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Correlation between Telomere Length and Chronic Obstructive Pulmonary Disease–Related Phenotypes: Results from the Chronic Obstructive Pulmonary Disease in Dusty Areas (CODA) Cohort

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Background: Chronic obstructive pulmonary disease (COPD) is a common chronic respiratory disease with increased prevalence in the elderly. Telomeres are repetitive DNA sequences found at the end of the chromosome, which progressively shorten as cells divide. Telomere length is known to be a molecular marker of aging. This study aimed to assess the relationship between telomere length and the risk of COPD, lung function, respiratory symptoms, and emphysema index in Chronic Obstructive Pulmonary Disease in Dusty Areas (CODA) cohort.

Methods: We extracted DNA from the peripheral blood samples of 446 participants, including 285 COPD patients and 161 control participants. We measured absolute telomere length using quantitative real-time polymerase chain reaction. All participants underwent spirometry and quantitative computed tomography scan. Questionnaires assessing respiratory symptoms and the COPD Assessment Test was filled by all the participants.

Results: The mean age of participants at the baseline visit was 72.5±7.1 years. Males accounted for 72% (321 participants) of the all participants. The mean telomere length was lower in the COPD group compared to the non-COPD group (COPD, 16.81±13.90 kb; non-COPD, 21.97±14.43 kb). In COPD patients, 112 (75.7%) were distributed as tertile 1 (shortest), 91 (61.1%) as tertile 2 and 82 (55%) as tertile 3 (longest). We did not find significant associations between telomere length and lung function, exacerbation, airway wall thickness, and emphysema index after adjusting for sex, age, and smoking status.

Conclusion: In this study, the relationship between various COPD phenotypes and telomere length was analyzed, but no significant statistical associations were shown.

Keywords: Telomere Length; Chronic Obstructive Pulmonary Disease; Phenotype

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Introduction

Chronic obstructive pulmonary disease (COPD) is a major and increasing global health problem with large healthcare costs[1]. COPD is a heterogeneous disease, it comprises of emphysema in the lungs parenchyma, large central airway inflammation, mucociliary dysfunction, bronchiolitis, and small airway structural changes[2]. Airflow limitation, measured by reduced forced expiratory volume in 1 second (FEV_1), progresses very slowly over several decades. Therefore most patients with symptomatic COPD are in the late middle-aged or elderly. An accelerated rate of lung function decline with age is one of the central pathophysiological characteristics of COPD. Therefore COPD prevalence increases with age[1].

Telomeres are repetitive DNA sequences, with high G-C content, at the end of chromosome protection. They protect chromosomal ends from being recognized as double-strand breaks and therefore protecting them from end-to-end fusion and degradation[3]. DNA polymerases cannot fully replicate chromosomes, because one RNA primer remains on each daughter DNA strand. This loss of base pairs is a partial consequence of the end-replication problem[4]. Therefore, DNA cannot be duplicated at the end of the chromosome. Each duplication results in a gradual shortening of telomeres, until a critical length is reached at which point cells undergo apoptosis[5]. In addition, exposure to oxidative stress and inflammation aggravates this shortening[6]. Based on this, some studies have shown that telomere length is a biomarker of cellular aging[7,8].

Several studies have shown a significant relationship between reduced telomere length in peripheral blood leukocytes and increased risk of malignancy, cardiovascular disease, and diabetes mellitus[9-11]. In these studies, leukocyte telomere length was used as a biomarker of aging based on the hypothesis that it reflects the physiological age of individuals. Since COPD is an age-dependent process, assessment of telomere length may be useful for better understanding of the disease pathogenesis.

Since COPD is a heterogeneous disease with variable phenotypes[12], in the present study, we assumed that the shorter the telomere length, the more depressed the lung function, and the higher the exacerbation rate and degree of emphysema. Accordingly, this study aimed to assess the relationship between telomere length and the lungs function, exacerbation, and visual assessments of emphysema as well as smoking exposure in a Korean COPD cohort residing near cement plants.

Materials and Methods

1. Study design and population

The Participants of the Chronic Obstructive Pulmonary Disease in Dusty Areas (CODA) cohort were analyzed[13]. The CODA study enrolled participants living near six cement plants in the Kangwon and Chungbuk provinces of South Korea. Overall, 504 participants (362 men and 142 women) were enrolled for baseline examinations between 2012 and 2017 (Figure 1). Twenty-five participants whose chest computed tomography (CT) scans showed signs of pneumoconiosis, bronchiectasis or destroyed lung were excluded, four were without completed questionnaire, five without telomere length results, and 23 with extreme telomere length results. Finally, a total of 446 participants were enlisted as eligible participants.

At baseline examinations, a medical interview and survey questionnaire were administered, and spirometry, physical

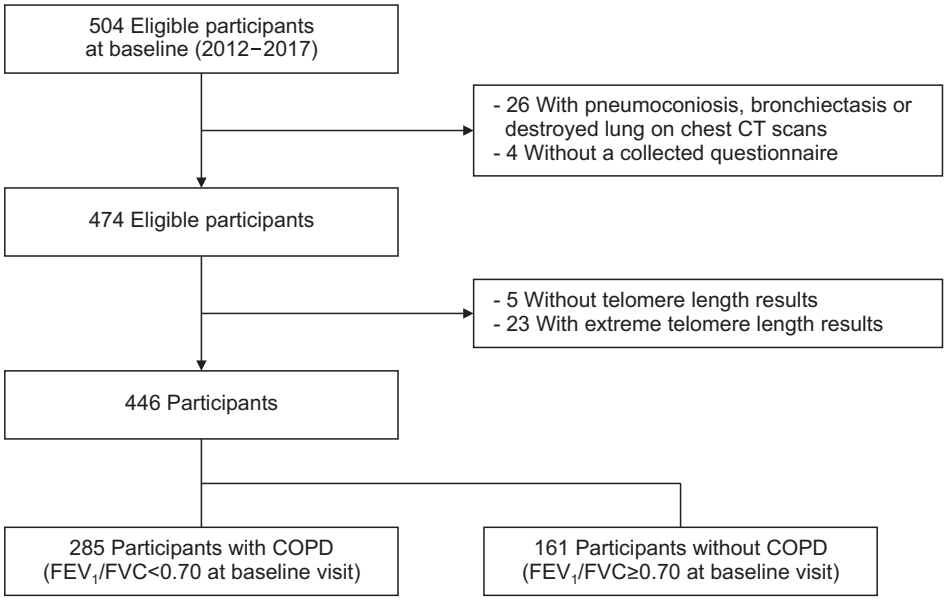

Figure 1. Flowchart of the study population. CT: computed tomography; COPD: chronic obstructive pulmonary disease; FEV_1: forced expiratory volume in 1 second; FVC: forced vital capacity.

examination, blood/urine sampling, and CT were performed for all participants. The questionnaire evaluated demographic factors, lifestyle factors, medical history, exacerbation history, and respiratory symptoms during the past year. We defined moderate exacerbation as a history of antibiotics or steroid use for more than two times, and severe exacerbation as more than one hospitalization due to respiratory symptoms within a year.

A written informed consent was given by each participant. This study also received ethical approval from the Institutional Review Board of Kangwon National University Hospital (KNUH 2020-06-007).

2. Measurement

Dyspnea was evaluated using the modified Medical Research Council (mMRC) scoring system[14]. Quality of life was assessed using a patients-reported COPD Assessment Test (CAT).

Spirometry was measured yearly using the Easy One Kit (NDD Medizintechnik AG, Zurich, Switzerland), before and after inhalation of 400-μg salbutamol. All pulmonary function tests were performed according to the guidelines of the American Thoracic Society/European Respiratory Society[15].

3. CT image analysis

All participants underwent volumetric, thin-section, chest CT at full inspiration and expiration in the supine position. CT images were acquired using a first-generation, dual-source scanner (Somatom Definition, Siemens Healthcare, Forchheim, Germany) in the caudocranial direction using the following parameters: 140 kVp, 100 mA, 0.9–1 beam pitch, and slice thickness of 0.6 mm and 3 mm. The CT data were reconstructed using a soft convolution kernel (B30f)[16]. Emphysema was evaluated by automatically extracting all lung images from the chest wall, mediastinum, and large airways. The attenuation coefficients of pixels in these images were then measured. The emphysema index was defined as the volume fraction (%) of the lung below –950 HU in full inspiration[17]. Mean wall area percentage was calculated as a percentage of the mean values measured in two segmental bronchi (wall area/[wall area+lumen area]×100)[18]. The visually defined subtype of COPD were evaluated by two radiologists (with 3 and 11 years of experience) based on the Fleischner Society classification system[19]. Differences in interpretation were resolved through consensus. The subtype were classified into the following seven types: (1) normal, (2) paraseptal emphysema (subjects with substantial paraseptal emphysema), (3) bronchial airway disease, (4) trace centrilobular emphysema, (5) mild centrilobular emphysema, (6) moderate centrilobular emphysema, and (7) confluent and advanced destructive emphysema[20].

4. Telomere length measurement

Venous blood samples were obtained at baseline and DNA was extracted from the buffy coat. Telomere length was measured in DNA isolated from leukocytes. We modified the Cawthon method for relative measurement of telomere length by introducing an oligomer standard to measure absolute telomere length (aTL). In this approach, aTL was calculated by quantitative polymerase chain reaction according to by O'Callaghan and Fenech method[21], where a standard curve was generated from the fluorescent signals obtained from a series of known concentrations of telomere oligomer DNA (TTAGG ×14). The concentration of each test sample was predicted by plotting the fluorescence signal of the sample onto a standard curve. To serve as a reference gene, the concentration of a single copy gene (36B4) DNA in each sample was measured using the same method. Telomere length was calculated as the ratio of telomere DNA length from the standard curve to the 36B4 DNA length.

The telomere lengths of all samples were normalized to a reference cell line control sample, which was evaluated on each plate. Telomere length measurements (kb/genome) were normalized by natural log-transformation. For analysis, we divided the participants into three tertiles according to their telomere lengths.

5. Statistical analysis

Four hundred and forty-six participants were divided into were divided into two groups; COPD and non-COPD groups. COPD was defined according to GOLD (Global Initiative for Chronic Obstructive Lung Disease) with post-bronchodilator FEV_1/forced vital capacity (FVC) <0.70. For analysis, the telomere length for each group (all participants, COPD group and non-COPD group) were divided into tertile groups. Comparison of baseline characteristics between COPD group and non-COPD group were performed using a Student t test and chi-square test. Categorical variable were described as number (%). Continuous variables were reported as the mean±standard deviation. The lung function, mMRC, and CAT score were evaluated using a general linear model adjusting for age, sex, smoking status, and height. To compare the trend of lung function decline according to the tertile groups, we used a mixed model adjusting for age, sex, and smoking status. Logistic regression was used to find the association between telomere length and COPD exacerbation. Odds ratios (ORs) and 95% confidence intervals (CI) were calculated using logistic regression model after adjusting for sex, age, and smoking status. For trend tests, individuals were categorized according to telomere length tertile (coded 1–3) with the first tertile consisting of individuals with the shortest telomere lengths. Those with p-values less than 0.05 were considered statistically significant. All analyses were performed using SAS

version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

1. Clinical characteristics, respiratory symptoms and lung functions of the all participants and COPD patients

The clinical characteristics, respiratory symptoms, and lung functions of the 446 participants at baseline are summarized in Table 1. There were 285 participants (63.9%) in the COPD group and 161 (36.1%) in the non-COPD group. The average telomere length was 18.68±14.29 kb. The mean telomere length was shorter in the COPD group than in the non-COPD group (COPD, 16.81±13.90 kb; non-COPD, 21.97±14.43 kb). The mean age of participants at the baseline was 72.5±7.1 years and 72% (321 participants) of the cohort were men (Table 1).

We divided the participants into three groups depending on the telomere length (tertile 1, <8.54; tertile 2, 8.54–23.54; tertile 3, >23.54). A total of 285 participants (63.9%) had a FEV_1/FVC <0.70. In COPD patients, 112 (75.7%) were distributed as tertile 1, 91 (61.1%) as tertile 2, and 82 (55%) as tertile 3 (Table

Table 1. Baseline characteristics of the study participants

Characteristic	Total	COPD	Non-COPD	p-value
Participants	446	285 (63.9)	161 (36.1)	
Telomere length, kb	18.68±14.29	16.81±13.90	21.97±14.43	<0.001
Sex				<0.001
Male	321 (72.0)	227 (79.7)	94 (58.4)	
Female	125 (28.0)	58 (20.3)	67 (41.6)	
Age, yr	72.54±7.09	72.86±7.01	71.96±7.22	0.199
Smoking				<0.001
Current	95 (21.3)	74 (26.0)	21 (13.0)	
Former	185 (41.5)	134 (47.0)	51 (31.7)	
None	166 (37.2)	77 (27.0)	89 (55.3)	
Pack-year	17.40±23.36	20.22±25.08	12.26±18.98	0.001
CAT	16.20±9.63	17.11±9.60	14.60±9.50	0.008
mMRC	1.37±1.14	1.47±1.14	1.18±1.10	0.009
Pre-bronchodilator				
FVC, L	2.86±0.80	2.89±0.82	2.79±0.75	0.195
FVC, % predicted	93.46±19.99	92.28±20.86	95.57±18.21	0.095
FEV_1, L	1.86±0.59	1.74±0.58	2.08±0.54	<0.001
FEV_1, % predicted	83.88±23.29	76.19±21.07	97.48±20.73	<0.001
FEV_1/FVC	65.13±11.49	59.78±9.22	74.58±8.68	<0.001
Post-bronchodilator				
FVC, L	2.99±0.80	3.10±0.81	2.81±0.75	0.001
FVC, % predicted	97.74±19.21	98.55±19.36	96.32±18.92	0.239
FEV_1, L	1.94±0.59	1.83±0.57	2.14±0.56	<0.001
FEV_1, % predicted	87.47±22.63	80.10±19.99	100.50±21.15	<0.001
FEV_1/FVC	65.25±11.44	58.84±8.61	76.58±5.45	<0.001
IL-8 (n=359)	18.06±22.31	16.89±18.10	21.27±30.96	0.194
IL-6 (n=359)	2.52±3.48	2.51±3.66	2.57±2.94	0.867
CRP (n=359)	0.28±0.62	0.26±0.59	0.31±0.70	0.475

Values are presented as number (%) or mean±SD and analyzed with the t test or chi-square test.
COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; IL-8: interleukin-8; IL-6: interleukin-6; CRP: C-reactive protein.

Table 2. Clinical demographic characteristics, respiratory symptom and lung function of all participants (n=446)

	Total	Tertile 1 (<8.54)	Tertile 2 (8.54–23.54)	Tertile 3 (>23.54)	Unadjusted p trend	Adjusted p trend
Participants	446	148 (33.2)	149 (33.4)	149 (33.4)		
Telomere length, kb	18.68±14.29	4.73±2.52	15.46±4.53	35.75±9.43	<0.001	
COPD					<0.001	
Yes	285 (63.9)	112 (75.7)	91 (61.1)	82 (55.0)		
No	161 (36.1)	36 (24.3)	58 (38.9)	67 (45.0)		
Sex					0.437	
Male	321 (72.0)	112 (75.7)	106 (71.1)	103 (69.1)		
Female	125 (28.0)	36 (24.3)	43 (28.9)	46 (30.9)		
Age, yr	72.54±7.09	72.96±6.86	71.85±7.39	72.80±7.02	0.346	
Smoking					0.150	
Current	95 (21.3)	41 (27.7)	26 (17.5)	28 (18.8)		
Former	185 (41.5)	61 (41.2)	64 (42.9)	60 (40.3)		
None	166 (37.2)	46 (31.1)	59 (39.6)	61 (40.9)		
Pack-year	17.40±23.36	21.28±25.45	14.05±18.87	16.97±24.82	0.029	
CAT	16.20±9.63	16.74±0.91	16.17±0.93	15.79±0.93	0.772	0.697
mMRC	1.37±1.14	1.31±0.11	1.38±0.11	1.33±0.11	0.863	0.855
Pre-bronchodilator						
FVC, L	2.86±0.80	2.73±0.06	2.77±0.07	2.83±0.06	0.943	0.369
FVC, % predicted*	93.46±19.99	94.16±1.79	93.53±1.84	97.07±1.82	0.176	0.249
FEV_1, L	1.86±0.59	1.76±0.05	1.82±0.05	1.88±0.05	0.410	0.143
FEV_1, % predicted*	83.88±23.29	83.50±2.02	83.78±2.08	88.66±2.05	0.034	0.077
FEV_1/FVC	65.13±11.49	64.19±1.00	66.03±1.03	66.90±1.02	0.031	0.096
Post-bronchodilator						
FVC, L	2.99±0.80	2.89±0.06	2.87±0.06	2.97±0.06	0.793	0.284
FVC, % predicted*	97.74±19.21	99.38±1.73	96.80±1.78	101.64±1.76	0.081	0.086
FEV_1, L	1.94±0.59	1.84±0.05	1.89±0.05	1.96±0.05	0.492	0.135
FEV_1, % predicted*	87.47±22.63	87.23±1.98	86.68±2.03	92.20±2.01	0.027	0.052
FEV_1/FVC	65.25±11.44	63.84±1.01	65.94±1.03	66.66±1.02	0.213	0.072
IL-8 (n=263)	16.89±18.10	16.82±17.86	15.73±13.28	18.37±22.92	0.664	
IL-6 (n=263)	2.51±3.66	2.56±4.18	2.71±3.49	2.19±2.95	0.668	
CRP (n=263)	0.26±0.59	0.27±0.58	0.29±0.73	0.22±0.41	0.740	
Exacerbation						
Moderate	10 (3.5)	3 (2.7)	3 (3.3)	4 (4.9)	0.707	
Severe	13 (4.6)	4 (3.6)	4 (4.4)	5 (6.1)	0.704	
Moderate or severe	18 (6.3)	6 (5.4)	6 (6.6)	6 (7.3)	0.850	

Values are presented as number (%) or mean±SD and analyzed with the t test or chi-square test.
Study participants were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest.
Adjusted variables: sex, age, smoking status, height.
*Adjusted variables: sex, age, smoking status.
COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; IL-8: interleukin-8; IL-6: interleukin-6; CRP: C-reactive protein.

2). There were no statistically significant associations between lung function and telomere length after adjusting for sex, age, and smoking status. However, shorter telomere length showed the tendencies that decreased FVC at pre-bronchodilator and FVC, FVC % predicted at post-bronchodilator in COPD patients (p trend, 0.217, 0.157, and 0.319, respectively) (Table

Table 3. Clinical demographic characteristics, respiratory symptom and pulmonary function of COPD patients (n=285)

		Tertile 1* (<7.39)	Tertile 2* (7.39–20.58)	Tertile 3* (>20.58)	Unadjusted p trend	Adjusted p trend
Participants	285	95 (33.3)	95 (33.3)	95 (33.3)		
Telomere length	18.68±14.29	4.11±2.30	12.89±4.13	33.44±10.17	<0.001	
Sex					0.206	
Male	227 (79.6)	79 (83.2)	70 (73.7)	78 (82.1)		
Female	58 (20.4)	16 (16.8)	25 (26.3)	17 (17.9)		
Age	72.86±7.01	73.29±7.04	72.69±7.32	72.61±6.73	0.768	
Smoking					0.215	
Current	74 (26.0)	28 (29.5)	25 (26.3)	21 (22.1)		
Former	134 (47.0)	48 (50.5)	38 (40.0)	48 (50.5)		
None	77 (27.0)	19 (20.0)	32 (33.7)	26 (27.4)		
Pack-year	20.30±25.08	25.31±27.03	15.05±19.10	20.71±27.44	0.020	
CAT	17.11±9.60	16.87±1.18	17.57±1.21	16.67±1.27	0.680	0.886
mMRC	1.47±1.14	1.36±0.14	1.56±0.14	1.43±0.15	0.283	0.697
Pre-bronchodilator						
FVC, L	2.89±0.82	2.77±0.08	2.88±0.09	2.89±0.09	0.823	0.217
FVC, % predicted†	92.28±20.86	93.86±2.44	96.56±2.41	96.37±2.53	0.525	0.403
FEV_1, L	1.74±0.58	1.68±0.06	1.74±0.06	1.72±0.07	0.962	0.593
FEV_1, % predicted†	76.19±21.07	77.55±2.47	79.66±2.44	77.90±2.56	0.637	0.908
FEV_1/FVC	59.79±9.22	60.31±1.09	60.10±1.08	59.51±1.13	0.853	0.552
Post-bronchodilator						
FVC, L	3.10±0.81	2.93±0.08	3.00±0.08	3.06±0.08	0.517	0.157
FVC, % predicted†	98.55±19.36	99.22±2.28	100.67±2.25	102.23±2.37	0.562	0.319
FEV_1, L	1.83±0.57	1.76±0.06	1.79±0.06	1.81±0.06	0.734	0.512
FEV_1, % predicted†	80.10±19.99	81.25±2.35	82.12±2.32	81.66±2.45	0.881	0.889
FEV_1/FVC	58.84±8.61	59.46±1.02	59.33±1.01	58.97±1.06	0.931	0.695
IL-8 (n=263)	16.89±18.10	17.10±19.12	16.35±12.85	17.24±21.65	0.941	
IL-6 (n=263)	2.51±3.66	2.51±4.27	2.91±3.67	2.06±2.78	0.311	
CRP (n=263)	0.26±0.59	0.25±0.54	0.33±0.77	0.20±0.38	0.378	
Exacerbation						
Moderate	10 (3.5)	3 (3.2)	3 (3.2)	4 (4.2)	0.902	
Severe	13 (4.6)	4 (4.2)	4 (4.2)	5 (5.3)	0.923	
Moderate or severe	18 (6.3)	6 (6.3)	6 (6.3)	6 (6.3)	-	

Values are presented as number (%) or mean±SD and analyzed with the t test or chi-square test.
Adjusted variables: sex, age, smoking status, height.
*COPD patients were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest. †Adjusted variables: sex, age, smoking status.
COPD: chronic obstructive pulmonary disease; CAT: COPD Assessment Test; mMRC: modified Medical Research Council; FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; IL-8: interleukin-8; IL-6: interleukin-6; CRP: C-reactive protein.

3). In the non-COPD group, shorter telomere length in tertile showed tendencies of decreased FEV_1/FVC at pre-bronchodilator and post-bronchodilator (p trend, 0.03 and 0.005, respectively) (Supplementary Table S1).

2. The relationship between telomere length and lung function decline

In all participants and COPD patients, shorter telomere length in tertile was associated with decreased FVC L at pre-bronchodilator (p trend, <0.001 and <0.001, respectively) (Tables 4, 5). In non-COPD group, longer telomere length in tertile showed tendencies of increased FVC L at post-bronchodilator (p trend, <0.001) (Supplementary Table S2).

3. The relationship between telomere length and visual and quantitative CT imaging features

Of the 446 participants, 25 were excluded from the visual assessment of the CT scans due to severe lung distortion and other lung morbidity. Finally, we analyzed 421 participants. Among the 285 patients with COPD, 13 were excluded from the visual assessment of CT scans; only 272 patients were included in the analysis. There were no statistically significant associations between telomere length and emphysema index, mean wall area, and CT subtypes in all participants and COPD patients (Table 6, Supplementary Table S3). In non-COPD participants, decreasing telomere length was associated with increased mean wall area (p trend, 0.415) (Supplementary Table S4).

4. The relationship between telomere length and acute exacerbation

We did not establish a significant association between telomere length and COPD exacerbation in COPD patients. In multivariable analyses, OR for the shortest versus the longest telomere tertile was 0.707 (95% CI, 0.153–3.274) for moderate exacerbation and 0.788 (0.203–3.057) for severe exacerbation (Table 7).

Discussion

We investigated the relationship between telomere length and the lung function, respiratory symptoms, emphysema

Table 4. Change in FVC and FEV_1 according to telomere length (all participants, n=446)

	Tertile 1 (<8.54)	Tertile 2 (8.54–23.54)	Tertile 3 (>23.54)	p trend
Pre-bronchodilator				
FVC, mL/yr	−4.294±1.707	−5.086±1.898	−6.044±2.187	<0.001
FEV_1, mL/yr	−2.675±1.692	−3.796±1.820	−3.304±2.000	0.736
Post-bronchodilator				
FVC, mL/yr	−2.467±1.577	−3.480±1.737	−2.578±1.990	0.952
FEV_1, mL/yr	−2.199±0.903	−2.709±0.975	−1.364±1.094	0.409

Study participants were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest.
Adjusted variables: sex, age, smoking status, height.
FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second.

Table 5. Change in FVC and FEV_1 according to telomere length (COPD patients, n=285)

	Tertile 1* (<7.39)	Tertile 2* (7.39–20.58)	Tertile 3* (>20.58)	p trend
Pre-bronchodilator				
FVC, mL/yr	−5.652±2.004	−6.358±2.248	−7.346±2.706	<0.001
FEV_1, mL/yr	−3.297±2.005	−5.225±2.197	−4.206±2.477	0.679
Post-bronchodilator				
FVC, mL/yr	−5.003±1.900	−5.368±2.114	−4.606±2.518	0.856
FEV_1, mL/yr	−2.463±0.975	−2.958±1.078	−1.998±1.269	0.674

Adjusted variables: sex, age, smoking status, height.
*COPD patients were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest.
FVC: forced vital capacity; FEV_1: forced expiratory volume in 1 second; COPD: chronic obstructive pulmonary disease.

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Table 6. The association between telomere length and visual and quantitative CT imaging features in all participants (n=421)

Variable	Total		Tertile 1 (<8.54)		Tertile 2 (8.54–23.54)		Tertile 3 (>23.54)		p trend
	No. (%)	Mean±SD	No. (%)	Mean±SD	No. (%)	Mean±SD	No. (%)	Mean±SD	
Participants	421		142 (33.7)		139 (33.0)		140 (33.3)		
Emphysema index		5.69±6.55		6.22±6.35		5.33±5.84		5.51±7.38	0.486
Mean wall area, %		68.85±5.19		69.85±0.56		68.95±0.63		70.79±0.68	0.669
CT subtype									
Normal	199 (47.3)	19.02±1.27	55 (38.7)	4.31±0.96	67 (48.2)	15.20±0.92	77 (55.0)	34.67±0.87	
PSE	30 (7.1)	15.18±2.75	14 (9.9)	5.19±2.51	10 (7.2)	16.64±2.22	6 (4.3)	34.09±3.09	
Bronchial	10 (2.4)	24.11±4.47	0 (0)		5 (3.6)	15.90±5.21	5 (3.6)	33.78±5.93	
Trace	48 (11.4)	14.94±2.17	23 (16.2)	2.10±1.58	12 (8.6)	15.22±1.86	13 (9.3)	34.43±1.93	
Mild	82 (19.5)	16.90±1.75	29 (20.4)	4.63±1.48	32 (23.0)	12.81±1.62	21 (15.0)	35.33±1.74	
Moderate	38 (9.0)	18.01±2.44	17 (12.0)	4.61±2.95	11 (7.9)	16.42±3.77	10 (7.1)	38.50±3.75	
Confluent and advanced	14 (3.3)	23.90±3.94	4 (2.8)	0.64±5.32	2 (1.4)	11.38±5.78	8 (5.7)	35.47±3.14	
p trend		0.179		0.537		0.518		0.830	

Study participants were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest.
Adjusted variables: sex, age, smoking status.
CT: computed tomography; SD: standard deviation; PSE: paraseptal emphysema.

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Table 7. The OR of exacerbation according to telomere length (COPD patients, n=285)

	Moderate	Severe	Moderate or severe
Telomere length			
Tertile 1* vs. tertile 3*	0.707 (0.153–3.274)	0.788 (0.203–3.057)	0.997 (0.307–3.241)
Tertile 2* vs. tertile 3*	0.681 (0.146–3.184)	0.781 (0.200–3.050)	0.966 (0.295–3.157)
p-value	0.859	0.919	0.998

Adjusted variables: sex, age, smoking status, height.
*COPD patients were divided into three groups based on telomere length, with the first tertile being the shortest and the third tertile being the longest.
OR: odds ratio; COPD: chronic obstructive pulmonary disease.

extent, and airway wall thickness in a Korean COPD cohort living near cement plants. Disappointingly, we did not observe significant associations between telomere length and lung function, exacerbation, airway wall thickness, and emphysema index after adjusting for sex, age, and smoking status. However, although no statistical significances have been shown, some tendencies were shown along the telomere length tertile. It was shown that FEV_1/FVC (pre-, post-bronchodilator) decreased with shorter telomere length in all participants and in the non-COPD group. The shorter telomere length was shown to decrease FVC (pre-, post-bronchodilator) in COPD group. In all participants and COPD patients, the shorter the telomere length, the lower the FVC (pre-bronchodilator), indicating a decline in the lung function change. On the other hand, in the non-COPD group, the shorter the telomere length, the lower the FVC (post-bronchodilator), indicating an increase in the lung function change. In addition, the shorter the telomere length, the wider the mean wall area in non-COPD group.

COPD is an age-related disease. An accelerated rate of lung function decline with age is one of the central pathophysiological characteristics of COPD. Previous studies have shown that leukocyte telomeres can be like biomarkers in cellular aging[7,22,23]. Some studies have shown that decreased leukocyte telomere length is associated with a decline in lung function[24,25]. In our study, some tendencies between short telomere length and decreased lung function were shown, but they were not statistically significant.

Rode et al. reported that FEV_1, FVC and FEV_1/FVC decreased with decreasing telomere length quartile (p trend, 5×10^{-51}, 5×10^{-35}, and 6×10^{-137}, respectively) but the associations attenuated after age and multivariable adjustments. In addition, participants with shorter telomeres were 2.06-fold more likely to develop COPD. The results showed that short telomere length is associated with reduced lung function and an increased prevalence of COPD[6]. Furthermore, data from seven studies demonstrated highly significant positive association between telomere length and spirometric measurements including FEV_1 (β=0.0455, $p=1.07\times10^{-7}$ with fixed and random effects; I^2=0%), FVC (β=0.0401, $p=2.07\times10^{-7}$ with fixed and random effects; I^2=0%), and FEV_1/FVC (β=0.0238, $p=5.27\times10^{-7}$ with fixed and random effects; I^2=0%)[25].

One study reported that shorter leukocyte telomere length may be a biomarker associated with a poor clinical prognosis in COPD, where short telomere length was associated with reduced quality of life and increased risk of exacerbation and mortality in patients with moderate-to-severe COPD[26]. However, our study did not show any relationship between acute COPD exacerbation and telomere length.

No significant associations were found between the emphysema index, mean wall area and telomere length in the all participants and COPD patients (p trend, 0.486, 0.669, 0.553, and 0.328, respectively). In the sub-analysis, the correlation of the average telomere length and emphysema CT subtype did not show a statistically significant trend in all participants and COPD group (p trend, 0.179 and 0.390, respectively). In addition, we did not observe any association between telomere length and airway wall thickness, emphysema index and visual CT image features in non-COPD group. However, we established that the shorter the telomere length, the wider the mean wall area in non-COPD group.

The MESA (Multi-Ethnic Study of Atherosclerosis) study found that the presence of centrilobular and panlobular emphysema correlated with increased dyspnea and reduced exercise capacity[27]. Airway wall thickness correlated with reduced lung function and increased symptoms in smoker in a cross-sectional study[28]. Image biomarkers have been useful predictors of disease progression. As shown earlier, previous studies showed that telomeres were shorter in peripheral leukocytes of COPD patients and have been related to lung function. However, we did not find other studies on the relationship between CT-based visual assessments and telomere length.

Smoking is a well-known environmental factor that promotes aging and cellular senescence[29]. A large population study showed that a smoking history and the cumulative pack-years were associated with telomere length in 46,396 adults[30]. Another study found that smoking promotes shortening of telomere length. Within the same age range, telomere length decreased with age in smokers, irrespective of the presence or

absence of COPD (p=0.05, r=–0.27). The influence of cumulative smoking exposure on telomere length is further supported by the significant dose-effect relationship demonstrated between pack-years and telomere length (p<0.001, r=–0.45)[31]. In this study, when analyzing the relationship between telomere length and pack-year (p trend, 0.029 and 0.020, respectively), we observed statistical significances, but we did not establish a trend in all participants and COPD patients.

It is worth noting that this is the first study to examine the relationship between telomere length and the phenotypes of COPD in Koreans. Our study investigated the relationship between telomere length and the extent of emphysema, airway wall thickness, and visual assessment on CT scans. Some studies have demonstrated that emphysema as assessed by CT imaging is a good predictor of mortality in COPD patients at various stages of the disease. Although it is still unclear whether emphysema predisposes COPD patients to such systemic manifestations and whether these systemic manifestations contribute to the development of emphysema, it is apparent that recognizing the extent of emphysema is important in evaluating COPD. Taken together, the evaluation of emphysema seems to be beneficial in the management of COPD[32].

Nevertheless, this study has several limitations. First, the small sample size resulted in limited power to detect differences between telomere length and COPD-related phenotypes. Further large-scale studies with longer follow-up periods involving several serial assessments are needed to validate our findings.

Second, telomere length is a complex characteristic that is shaped by several factors, including genetic, epigenetic, lifestyle and environmental determinants. The complex interactions of these factors remain unclear[33]. The association between telomere length and environmental, occupational, and medical risk factors has been reported in several cross-sectional epidemiological studies[34,35]. However, this study did not consider such environmental and occupational factors. This study consisted participants living in dusty areas near cement plants, thus the results might differ from the general COPD populations. In CODA cohort study, we have records of exposure such as air pollution (PM_{10}, NO_2); however, additional analysis could not be carried out due to insufficient number of participants.

Third, we measured the leukocyte telomere length. Regarding this point, it is important to note that a correlation between lung and blood telomere length has not been unequivocally demonstrated. This suggests that the associations between telomere length and various diseases cannot easily be interpreted as causative relationship.

In conclusion, the correlation between lung function, respiratory symptoms, or extent and visual assessment and telomere length were analyzed, we did not find statistically significant results. Further studies are needed on the role of telomere length in COPD pathogenesis, as well as the relationship between telomere length and environmental factors including air pollution.

Authors' Contributions

Conceptualization: Kim WJ, Moon DH. Methodology: Kim WJ, Moon DH, Kim J. Formal analysis: Lim MN. Data Curation: Lim MN. Software: Lim MN. Validation: Lim MN, Kim WJ, Moon DH. Investigation: Kim WJ, Moon DH, Kim J. Writing – original draft preparation: Moon DH, Kim WJ. Writing – review and editing: Moon DH, Kim J, Lim MN, Bak SH, Kim WJ. Approval of the final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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Supplementary Material

Supplementary material can be found in the journal homepage (http://www.e-trd.org).

Supplementary Table S1. Clinical demographic characteristics, respiratory symptom and pulmonary function of non-COPD patients (n=161).

Supplementary Table S2. Change in FVC and FEV_1 according to telomere length (non-COPD patients, n=161).

Supplementary Table S3. The association between telomere length and visual and quantitative CT imaging features in COPD patients (n=272).

Supplementary Table S4. The association between telomere length and visual and quantitative CT imaging features in non-COPD participants (n=149).

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