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Impact of Body Mass Index Change on the Prognosis of Chronic Obstructive Pulmonary Disease

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Keywords
Chronic obstructive pulmonary disease · BMI · Exacerbation · Mortality

Abstracts
Background: Low body mass index (BMI) is an important prognostic factor in chronic obstructive pulmonary disease (COPD). However, the prognostic value of longitudinal BMI change in COPD has not been well studied. ***Objective:*** We aimed to evaluate the association between longitudinal change of BMI and prognosis of COPD in Korean COPD cohort. ***Methods:*** This study was conducted in a prospective Korean Obstructive Lung Disease (KOLD) cohort where COPD patients were recruited on an outpatient basis at 17 hospitals in South Korea. Annual BMI was measured over a period of 3 years or more. All patients were categorized into underweight (UW), normal weight (NW), and overweight (OW) groups by BMI. Clinical characteristics and outcomes including exacerbation and mortality were compared based on initial BMI grade and longitudinal change of BMI. ***Results:*** This analysis included 537 COPD patients (mean age = 67.4 ± 7.9 years, male = 97.0%, mean BMI = 23.0 ± 3.1) of KOLD cohort. The proportions of UW, NW, and OW groups were 6.9% (n = 37), 68.9% (n = 370), and 24.2% (n = 130) respectively. The UW group showed lower forced expiratory volume in 1 s (FEV_1) ($p < 0.001$), shorter 6-minute walk distance ($p < 0.001$), higher modified Medical Research Council score ($p = 0.002$), higher St. George Respiratory Questionnaire score ($p < 0.001$), higher emphysema index ($p < 0.001$) and air-trapping index ($p < 0.001$), and more frequent ($p < 0.001$) and severe exacerbations ($p = 0.003$). Multivariable analyses demonstrated that decrease of BMI (hazard ratio [HR] = 0.786, $p = 0.038$) and the descent of BMI group (HR = 3.167,

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p = 0.016) at 3-year follow-up along with age, initial BMI, post-bronchodilator FEV_1, and severe exacerbations were significantly associated with mortality. ***Conclusions:*** This study demonstrated that BMI decrease during follow-up was independently associated with exacerbation and higher mortality of COPD, suggesting BMI reduction in COPD should be carefully managed.

Introduction

Chronic obstructive pulmonary disease (COPD) characterized by airflow limitation is accompanied by several comorbidities contributing to mortality due to systemic inflammation [1–4]. In COPD, increased metabolic demands followed by basal oxygen consumption and the release of cachexia-producing cytokines such as tumor necrosis factor α and interleukin-6 often result in malnutrition [5, 6]. Previous studies suggested that body mass index (BMI) reflecting nutritional status in COPD is associated with poor prognosis and high mortality [7–9]. BODE index, including BMI along with airflow obstruction, dyspnea, and exercise is reported to be better than forced expiratory volume in 1 s (FEV_1) for the prediction of the risk of death from any cause and from respiratory causes in COPD [10].

Usually, obesity is recognized as a risk factor for insulin resistance, obstructive sleep apnea, and cardiovascular disease [11–13]. However, a recent meta-analysis showed that being overweight (OW) has a protective effect with a lower risk of all-cause mortality in COPD patients [14]. This obesity paradox based on a protective effect of adipose tissue against mortality has been observed in various chronic diseases, including cardiovascular disease, chronic heart failure, and diabetes mellitus [11, 12, 15].

Nonetheless, the role of BMI with regard to prognosis in an Asian COPD population is not well known and should be further validated. Asian populations have a higher risk of developing comorbidities such as diabetes and cardiovascular disease even within normal BMI range of 18.5–24.9 by World Health Organization (WHO) guidelines [13]. In addition, the association between BMI and body fat percentage in Asians is different from that observed in Europeans; for the same BMI, Asians have a higher percentage of body fat than non-Asians [16]. Accordingly, BMI data obtained from Western populations may not be generalized to Asian population. Previous studies have usually focused on the prognostic value of a single BMI measurement in COPD [7–10]. Hence, this study was conducted to evaluate the prognostic value of longitudinal BMI change in Korean COPD population by exploring the impact of longitudinal BMI changes on the survival and exacerbations of COPD.

Materials and Methods

Study Design

Patients

This study was undertaken using the Korean Obstructive Lung Disease (KOLD) cohort which consisted of 664 patients with COPD or asthma enrolled from pulmonary clinics of 17 hospitals throughout Korea between June 2005 and May 2017. In this KOLD cohort, 537 COPD patients were enrolled by the following 3 criteria: more than 10 pack-years of smoking history; post-bronchodilator ratio of FEV_1 to forced vital capacity <0.7 after administration of 400 μg of inhaled albuterol; and no or minimal abnormality on chest radiography.

During follow-up, each patient regularly visited the outpatient clinic every 3 months. BMI was calculated as the body weight divided by the height squared (kg/m^2) and categorized into 4 groups according to WHO guidelines: underweight (UW) (<18.5 kg/m^2, n = 37), normal weight (NW) (18.5–24.9 kg/m^2, n = 370), OW (25.0–29.9 kg/m^2, n = 130), and obese (>30 kg/m^2) [13]. The obesity group was small (n = 7) and so was included in the OW group in the analysis.

Collection of Clinic-Physiologic Data in the KOLD Cohort

The demographic and clinical data, including age, sex, smoking, BMI, Charlson's comorbidity score, and previous history of exacerbations within 1 year were collected. Dyspnea was assessed by the modified Medical Research Council (mMRC) Dyspnea Scale [17]. Health-related quality of life was assessed by the St. George Respiratory Questionnaire (SGRQ) [18]. Pre- and post-bronchodilator spirometry, diffusing capacity, lung volume using V_{max22} (SensorMedics, Yorba Linda, CA, USA; PFDX instrument; MedGraphics, St Paul, MN, USA) and 6-minute walk test were performed according to American Thoracic Society guidelines [19].

BMI, medication history, smoking status, mMRC score, and acute exacerbation history were obtained at each visit. Pre- and post-bronchodilator spirometry was performed with 6-month intervals; diffusing capacity, lung volume, 6-minute walk test, and SGRQ score were performed annually [20]. The mean follow-up duration is 5.93 ± 3.96 years (range: 0.02–13.60 years).

The difference between BMI at enrollment and 3-year follow-up was classified based on quartiles. Longitudinal changes of the BMI group at 3-year follow-up were classified as (1) ascent, (2) no change, and (3) descent according to the change of BMI grouping from enrollment and subsequent BMI group at 3-year follow-up.

Chest Computed Tomography Indices for COPD Assessment

All patients underwent volumetric computed tomography (CT) scans at full inspiration and expiration with a 16-MDCT scanner (the Somatom Sensation 16, Siemens Medical Solutions, Forchheim, Germany; the GE Lightspeed Ultra, General Electric Healthcare, Milwaukee, WI, USA; orthe Philips Brilliance 16, Philips Medical Systems, Best, Netherlands) [21]. The emphysema index, CT air-trapping index, and airway dimensions were determined from chest CT data as in Supplement [21–24].

Table 1. Baseline characteristics of the subjects and comparison according to BMI

Parameter (N = 537)	Total (n = 537)	UW (n = 37)	NW (n = 370)	OW (n = 130)	p value
Age, years	67.4±7.9	70.1±7.4	67.3±8.0	67.0±7.8	0.100
Male	521 (97.0)	37 (100.0)	363 (98.1)	121 (93.1)	0.008#
Smoking amount, pack-year	46.4±26.5	42.6±19.8	46.3±25.5	47.6±30.8	0.602
Current smoker	191 (35.6)	14 (37.8)	142 (38.4)	35 (26.9)	0.040#
BMI, kg/m^2	23.0±3.1	17.0±1.3	22.3±1.7	26.9±1.7	<0.001*
Pre-BD FEV_1, % predicted	50.7±15.9	37.5±12.7	50.1±15.7	55.9±14.7	<0.001*
Post-BD FEV_1, % predicted	58.7±18.9	41.8±14.3	58.8±19.3	63.4±15.9	<0.001*
6MWD, m (n = 492)	416.7±86.7	361.1±92.6	417.5±85.4	429.9±83.0	<0.001**
Charlson's comorbidity score	1.3±0.7	1.2±0.4	1.3±0.7	1.4±0.9	0.177
Dyspnea, mMRC	1.6±1.1	2.1±1.1	1.6±1.0	1.4±1.0	0.002**
SGRQ (n = 474)	30.4±18.3	42.8±18.5	30.0±18.0	28.0±17.6	<0.001**
FEV_1 decline, mL/year (n = 337)	−24.3±24.5	−19.3±23.3	−24.2±24.9	−26.2±23.8	0.431
Radiologic findings					
Emphysema index, %	20.0±15.3	37.5±16.3	22.9±14.5	13.6±12.1	<0.001*
Wall area, %	17.9±3.8	16.8±3.0	17.7±3.6	18.5±3.9	0.017¶
Air-trapping index	0.94±0.04	0.97±0.02	0.95±0.03	0.93±0.04	<0.001*
Serum laboratory findings					
Leukocyte, ×10^3/μL	7.3±2.0	6.6±1.0	7.4±2.1	7.3±2.0	0.107
Hemoglobin, g/dL	14.7±1.4	14.3±1.3	14.8±1.4	14.9±1.4	0.801
Platelet, ×10^3/μL	240.5±66.8	242.8±74.5	244.3±68.6	228.8±58.7	0.104
Protein, g/dL	7.1±0.5	6.8±0.6	7.1±0.5	7.2±0.5	<0.001*
Albumin, g/dL	4.3±0.8	4.1±0.4	4.2±0.4	4.3±0.3	0.020#
Cholesterol, mg/dL	173.5±57.4	145.8±62.9	172.4±56.1	178.0±62.3	0.025**
hs-CRP, mg/dL	0.4±1.0	0.7±2.1	0.4±0.9	0.3±0.5	0.156
Creatinine, mg/dL	1.0±0.2	0.9±0.2	1.0±0.2	1.1±0.2	<0.001*

Data are presented as n (%) or mean ± SD. UW, underweight; NW, normal weight; OW, overweight; BMI, body mass index; BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; hs-CRP, high-sensitivity C-reactive protein; SD, standard deviation. p value <0.05 in comparison between groups. * UW versus NW versus OW. ** UW versus NW, OW. # OW versus UW, NW. ¶ UW versus OW.

Definition of Clinical Outcomes

Acute exacerbation of COPD (AE-COPD) was defined as worsening of symptoms (dyspnea, cough, or sputum) requiring systemic steroids and/or antibiotics. Severe AE-COPD was defined as hospitalization or visiting the emergency department due to COPD worsening [25]. A frequent exacerbator was defined as 2 or more exacerbations or 1 or more severe exacerbations per year. Annual decline in post-bronchodilator FEV_1 was analyzed by random-slope and random-intercept mixed linear regression as previously mentioned [26]. Mortality data were collected during the follow-up period.

Statistical Analysis

All data were analyzed with SPSS 21.0 (IBM Corp., Armonk, NY, USA). All values except for survival period by mean ± standard error were expressed as mean ± standard deviation for continuous data and number (percentage) for categorical data.

Student's t test, one way ANOVA test, or Kruskal-Wallis test was performed for continuous variables. χ^2 test or Fisher's exact test was used for categorical data. Pearson correlational analysis was used for analyzing the relationship between BMI and other clinical markers. Multivariable analyses comprising parameters with p values ≤0.05 in univariate analysis were performed to find significant variables. Multiple logistic and linear regression analyses were used to choose significant variables associated with acute exacerbation of COPD and BMI. A Kaplan-Meier analysis with a log-rank test was conducted to evaluate survival. A Cox proportional hazard regression analysis was performed to find significant variables associated with survival. A p value of <0.05 was deemed significant.

Results

Comparison of Baseline Clinical Characteristics

Baseline characteristics (n = 537) are presented in Table 1; 97.0% were male, mean age was 67.4 ± 7.9 years, 35.6% were current smokers, and the mean post-bron-

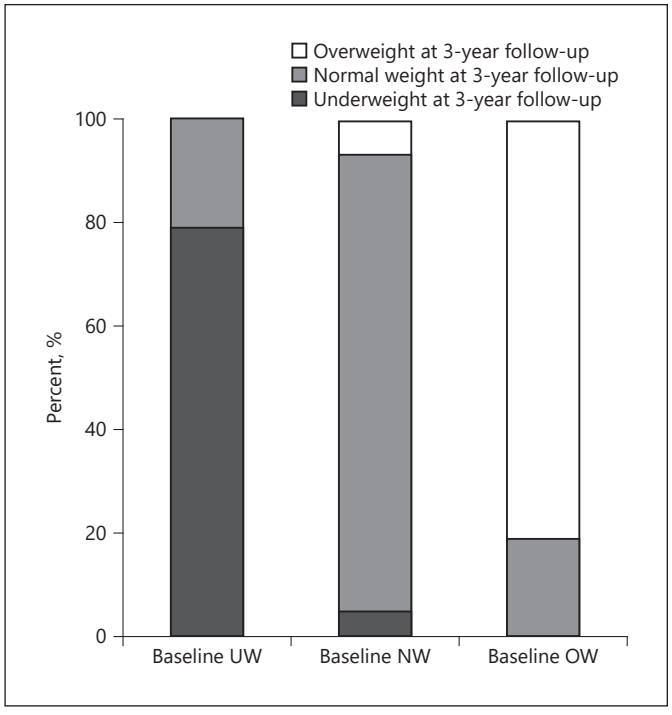

Fig. 1. Longitudinal changes of the BMI group during the follow-up period at 3 years (n = 270). (1) Initial UW group (n = 19), UW = 78.9% (n = 15), NW = 21.1% (n = 4), and OW = 0% (n = 0). (2) Initial NW group (n = 175), UW = 4.0% (n = 7), NW = 89.1% (n = 156), and OW = 6.9% (n = 12). (3) Initial OW group (n = 76), UW = 0.0% (n = 0), NW = 18.4% (n = 14), and OW = 81.6% (n = 62). UW, underweight; NW, normal weight; OW, overweight.

chodilator FEV_1 was 58.7 ± 18.9%. Among current smokers, 27 patients (5.0%) quit smoking during follow-up.

Comparison of baseline clinical variables based on BMI groups showed that the UW group had lower BMI ($p < 0.001$), lower FEV_1 ($p < 0.001$), lower serum protein level and serum creatinine level ($p < 0.001$) than the NW or OW group (Table 1). Serum cholesterol level was lower in the UW group than the other groups ($p = 0.025$). The 6-minute walk distance was shorter in the UW group ($p < 0.001$). Dyspnea grade measured by mMRC was higher in the UW group ($p = 0.002$). The UW group had significantly worse health-related quality of life than NW and OW groups ($p < 0.001$) (Table 1).

Radiological evaluations demonstrated that emphysema index and air-trapping index were higher in the UW group ($p < 0.001$). Inflammatory markers including serum leukocyte count and high-sensitivity C-reactive protein level were not different among the 3 groups (Table 1).

During 3-year follow-up, 49.7% (n = 267) of total patients were untraced. Of the 267 untraced patients during 3-year follow-up, 21 patients died, 114 dropped out at the patients' discretion, and 132 patients were lost to follow-up (online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000511022). The characteristics of untraced patients in comparison with traced patients were shown in online suppl. Table 1.

Longitudinal Changes in BMI

Among the enrolled patients, 270 and 159 patients completed follow-up at 3 and 5 years. At the time of enrollment, 78.9 and 66.7% of UW group remained in the UW group at 3- and 5-year follow-up, respectively. Twenty-one percent of the UW group at the time of enrollment changed to the NW group at 3-year follow-up without any intervention (Fig. 1). Normal weight was maintained in 89.1% of the NW group at 3-year follow-up. On the other hand, 81.6% of the OW group at the time of enrollment still remained in the OW group at 3-year follow-up (Fig. 1). Three years later, repeated measurements of BMI showed a descent of BMI group in 7.8% (n = 21), no change in 86.3% (n = 233), ascent of BMI group in 5.9% (n = 16) (Table 2).

Comparison of clinical characteristics according to longitudinal changes of the BMI group showed no difference (Table 2). Body weight change in each group was presented in online suppl. Table 2.

Exacerbations during Follow-Up

Table 3 shows comparisons of exacerbation and mortality according to initial BMI groups. A history of AE-COPD in the previous year was found in 20.2% of total patients; the incidence of AE-COPD in the previous year was higher in the UW group. During the follow-up period, AE-COPD and severe AE-COPD occurred in 50.8 and 19.6% of the entire population; 137 (25.5%) were annual exacerbators (AE ≥1 per 1 year) and 69 (12.8%) were frequent exacerbators. Sixty-nine patients (12.8%) died during the follow-up period.

The annual incidence of AE-COPD was higher in the UW group (1.53 ± 1.53 vs. 0.70 ± 1.25 vs. 0.62 ± 1.04/year, $p < 0.001$) (Table 3). Severe AE-COPD had a tendency to occur more frequently in the UW group than in NW or OW group (0.27 ± 0.52 vs. 0.15 ± 0.59 vs. 0.07 ± 0.24/year, $p = 0.089$). The proportion of annual exacerbators and frequent exacerbators was both higher in the UW group than in the NW or OW group (48.6 vs. 23.8% vs. 23.8%, $p = 0.045$; 35.1 vs. 11.9% vs. 9.2% $p < 0.001$) (Table 3).

Table 2. Comparison of clinical characteristics according to longitudinal changes of the BMI group after 3-year follow-up

Parameter	Total (n = 270)	Descent of BMI group (n = 21)	No change of BMI group (n = 233)	Ascent of BMI group (n = 16)	p value
Age, years	66.3±7.4	64.5±8.2	66.5±7.2	66.9±8.6	0.415
Male	264 (97.8)	21 (100.0)	228 (97.9)	15 (93.8)	0.432
Smoking amount, pack-year	46.9±27.4	59.7±37.4	46.6±26.8	34.5±10.7	0.062
Current smoker	64 (23.7)	3 (14.3)	57 (24.5)	4 (25.0)	0.571
BMI, kg/m^2	23.3±3.2	23.8±3.5	23.3±3.2	22.6±2.7	0.439
Pre-BD FEV_1, % predicted	48.6±14.8	45.4±19.3	49.1±14.4	45.9±14.3	0.428
Post-BD FEV_1, % predicted	54.1±15.4	51.0±21.2	54.5±14.9	52.3±14.3	0.676
6MWD, m	442.5±78.7	455.3±98.6	440.9±78.1	448.9±58.4	0.363
Charlson's comorbidity score	1.3±0.6	1.1±0.4	1.3±0.6	1.4±0.6	0.416
Dyspnea, initial *m* MRC	1.6±1.0	1.6±0.9	1.6±1.1	1.6±1.0	0.954
SGRQ	32.2±17.6	36.1±19.9	31.7±17.2	35.5±19.8	0.520
FEV_1 decline, mL/year	−24.7±27.9	−24.5±29.9	−25.1±28.0	−19.1±25.6	0.482
Radiologic findings					
Emphysema index, %	20.9±14.7	25.6±15.3	20.8±14.6	17.2±15.0	0.220
Wall area, %	17.6±3.6	16.7±2.7	17.8±3.6	16.9±4.1	0.378
Air-trapping index	0.95±0.03	0.94±0.04	0.95±0.03	0.93±0.03	0.209
Serum laboratory findings					
Leukocyte, ×10^3/μL	7.1±1.8	7.1±1.7	7.2±1.8	6.8±1.6	0.641
Hemoglobin, g/dL	14.9±1.2	15.3±1.3	14.9±1.2	14.7±0.7	0.433
Platelet, ×10^3/μL	238.6±56.9	241.5±64.5	237.5±55.2	251.1±73.3	0.814
Protein, g/dL	7.1±0.5	7.3±0.5	7.1±0.5	7.1±0.4	0.216
Albumin, g/dL	4.3±0.4	4.3±0.3	4.3±0.4	4.2±0.4	0.534
Cholesterol, mg/dL	166.9±66.6	167.4±80.6	167.7±66.7	156.9±47.7	0.163
hs-CRP, mg/dL	0.4±1.1	0.4±0.5	0.3±0.9	1.2±2.8	0.106
Creatinine, mg/dL	1.0±0.2	1.0±0.1	1.0±0.2	1.0±0.2	0.371
BMI group at enrollment					
UW	19	0	15	4	
NW	175	7	156	12	
OW	76	14	62	0	

Data are presented as n (%) or mean ± SD. UW, underweight; NW, normal weight; OW, overweight; BMI, body mass index; BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; Hs-CRP, high-sensitivity C-reactive protein; 6MWD, 6-minute walk distance; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; SD, standard deviation.

Table 3. Comparison of exacerbation and mortality among the groups

Parameter	Total (n = 537)	UW (n = 37)	NW (n = 370)	OW (n = 130)	p value
History of AE in previous 1 year (n = 480)	97 (20.2)	14/35 (40.0)	66/325 (20.3)	17/120 (14.2)	0.003
Follow-up duration, years	5.93±3.96	5.24±4.07	5.74±3.84	6.69±4.18	0.033
AE-COPD	273 (50.8)	28 (75.7)	175 (47.3)	70 (53.8)	0.003
Severe AE-COPD	105 (19.6)	15 (40.5)	70 (18.9)	20 (15.4)	0.003
AE-COPD/year	0.74±1.24	1.53±1.53	0.70±1.25	0.62±1.04	<0.001
Severe AE-COPD/year	0.14±0.53	0.27±0.52	0.15±0.59	0.07±0.24	0.089
Exacerbator (AE/year ≥1)	137 (25.5)	18 (48.6)	88 (23.8)	31 (23.8)	0.045
Frequent exacerbator (AE/year ≥2)	69 (12.8)	13 (35.1)	44 (11.9)	12 (9.2)	<0.001
Survival rate for 3 years	95.8%	84.4%	95.1%	98.5%	<0.001
Survival rate for 5 years	90.7%	57.0%	90.4%	98.5%	<0.001

UW, underweight; NW, normal weight; OW, overweight; AE-COPD, acute exacerbation of chronic obstructive pulmonary disease; severe AE-COPD, hospitalization or visit to ER; frequent exacerbator , AE-COPD/year ≥2 or severe AE-COPD/year ≥1.

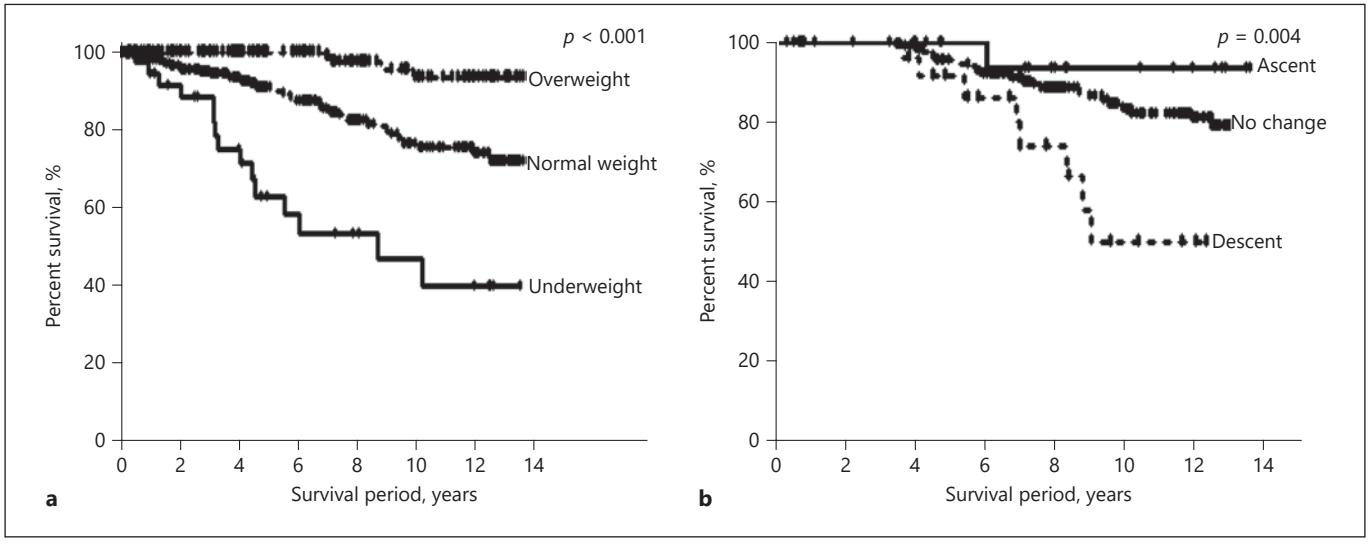

Fig. 2. Survival analyses by the Kaplan-Meier method (survival period is presented as mean ± standard error). **a** UW (8.24 ± 0.95 years), NW (11.52 ± 0.26 years), and OW (13.20 ± 0.17 years) according to the baseline BMI ($p < 0.001$). **b** Descent (9.51 ± 0.74 years), no change (12.17 ± 0.21 years), and ascent (12.98 ± 0.60 years) according to the change of the BMI group after 3-year follow-up ($p = 0.004$). UW, underweight; NW, normal weight; OW, overweight.

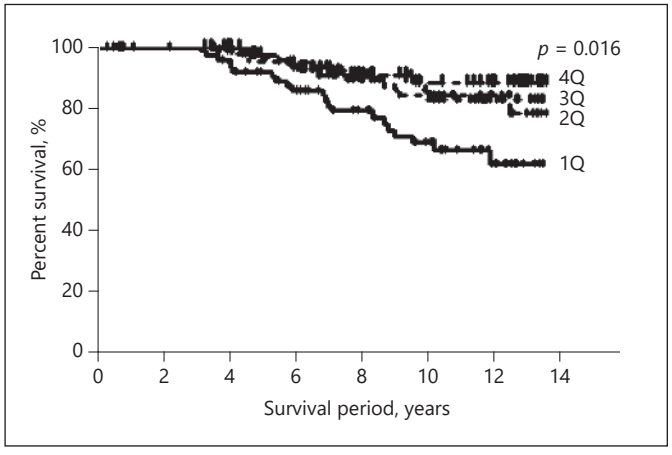

Fig. 3. Survival analyses by the Kaplan-Meier method according to the difference of BMI (third year BMI minus baseline BMI) based on quartile classification ($n = 270$) (survival period is presented as mean ± standard error) $p = 0.016$. 1Q: < −0.75 (11.0 ± 0.5 years), 2Q: −0.72 ~ −0.05 (12.2 ± 0.4 years), 3Q: 0.00 ~ 0.36 (12.3 ± 0.3 years), and 4Q: ≥0.66 (12.7 ± 0.3 years).

Association of BMI with Acute Exacerbation

Logistic regression analysis was performed to analyze risk factors for acute exacerbations of COPD. Age, lung function (post-bronchodilator FEV_1), previous history of exacerbation, and the change of BMI group at 3-year follow-up were independent risk factors for exacerbation of COPD, whereas initial BMI was not ($p < 0.05$) (Table 4).

Association of BMI with Mortality

Of the 69 patients with COPD who died during the observation period, death was most frequently due to respiratory failure (17 patients). Other causes were pneumonia (11 patients), lung cancer (8 patients), cancers other than lung cancer (7 patients), myocardial infarction (4 patients), pneumothorax (1 patient), liver cirrhosis (1 patient), trauma (1 patient), and suicide (1 patient). The cause of death was unclear in eighteen patients. Since the cause of death was unidentified for 21.17%, only all-cause mortality was used for the survival analyses.

Kaplan-Meier survival analysis showed a shorter survival period in patients with a lower BMI at baseline (Fig. 2a, $p < 0.001$). Furthermore, during 3-year follow-up, the descent of BMI group was associated with a significantly higher mortality and the ascent of BMI group observed in 5.9% of this cohort was associated with lower mortality (Fig. 2b, $p = 0.004$).

When the total patients were divided into 4 quartiles according to the difference between the absolute value of baseline BMI and 3-year follow-up, BMI decrease showed significantly higher mortality ($p < 0.05$) (Fig. 3). In addition, univariate cox regression analysis showed that body weight loss for 3 years in NW group ($p = 0.019$) and UW group ($p = 0.080$) were associated with higher mortality, whereas body weight change for 1 year was not related to mortality (online suppl. Table 3).

Table 4. Risk factors associated with exacerbating COPD (exacerbation/year ≥1)

Parameter (n = 537)	Univariate			Multivariable		
	OR	95% CI	p value	OR	95% CI	p value
Age, years	1.054	1.029–1.080	<0.001	1.054	1.016–1.094	0.005
Male	0.880	0.325–2.384	0.802			
Smoking amount, pack-year	1.005	0.999–1.011	0.115			
Current smoker	0.833	0.559–1.239	0.366			
BMI, kg/m^2	0.910	0.862–0.960	0.001	0.960	0.897–1.028	0.245
Post-BD FEV_1, % predicted	0.983	0.971–0.994	0.003	0.977	0.960–0.995	0.011
6MWD, m	0.996	0.994–0.998	<0.001	1.002	0.998–1.005	0.428
Charlson's comorbidity score	0.951	0.703–1.287	0.746			
mMRC	1.334	1.135–1.568	<0.001	1.252	0.977–1.605	0.076
SGRQ	1.023	1.014–1.031	<0.001	1.010	0.994–1.026	0.210
FEV_1 decline, mL/year (n = 337)	1.002	0.995–1.008	0.660			
History of AE in previous 1 year	2.228	1.508–3.291	<0.001	1.966	1.128–3.425	0.017
Change of BMI group at 3-year follow-up			0.043			0.004
No change	Reference					
Descent	2.080	0.991–4.368	0.053	2.618	1.207–5.677	0.015
Ascent	0.445	0.156–1.269	0.130	0.286	0.094–0.869	0.027

BMI, body mass index; BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; 6MWD, 6-min walk distance; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; AE, acute exacerbation; OR, odds ratio; CI, confidence interval.

Prognostic factors associated with the survival of COPD by univariate Cox regression analysis were presented in Table 5. The multivariable Cox regression analysis including age, mMRC, SGRQ, BMI, post-bronchodilator FEV_1, 6-minute walk distance, annual incidence of severe exacerbation, and the change of BMI group at 3 year (model 1) revealed that an older age (hazard Ratio [HR] = 1.117, $p < 0.001$), initial BMI (HR = 0.863, $p = 0.003$), post-bronchodilator FEV_1 (HR = 0.962, $p = 0.006$), annual incidence of severe exacerbation (HR = 2.549, $p = 0.005$) and descent of BMI group at 3-year follow-up (HR = 3.167, $p = 0.016$) were significant predictors of all-cause mortality (Table 6).

The other multivariable cox proportional hazard analysis (model 2) revealed that initial BMI and the absolute difference of third year BMI minus initial BMI along with age and lung function were independently associated with mortality (Table 6).

Factors Associated with BMI

This analysis was performed to identify independent factors associated with BMI. Multiple linear regression analysis using all possible risk factors demonstrated that emphysema index ($B = -0.080$, $p < 0.001$), serum hemoglobin ($B = 0.333$, $p = 0.009$), serum creatinine ($B = 1.955$, $p = 0.032$), and serum protein ($B = 0.763$, $p = 0.021$) were the independent factors associated with BMI (online suppl. Table 4).

Discussion

The aim of our study was to explore the impact of longitudinal BMI changes on the prognosis of Asian patients with COPD. Our results highlighted the prognostic role of BMI change in Korean COPD patients by showing that the decrease of BMI during follow-up was an independent predictor of mortality in COPD.

The decrease of BMI during 3-year follow-up was an independent predictor of mortality and annual exacerbation in our COPD cohort. Our analysis also indicated that being UW significantly increased the risk of all-cause mortality.

Our finding of low BMI as an independent predictor for frequent exacerbation and mortality is supported by previous reports [27, 28]. However, no previous studies examined the association between BMI change and the prognosis of COPD on a long term basis. This is the first paper to show that the longitudinal decrease of BMI is a risk factor for exacerbation and mortality of COPD. In

Table 5. Prognostic factors associated with the survival of patients with COPD by univariate Cox regression analysis

Parameter (n = 537)	HR	95% CI	p value
Age, years	1.097	1.060–1.136	<0.001
Male	0.444	0.058–3.416	0.436
Smoking amount, pack-year	1.008	0.999–1.016	0.082
Current smoker at enrollment	0.735	0.408–1.323	0.304
Current smoker during follow-up	0.746	0.414–1.343	0.329
BMI, kg/m^2	0.759	0.704–0.818	<0.001
Pre BD FEV_1, % predicted	0.943	0.924–0.962	<0.001
Post BD FEV_1, % predicted	0.948	0.932–0.965	<0.001
Charlson's comorbidity score	1.151	0.838–1.582	0.386
Dyspnea, mMRC	1.986	1.564–2.522	<0.001
SGRQ	1.033	1.021–1.045	<0.001
6MWD, m	0.992	0.989–0.994	<0.001
Number of severe exacerbation/year	1.413	1.175–1.699	<0.001
Change of BMI group at 3-year follow-up			0.008
No change	Reference		
Descent	3.106	1.439–6.704	0.015
Ascent	0.385	0.053–2.806	0.346
Absolute difference			
BMI at 3-year follow-up minus BMI at enrollment	0.839	0.733–0.961	0.011
Body weight at 1-year follow-up minus body weight at enrollment	1.012	0.924–1.108	0.797
Body weight at 3-year follow-up minus body weight at enrollment	0.936	0.888–0.986	0.013

Severe exacerbation = admission to hospital or visiting the emergency department. BMI, body mass index, BD, bronchodilator; FEV_1, forced expiratory volume in 1 s; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; HR, hazard ratio; CI, confidence interval.

Table 6. Prognostic factors associated with the survival of patients with COPD by multivariable Cox regression analysis

Parameter (n = 537)	Model 1			Model 2		
	HR	95% CI	p value	HR	95% CI	p value
Age,years	1.117	1.064–1.173	<0.001	1.101	1.052–1.152	<0.001
BMI, kg/m^2	0.863	0.784–0.951	0.003	0.843	0.759–0.937	0.001
Post-BD FEV_1, % predicted	0.962	0.936–0.989	0.006	0.961	0.933–0.990	0.008
Dyspnea, mMRC	1.282	0.857–1.917	0.226	1.138	0.751–1.726	0.542
SGRQ	0.994	0.973–1.016	0.596	0.988	0.967–1.011	0.302
6MWD, m	0.998	0.993–1.002	0.341	0.997	0.993–1.002	0.283
Number of severe exacerbation/year	2.549	1.330–4.888	0.005	3.009	1.529–5.922	0.001
Change of BMI group at 3-year follow-up			0.024			
No change	Reference					
Descent	3.167	1.240–8.089	0.016			
Ascent	0.275	0.037–2.069	0.210			
Absolute difference: BMI at third year minus initial BMI				0.786	0.626–0.987	0.038

Severe exacerbation = admission to hospital or visiting the emergency department. Model 1 included age, BMI, SGRQ, post-BD FEV_1, mMRC, 6-min walking distance, annual incidence of severe exacerbation, and the change of BMI group at 3 years, and model 2 used absolute difference of BMI at the third year minus initial BMI instead of the BMI group. BMI, body mass index; BD, bronchodilator; FEV_1 = forced expiratory volume in 1 s; mMRC, modified Medical Research Council; SGRQ, St. George's Respiratory Questionnaire; 6MWD, 6-minute walk distance; HR, hazard ratio; CI, confidence interval.

this study, most (86.3%) of this KOLD cohort maintained their initial BMI group and the descent of BMI group observed in 7.8% of this cohort during 3-year follow-up was associated with higher mortality and annual exacerbation.

BMI is one component of the BODE (BMI, obstruction, dyspnea, and exercise capacity) index which is a widely used tool to predict mortality in COPD patients [10]. The association between low BMI and poor survival in COPD can be explained by several factors such as diaphragmatic muscle weakness, decreased lung function, impaired gas exchange, impaired immune response, and loss of metabolically and functionally active fat-free mass [9, 29]. The impaired skeletal muscle performance by poor nutrition and systemic inflammation leading to low exercise capacity in COPD and heart failure can also explain this poor prognosis [30]. A common pathway for weight loss and development of cachexia may exist, because weight loss is a poor prognosticator in COPD and other chronic diseases [31, 32].

Leptin (an important regulator of food intake and energy expenditure) and tumor necrotizing factor-alpha were suggested to be associated with a pathophysiological mechanism of weight loss in COPD [33–35]. Previous studies reported that tumor necrotizing factor-α production is elevated in emphysematous phenotype and may be a factor contributing to the weight loss in COPD [33, 34]. Increased levels of leptin during acute exacerbations of COPD may lead to changes in nutritional parameters and body weight in the course of the disease [35]. Another interesting finding of this study is that emphysema index, serum hemoglobin level, serum creatinine, and serum protein were the independent factors associated with BMI, suggesting these factors may represent nutritional status.

Deleterious effects of malnutrition in COPD led to several studies concerning the efficacy of nutritional support [36, 37]. Planas et al. [36] reported that nutritional supplementation improved body weight, handgrip strength, airflow limitation, and quality of life in COPD. However, nutritional support was suggested as an add-on therapeutic approach in some subgroups of COPD [37]. Therefore, nutritional support as a therapeutic intervention to improve COPD outcomes requires further validation.

Advanced emphysema which has been recognized to have a feature of low BMI is also reported to be associated with accelerated decline of FEV_1, hospitalization, high exacerbation rate and mortality by previous studies [38–41]. COPD patients with severe emphysema can suffer an excessive tissue loss over time in several organs, including lungs, bones, skeletal muscle, and adipose tissue, which is probably related to abnormal tissue maintenance and worse clinical outcomes [40].

However, unmeasured confounders can be a limitation of this study because all possible causes for weight change were not able to be investigated. Weight loss can be attributable to other comorbidities and confounding factors such as malignancy, depression, diabetes, poor diet, oxidative stress, skeletal muscle atrophy, sedentarism, endocrine disruption, and systemic inflammation [42]. Therefore, further evaluations seem to be necessary regarding this area.

In general populations, excess body weight is associated with increased mortality in middle adulthood [43]. However, the relationship between body weight change and prognosis in chronic diseases is controversial. Our data showed that being OW had a protective effect against death in COPD, as reported in previous studies [14, 27, 28]. A protective effect of adipose tissue against mortality has been observed in chronic diseases including COPD, heart failure, and diabetes mellitus, although the pathophysiological mechanism is not fully elucidated [11, 12, 15].

Nonetheless, sarcopenia obesity representing the coexistence of sarcopenia and obesity is frequently present in COPD [44]. This condition is often associated with poor physical performance, cardiovascular disease risk, and higher all-cause mortality [44–46]. Hence, research investigating a body composition phenotype considering sarcopenia and fat-free mass index seems to be necessary to better define the role of BMI in COPD.

This study has several limitations. First, although several factors adjusted for potential covariates, we could not rule out the influence of unmeasured confounders. Second, the information on the cause of weight loss was not obtained in this cohort. Third, this study analyzed the BMI category based on WHO classification. However, the validation of BMI category among Asians is required because each study used different BMI categories for the definition of UW. Fourth, COPD patients in our study may not fully represent the general COPD population of Korea because this study only enrolled symptomatic COPD patients referred to pulmonologists in Korea. Also, the small percentage of obese patients and women is a limitation in the analysis of this cohort. Therefore, selection bias could be inherent in this cohort. Fifth, this study cannot determine a causal link between the decline of BMI and mortality. Sixth, the small number of patients in the change of BMI group is a limitation in the analysis

of this data. Seventh, the absence of body composition analysis is a major limitation to evaluate the nutritional assessment to supplement BMI change.

In conclusion, this study demonstrated that initial UW and BMI decrease during follow-up were independently associated with exacerbations and higher mortality of COPD, suggesting BMI reduction in COPD should be carefully managed.

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Conflict of Interest Statement

Dr. Singh reports grants and personal fees from Apellis, AstraZeneca, Boehringer Ingleheim, Chiesi, Cipla, Glenmark, Merck, Mundipharma, Novartis, Peptinnovate, Pfizer, Pulmatrix, and Teva.

Statement of Ethics

This study was approved by the institutional review board of the Asan Medical Center (Approval No. 2005-0345) and the other 16 hospitals. Written informed consent was obtained from all patients.

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Author Contributions

Eun Kyung Kim designed this study and helped in the preparation of this manuscript. Dave Singh contributed to the critical review and revision of the manuscript. Joo Hun Park coordinated this study, helped in the preparation of this manuscript, and is responsible for the integrity of this paper as a corresponding author. Eun Kyung Kim, Bumhee Park, and Kim Seung-Il contributed to statistical analysis of our data. Yong Bum Park, Jisoo Park, Jung-hyun kim, Mi-Ae Kim, Ji-Hyun Lee, Tae-Hyung Kim, Hyoung Kyu Yoon, and Yeon-Mok Oh contributed to data collection and reviewed the manuscript.

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