 10.55	47.40 ± 11.38	< 0.001
LDL cholesterol, mg/dL	120.35 ± 34.26	118.73 ± 36.42	0.076
Triglyceride, mg/dL	159.57 ± 101.14	154.78 ± 103.45	0.073

Data are expressed as mean ± standard deviation, median (interquartile range), or number (percentage).
AST = aspartate aminotransferase, ALT = alanine aminotransferase, BUN = blood urea nitrogen, CRP = C-reactive protein, FEF$_{25-75}$ = forced expiratory flow between 25-75% of vital capacity, FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, GGT = Gamma glutamyl transpeptidase, HDL = high-density lipoprotein, IU = international unit, LDL = low-density lipoprotein.
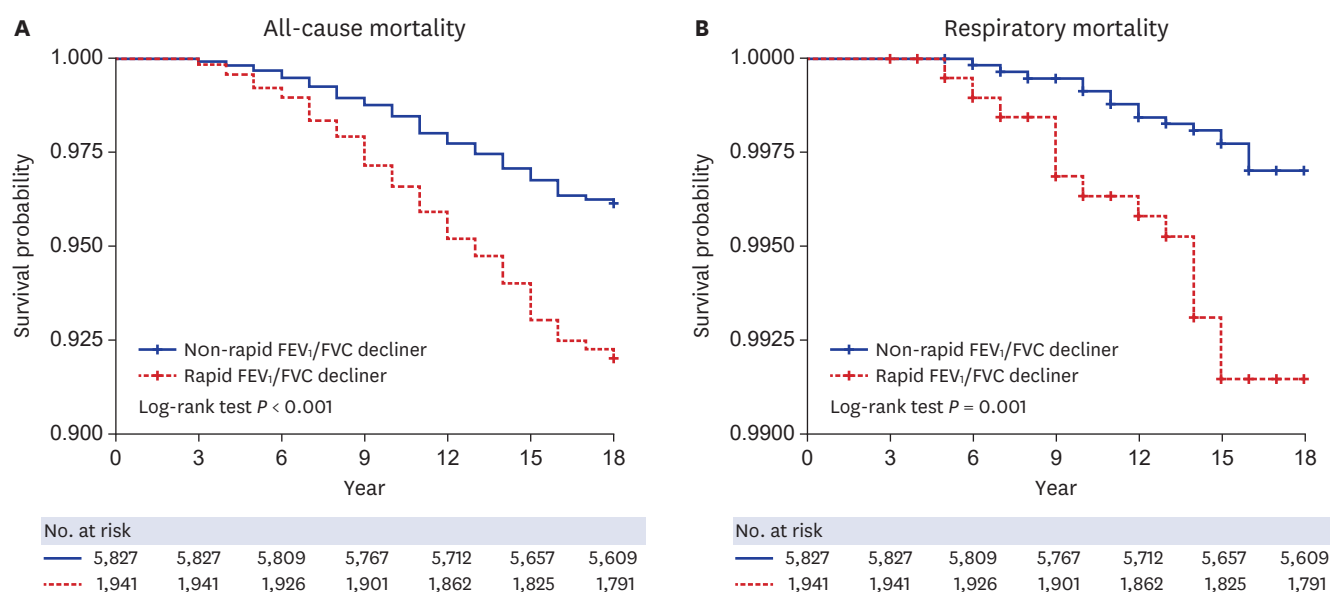
Fig. 2. Kaplan–Meier survival curve for all-cause and respiratory mortality. Survival probability was compared between non-rapid FEV$_1$/FVC decliner and rapid FEV$_1$/FVC decliner in terms of (**A**) all-cause mortality and (**B**) respiratory mortality.
FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity.

Table 3. Independent risk factors for all-cause mortality

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.146 (1.131–1.162)	< 0.001	1.118 (1.101–1.135)	< 0.001
Male	1.698 (1.386–2.080)	< 0.001	1.984 (1.569–2.511)	< 0.001
Body mass index, kg/cm²	0.929 (0.899–0.962)	< 0.001	0.861 (0.813–0.911)	< 0.001
Waist circumference, cm	1.030 (1.018–1.041)	< 0.001	1.057 (1.036–1.078)	< 0.001
Current smoker	1.533 (1.234–1.904)	< 0.001	1.369 (1.066–1.759)	0.014
≥ 10 pack years	1.622 (1.321–1.991)	< 0.001		
Physical exercise ≥ 2/wk	0.638 (0.501–0.813)	< 0.001		
Education history ≥ 6 yr	0.318 (0.259–0.389)	< 0.001		
Income < 873 dollars/mon	5.098 (4.104–6.332)	< 0.001	2.118 (1.660–2.703)	< 0.001
Cardiovascular disease	2.877 (1.655–5.002)	< 0.001		
Congestive heart failure	8.397 (3.975–17.730)	< 0.001	4.038 (1.900–8.580)	< 0.001
Hypertension	1.949 (1.560–2.434)	< 0.001		
Baseline FEV$_1$, L	0.568 (0.485–0.664)	< 0.001		
Baseline FVC, L	0.735 (0.651–0.831)	< 0.001		
Baseline FEV$_1$/FVC, %	0.936 (0.918–0.954)	< 0.001		
Baseline FEF$_{25-75}$, L	0.578 (0.517–0.648)	< 0.001		
Rapid FEV$_1$/FVC decline	2.101 (1.713–2.575)	< 0.001	1.450 (1.178–1.786)	< 0.001
Platelet, 10³/uL	0.996 (0.995–0.998)	< 0.001	0.998 (0.996–0.999)	0.002
hs-CRP, mg/L	1.102 (1.000–1.213)	0.049		
Albumin, g/dL	0.420 (0.311–0.567)	< 0.001		
BUN, mg/dL	1.045 (1.017–1.073)	0.001		
Total cholesterol, mg/dL	0.994 (0.991–0.997)	< 0.001		

FEF$_{25-75}$, % was not included in this multivariable analysis due to multicollinearity with FEV$_1$/FVC, %.
HR = hazard ratio, CI = confidence interval, FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity, FEF$_{25-75}$ = forced expiratory flow between 25–75% of vital capacity, hs-CRP high-sensitivity c-reactive protein, BUN = blood urea nitrogen.

we found that rapid FEV$_1$/FVC decline was independently related to all-cause mortality (adjusted HR, 1.374; 95% confidence interval [CI], 1.105–1.709; *P* = 0.004; **Table 3**).

Respiratory mortality

We found that rapid FEV$_1$/FVC decliners showed higher mortality due to respiratory disease than non-rapid FEV$_1$/FVC decliners (0.8% vs. 0.3%, *P* = 0.003, **Supplementary Table 7**). In the

Table 4. Independent risk factors for respiratory mortality

Variables	Univariable analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Age	1.148 (1.095–1.203)	< 0.001	1.151 (1.098–1.207)	< 0.001
Male	2.099 (1.033–4.266)	0.041	2.599 (1.268–5.326)	0.009
Body mass index, kg/cm^2	0.769 (0.681–0.870)	< 0.001		
Current smoker	2.882 (1.472–5.718)	0.002	3.092 (1.517–6.302)	0.002
≥ 10 pack years	3.069 (1.547–6.089)	0.001		
Physical exercise ≥ 2 /wk	0.314 (0.111–0.894)	0.030		
Education history ≥ 6 yr	0.191 (0.091–0.402)	< 0.001		
Income < 873 dollars/mon	6.028 (2.802–12.970)	< 0.001	5.359 (2.434–11.802)	< 0.001
Chronic lung disease	3.186 (0.763–13.310)	0.112		
Congestive heart failure	14.200 (1.940–103.900)	0.009	13.462 (1.777–101.995)	0.012
Baseline FEV$_1$, L	0.532 (0.309–0.913)	0.022		
Baseline FVC, L	0.692 (0.454–1.055)	0.087		
Baseline FEV$_1$/FVC, %	0.953 (0.894–1.015)	0.135		
Baseline FEF$_{25-75}$, L	0.553 (0.375–0.818)	0.003		
Rapid FEV$_1$/FVC decline	2.889 (1.460–5.718)	0.002	2.151 (1.069–4.328)	0.032
Albumin, g/dL	0.301 (0.105–0.863)	0.026		
Total cholesterol, mg/dL	0.984 (0.974–0.995)	0.003	0.987 (0.976–0.998)	0.024

FEF$_{25-75}$, % was not included in this multivariable analysis due to multicollinearity with FEV$_1$/FVC, %.
HR = hazard ratio, CI = confidence interval, FEF$_{25-75}$ = forced expiratory flow between 25–75% of vital capacity, FEV$_1$ = forced expiratory volume in 1 second, FVC = forced vital capacity.

Kaplan–Meier curve, the probability of respiratory mortality was significantly higher in the rapid FEV$_1$/FVC decliners (log-rank test $P = 0.001$, **Fig. 2B**). We summarized the unadjusted HRs for respiratory mortality according to various clinical variables (**Supplementary Tables 8** and **9**). In the multivariable Cox-regression model using the clinical variables with statistical significance, we found that rapid FEV$_1$/FVC decline was independently related to respiratory mortality (adjusted HR, 2.151; 95% CI, 1.069–4.328; $P = 0.032$; **Table 4**).

DISCUSSION

In our longitudinal study, the subjects without airflow limitation at baseline examinations were classified into rapid and non-rapid FEV$_1$/FVC decliners and observed for up to 18 years. The annual FEV$_1$/FVC decline rate was 0.32%p in the general population, similar to the results of a previous systematic review that reported 0.29%p of FEV$_1$/FVC per year.[16] Compared with non-rapid FEV$_1$/FVC decliners, rapid FEV$_1$/FVC decliners showed two times higher covariate-adjusted incidence rate of OLD; rapid FEV$_1$/FVC decliners had an increased risk of all-cause and respiratory mortality in the multivariable analyses. Annual FEV$_1$/FVC decline rate may be an independent clinical factor related to the incidence of OLD and the risk of mortality in the general population.

Our study suggests that rapid FEV$_1$/FVC decline may be a useful marker for detecting individuals with pre-COPD or those at high risk of developing COPD. Pre-COPD is a recently proposed concept for individuals who are currently without airflow limitation but have the potential to develop airflow limitation in their lifetime.[26] Rapid lung function decline leading to COPD is considered an important feature of pre-COPD.[27,28] Many studies have analyzed annual FEV$_1$ decline to evaluate the progression of airflow limitation; however, it has been limited to identifying when COPD develops or when treatment needs to be considered.[23] In addition, FEV$_1$ decline can worsen without progression of airway disease by factors such as low BMI that affects FVC.[29,30] Therefore, it is speculated that a comprehensive understanding of both FEV$_1$ decline and FEV$_1$/FVC decline would be helpful to find individuals with pre-COPD or make an early diagnosis of COPD.

Distinctive spirometric profiles were found in rapid FEV$_1$/FVC decliners. At baseline, a higher proportion of PRISM was found in rapid FEV$_1$/FVC decliners. This finding is consistent with a previous report that an accelerated FEV$_1$ decline rate was related with PRISM.[31] Considering a lower FVC % and FEV$_{1\%}$, a relatively smaller lung volume was suspected in rapid FEV$_1$/FVC decliners. Although annual FEV$_1$/FVC decline rate was attenuated by a higher baseline FEV$_1$/FVC or FEF$_{25-75}$%, a higher FEV$_1$/FVC or FEF$_{25-75}$ was a risk factor for rapid FEV$_1$/FVC decliners. Similarly, a higher baseline FEV$_1$ function was reportedly related with an accelerated FEV$_1$ decline rate.[32,33] This finding suggests that other clinical factors in participants with a higher baseline FEV$_1$/FVC or FEF$_{25-75}$ would aggravate the FEV$_1$/FVC decline rate.

The relationship between airflow limitation and mortality has been widely investigated.[6] The severity of airflow limitation was positively correlated with all-cause mortality.[34] Even after adjusting physical function and inflammatory and cardiac markers, FEV$_1$/FVC was independently associated with mortality.[35] In particular, decreased FEV$_1$ or worsened airflow limitation was associated with increased cardiovascular mortality.[36] Among the several clinical variables that have been considered to mediate the relationship between airflow limitation and mortality, chronic systemic inflammation might be the most important explanatory factor.[37] Our study is the first to elucidate that although there was no current airflow limitation, the individuals with rapid FEV$_1$/FVC decline had higher risks of all-cause and respiratory mortality. However, only a small proportion of all-cause mortality cases were accounted for by respiratory causes. This finding suggests that the chronic systemic inflammation in rapid FEV$_1$/FVC decliners may significantly affect mortality by causes other than respiratory disease.[38] Recent studies have shown that the susceptibility to airflow limitation by inhaled toxicants varies depending on genetic factors.[39,40] Further research on the genetic variants related to lung function decline rate may provide more plausible information on the biological mechanism between the progression of airflow limitation and mortality.

We found that old age, low BMI, current cigarette smoking, and low platelet count were the independent variables related to an increased risk of mortality and accelerated FEV$_1$/FVC decline. Despite statistical significance, the absolute differences in age, BMI, and platelet count between rapid and non-rapid FEV$_1$/FVC decliners were considered too small to imply clinical importance. A more impressive difference between the two groups was smoking status. Cigarette smoking increased COPD and mortality,[41,42] while smoking cessation improved accelerated lung function decline and reduced mortality.[43] It is commonly suggested that cigarette smoking worsens the FEV$_1$ decline rate through exacerbated airway inflammation, and the FVC decline rate through destruction of lung parenchyma.[44,45] The FEV$_1$ decline seems more dominant than the FVC decline in smokers, considering that FEV$_1$/FVC decline rate was accelerated in smokers with ≥ 10 pack-years.[44] However, our study showed that half of the rapid FEV$_1$/FVC declines were never smokers. Rapid FEV$_1$/FVC decline was still associated with the development of OLD and mortality even after adjusting for smoking status. Therefore, irrespective of smoking status, the FEV$_1$/FVC decline rate would be a biomarker for the development of airflow limitation and mortality.

Several limitations were found in this study. First, we used a fixed ratio of pre-bronchodilator FEV$_1$/FVC as a spirometric criterion for diagnosing OLD. Therefore, it was difficult to distinguish between COPD and asthma, and the incidence of OLD may be overestimated, particularly in young adults.[46,47] Second, a false normal FEV$_1$/FVC decline rate can be observed in certain clinical conditions that mainly worsen FVC, even though there is a definite progression of airflow limitation. In patients with combined pulmonary fibrosis

and emphysema, FEV$_1$ decline was more accelerated, but FEV$_1$/FVC decline was more attenuated than in COPD patients.[48] Therefore, it is necessary to check comorbidities that can continuously worsen FVC, such as interstitial lung disease, when interpreting the FEV$_1$/FVC decline rate. Third, environmental and occupational exposures are important factors that affect FEV$_1$/FVC, but it was not possible to analyze them in our study because relevant data were lacking. In individuals with lower income or educational status, a higher harmful occupational exposure is expected.[49] Considering that socioeconomic status was lower in rapid FEV$_1$/FVC decliners in our study, this group may be more exposed to toxic inhalants.

In conclusion, the annual FEV$_1$/FVC decline rate was 0.32%p in the general population in Korea. The incidence rate of OLD and the hazards of all-cause and respiratory mortality were increased in rapid FEV$_1$/FVC decliners. Further study is necessary to verify the benefit of periodic screening for rapid FEV$_1$/FVC decliners, such as early detection of OLD or prevention of mortality.

ACKNOWLEDGMENTS

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Clinical factors related with annual change of FEV$_1$/FVC (%p/year)

Click here to view

Supplementary Table 2
Independent risk factors related to rapid FEV$_1$/FVC decliner in the total included participants

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Supplementary Table 3
Independent risk factors related to rapid FEV$_1$/FVC decliner in the never-smoker patients

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Supplementary Table 4
Comparison of unadjusted and adjusted incidence rates of OLD between rapid and non-rapid FEV$_1$/FVC decliner

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Supplementary Table 5

Risk evaluation for all-cause mortality according to baseline characteristics

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Supplementary Table 6

Risk evaluation for all-cause mortality according to clinical features

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Supplementary Table 7

Specific cause of death in rapid and non-rapid FEV$_1$/FVC decliner

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Supplementary Table 8

Risk evaluation for respiratory mortality according to baseline characteristics

Click here to view

Supplementary Table 9

Risk evaluation for respiratory mortality according to clinical features

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Supplementary Fig. 1

Flow diagram for inclusion of study participants.

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Supplementary Fig. 2

Distribution of annual change of FEV$_1$/FVC (%p/year).

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Supplementary Fig. 3

Annual FEV$_1$/FVC change from baseline lung function. Annual FEV$_1$/FVC decline is graphically compared between rapid FEV$_1$/FVC decliner and non-rapid FEV$_1$/FVC decliner. Lines represent the mean value of FEV$_1$/FVC and the shaded regions represent the standard error of FEV$_1$/FVC.

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Supplementary Fig. 4

All-cause mortality according to quartiles of FEV$_1$/FVC decline rate. After excluding outlier values, the deciles of FEV$_1$/FVC decline rate (%p/year) were calculated.

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