Original Article

Body mass index of patients with chronic obstructive pulmonary disease is associated with pulmonary function and exacerbations: a retrospective real world research

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Background: Chronic obstructive pulmonary disease (COPD) is prevalent in China. The role of body mass index (BMI) in COPD progression and prognosis is unclear. We analyzed the association between BMI and pulmonary function, inflammation levels and exacerbation in Chinese COPD patients.

Methods: Our retrospective real world research included 744 patients with COPD diagnosed by spirometry and hospitalized from January 1st, 2014 to December 31st, 2016. The indicators were gathered from hospital records database and frequency of exacerbation in the three years were followed up. All 744 patients were divided into four groups by BMI grades. We analyzed the association between BMI and pulmonary function, inflammation levels and exacerbation by Spearman bivariate correlations, Kruskal-Wallis test, Mann-Whitney U test and logistic regression.

Results: The singly proportion (median of BMI) of these patients in underweight, normal weight, overweight and obesity was 7.80% (17.54), 45.97% (22.12), 27.96% (27.00) and 18.28% (31.25) respectively. With increasing of BMI grades, the values of forced expiratory volume in 1 second (FEV_1), peak expiratory flow (PEF), forced expiratory flow (FEF25/50/75) and diffusing capacity of carbon monoxide (DLCO) were correspondingly increasing; the percentage of neutrophils and C-reactive protein (CRP) presented significant declining trend while the trend of the percentage of eosinophils was negative; the dose of systemic corticosteroid and length of stay present decreasing tendency; the frequency of exacerbation and hospitalization were decreasing. These were similar results in gender, smoking status COPD subgroups.

Conclusions: In our study, BMI was moderately correlated with pulmonary function positively and exacerbations negatively. To some extent, BMI might be a useful indicator to predict the prognosis of COPD patients and for long-term management.

Keywords: Chronic obstructive pulmonary disease (COPD); body mass index (BMI); prognosis; pulmonary function; exacerbation

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Introduction

In China, the prevalence of chronic obstructive pulmonary disease (COPD) is high both in urban and rural area (1,2). The morbidity and mortality of COPD have a trend of increase in recent years. The previous COPD researches demonstrated that frequent exacerbations and accelerated decline of pulmonary function could lead to disease progression (3). Current evidence showed some drugs and interventions could partially delay COPD progression. So it is essential to find indicators to predict the prognosis and outcome of COPD.

As we all know, obesity played a detrimental role in asthma and obstructive sleep apnea hypopnea syndrome (4-6). However, conclusions on the roles of body mass index (BMI) in COPD were discrepant. It has been demonstrated that higher mortality in underweight COPD patients was partially due to the accelerated decline of forced expiratory volume in 1 second (FEV_1) (3,7). Unfortunately, most clinical studies concentrated on the effect of low weight and severe obesity on the mortality of patients with COPD, but few studies focused on the relationship of BMI and other factors during the progression of COPD (8-12). Moreover, most of the previous studies were only small sample randomized controlled trials, which limited to generalize the conclusions. Therefore, it would be meaningful to add data from real world and study other factors. The aim of our retrospective research was to study the effects of BMI on COPD progression.

Methods

Study design and patients

With a retrospective real world research design, all cases with COPD as one of discharge diagnosis in Shandong Provincial Hospital or Shanghai Zhongshan Hospital from January 1st, 2014 to December 31st, 2016 were gathered from hospital records databases. Patients must be over 40 years old, had records of pulmonary function tests, and be alive when discharged from hospital.

Data collection

All data during the above mentioned period were sequentially collected by manual extraction from electronic medical records through hospital records databases in two centers, including basic information (gender, age, height and weight), history of smoking, co-morbidities, laboratory blood tests—white blood cell (WBC), neutrophils, eosinophils, C-reactive protein (CRP), pulmonary function tests—forced expiratory volume in 1 second (post bronchodilator FEV_1), forced expiratory vital capacity (FVC), peak expiratory flow (PEF), forced expiratory flow (FEF_{25-75}) and diffusing capacity of carbon monoxide (DLCO), pulmonary arterial pressure (PAP) measured by Doppler cardiac ultrasound, the dose of systemic corticosteroid and length of stay. From March to May of 2017, all recruited patients were followed up by phone calls and hospital record systems to record their moderate and severe acute exacerbation events from January 1st, 2014 to December 31st, 2016.

Study variables

BMI was used as the independent variable. According to the standard of the World Health Organization (WHO), all participants were classified into four subgroups, underweight (BMI <18.5), normal weight (18.5≤ BMI <25), overweight (25≤ BMI <30) and obesity (BMI ≥30).

Parameters in pulmonary function tests and frequency of exacerbation were used as observable variables. (I) post bronchodilator FEV_1 %pred (here after termed FEV_1)was divided into four degrees according to Global Initiative for Chronic Obstructive Lung Disease (GOLD) 2014: GOLD1 (FEV_1 ≥80%pred), GOLD2 (50%pred ≤ FEV_1 <80%pred), GOLD3 (30%pred≤ FEV_1 <50%pred), GOLD4 (FEV_1 <30%pred). It is widely used to predict the severity of COPD (3). (II) PEF is defined as the maximal flow (or speed). To some degree, it could reflect the condition of airway obstruction, especially when combined with FEF_{25} to indicate the status of large airways and respiratory muscles strength. (III) FEF is usually presented as intervals of FEF_{25}, FEF_{50} and FEF_{75}, which represent FEF after 25%/50%/75% of FVC has been exhaled respectively. FEF_{25} is an indicator to reflect the flow of the early stage of expiration and will decline if large airway is obstructive. FEF_{50} and FFE_{75} reflect the flow of the middle stage and the later stage of expiration. FEF_{25-75} or FEF_{50-75} may be more sensitive parameters than FEV_1 in the assessment of small airway function. (IV) DLCO is used to reflect pulmonary diffusion function. (V) total times of exacerbations is the sum of moderate and severe exacerbations in three years. The definitions of acute exacerbation and its severities are according to GOLD 2014.

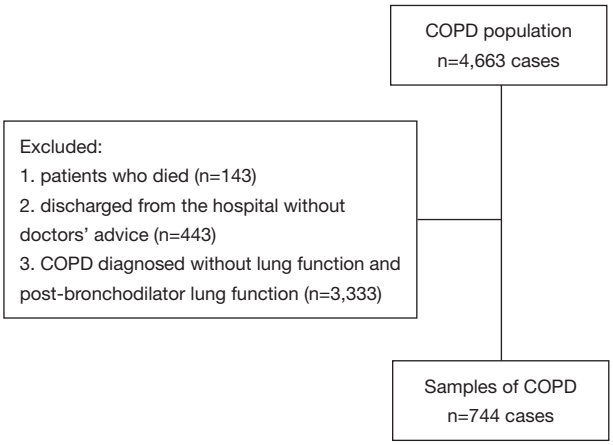

Figure 1 Certainly 744 patients with COPD were recruited. COPD diagnosis was confirmed by pulmonary function test. COPD, chronic obstructive pulmonary disease.

Statistical analysis

Data collection and record used EpiData (Version 3.1). Statistical analysis was performed using SPSS Version 23.0 (SPSS Inc.; Chicago, Illinois) and GraphPad Prism 7 (GraphPad, San Diego, CA). Parametric data were presented as mean ± standard error of the mean (SEM) or range. Non-parametric data were presented as median (interquartile range, IQR). We used Spearman bivariate correlations to investigate the correlation of BMI to each indicator. In the primary analysis, Kruskal-Wallis test was used to compare difference among multi-groups and then Mann-Whitney U test was used to compare in pairs. In Kruskal-Wallis test, variation tendency was analyzed by Mean Rank. The chi-squared test (χ^2) was used to contrast proportions among groups. In the secondary analysis, the ordinal multinomial logistic regression was used to analyze multivariable parameters. $P<0.05$ was considered as the threshold of significance for all statistical analysis.

Results

Finally, 744 COPD patients were retained (*Figure 1*). BMI had mild or moderate positively correlation with FEV_1, PEF, FEF_{25-75} and DLCO (*Table 1*).

In 744 cases, 77% were male with a median age (IQR) of 67 years. Among them, 57.53% were smokers and 32.93% were non-smokers. The smoking-history of other 9.54% patients was unclear. According to BMI grades, all cases were classified into four groups as follows: underweight (58 cases, BMI 17.54), normal weight (342 cases, BMI 22.12), overweight (208 cases, BMI 27.00) and obesity (136 cases, BMI 31.25) (*Table 2*).

There was no significant difference of WBC count among groups. The percentage of neutrophils presented significant declining trend with the increasing of BMI. As compared to obesity group, the value in each other three groups was significantly higher. But there was no marked difference among underweight, normal weight and overweight groups (*Figure 2A*). The percentage of eosinophils in obesity groups was higher than that of underweight, normal weight and overweight groups. The difference was only significant as compared to that of overweight group (*Figure 2B*). The value of CRP presented declining trend with the increasing of BMI. It was highest in underweight group, which was significantly higher than those of overweight and obesity groups but not that of normal weight group (*Figure 2C*).

FEV_1, PEF and DLCO were all significantly increased with the increase of BMI, except for the not significant differences between underweight and normal weight groups in FEV_1 and PEF (*Figure 3A,B,C*). The overall trend of FEF_{25}, FEF_{50} and FEF_{75} presented increasing with the increase of BMI (*Figure 4*). The values of FEF_{25}, FEF_{50} and FEF_{75} in underweight and normal weight groups were similar, which were significantly lower than those of overweight and obesity groups except for FEF_{75}. All FEF_{25}, FEF_{50} and FEF_{75} in obesity group were significantly higher than those of overweight group.

All together 271 patients had the Doppler cardiac ultrasound examination. Only the PAP in underweight group was higher than 40 mmHg. The PAP value was conversely correlated to BMI. It was markedly lower in obesity population than that of underweight or normal weight groups but not significantly among other groups comparison (*Figure 5*).

The length of stay and total dosage of systemic corticosteroid were not notably different among four BMI groups (*Table 2*).

The frequency of total exacerbations and severe exacerbations per year were significantly higher in underweight group than those in other three groups (*Figure 6*).

Subgroups analysis

Due to the baseline, such as gender and smoking, was not matched. We analyzed those indicators in each subgroup—male, female, smokers, non-smokers in order to keep the comparability among each BMI grades.

Table 1 All relative factors and BMI were performed by Spearman bivariate correlations

Spearman bivariate correlations	BMI			BMI grades		
	Correlation coefficient	P value	Cases	Correlation coefficient	P value	Cases
CRP	–0.164	<0.001	475	–0.125	0.007	475
WBC	0.01	0.79	744	0.000	0.993	744
Neutrophils percent	–0.096	0.009	744	–0.088	0.017	744
Eosinophils percent	–0.014	0.706	744	–0.004	0.909	744
FEV_1	0.29	<0.001	744	0.275	<0.001	744
FVC	0.127	0.001	744	0.132	<0.001	744
PEF	0.349	<0.001	744	0.341	<0.001	744
FEF_{25}	0.282	<0.001	740	0.254	<0.001	740
FEF_{50}	0.329	<0.001	743	0.311	<0.001	743
FEF_{75}	0.222	<0.001	700	0.226	<0.001	700
TLC	0.038	0.323	679	0.047	0.219	679
RV	–0.012	0.75	679	0.000	0.993	679
DLCO	0.415	<0.001	673	0.39	<0.001	673
DLCO/VA	0.464	<0.001	677	0.43	<0.001	677
PAP	–0.128	0.035	271	–0.141	0.02	271
Exacerbations in 3 years	–0.002	0.98	234	–0.019	0.774	234
Moderate exacerbations in 3 years	0.016	0.809	234	0.014	0.837	234
Severe exacerbations in 3 years	–0.115	0.08	234	–0.129	0.049	234
Exacerbations per year	0.002	0.978	234	–0.014	0.832	234

P<0.05 means the two indicators were significantly correlated. BMI, body mass index; CRP, C reactive protein; WBC, white blood cell; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure.

In each subgroup, the baseline is equally comparable. The results showed FEV_1, PEF, DLCO, FEF_{25}, FEF_{50} were all presented significant difference according to BMI deviation in male subgroup and in female subgroup (*Table 3*). The tendency of FEF_{75} in male patients was similar to that of whole samples (*Table 4*). Interestingly, the total lung capacity (TLC) and residual volume (RV) in female patients presented significant increasing trend with the increase of BMI but not in male patients. Like the whole sample, the frequency of severe exacerbation per year in underweight group was much higher than those of other three groups in male patients but not in female patients. FEV_1, PEF, $FEF_{25–75}$ and DLCO were significantly lower in underweight group compared to obesity group both in smokers' subgroup (*Table 5*) and non-smokers subgroup (*Table 6*). Compared with other three groups, the frequency of exacerbation and severe exacerbation per year of underweight patients was significantly higher in smoking patients. Those results manifested the conclusion of BMI and lung function and exacerbation is available.

Secondary analysis

FEV_1 is the most important indicator for COPD patients in lung function; GOLD grade is an indicator which could be standing for FEV_1 level in COPD. We performed ordinal multinomial logistic regression and choose GOLD grades as the dependent variable; age, gender, BMI, smoking status, WBC, neutrophils and eosinophils %, CRP and PAP as independent variables. Age, gender, BMI, PAP

Table 2 Clinical characteristics of total patients with COPD (n=744)

Characteristics	Underweight BMI <18.5 (n=58)	Normal weight 18.5≤ BMI <25 (n=342)	Overweight 25≤ BMI <30 (n=208)	Obesity BMI ≥30 (n=136)	P value
Male, n (%)	47 (81.0%)	276 (80.7%)	163 (78.4%)	87 (64.0%)	0.001
Age, years	68.67 [54–87]	68.05 [45–87]	67.12 [43–87]	65.68 [42–88]	0.144
History of smoking					
Smoker, cases	45 (83.3%)	224 (70.2%)	118 (63.4%)	41 (36.0%)	<0.001
Smoking-index	800 [230–1,050]	600 [0–1,000]	400 [0–825]	0 [0–600]	<0.001
WBC	8.19 (3.00–18.78)	7.61 (2.24–24.10)	8.05 (1.53–25.12)	7.52 (1.65–16.51)	0.208
Peripheral blood neutrophils count	4.97 (3.60–7.54)	4.57 (3.24–6.22)	4.69 (3.60–6.61)	4.01 (3.14–5.72)	0.038
% peripheral blood neutrophils count	68.97 (37.30–95.00)	65.90 (31.00–93.50)	66.97 (34.20–97.10)	63.01 (37.60–92.50)	0.008
Peripheral blood eosinophil count	0.11 (0.04–0.24)	0.11 (0.03–0.21)	0.09 (0.01–0.18)	0.12 (0.05–0.23)	0.073
% peripheral blood eosinophil count	1.60 (0.48–3.60)	1.70 (0.50–3.20)	1.45 (0.10–2.88)	1.85 (0.70–3.28)	0.099
Blood EOS ≥2%, cases	25 (43.1%)	152 (44.4%)	83 (39.9%)	65 (47.8%)	0.527
CRP	6.31 (2.13–85.21)	4.69 (1.40–19.06)	3.45 (1.73–11.51)	4.00 (1.14–8.21)	0.042
BMI	17.54 (16.96–18.14)	22.12 (20.57–23.51)	27.00 (25.85–28.31)	31.25 (30.48–32.81)	–
Main indicators of lung function					
FEV_1	45.65 (31.13–63.30)	46.80 (33.30–64.00)	52.65 (37.98–71.48)	68.70 (55.13–78.25)	<0.001
FVC	71.55 (60.15–86.15)	66.95 (54.20–80.00)	66.35 (56.43–80.45)	79.35 (66.13–87.18)	<0.001
PEF	36.40 (27.05–56.53)	40.05 (27.65–56.33)	49.95 (33.20–71.03)	65.40 (50.13–79.48)	<0.001
FEF25	18.65 (12.00–32.03)	19.15 (11.20–34.38)	27.90 (14.10–52.80)	29.70 (22.70–44.05)	<0.001
FEF50	14.50 (8.90–29.95)	16.85 (9.90–26.28)	20.60 (11.40–40.40)	33.95 (22.90–46.08)	<0.001
FEF75	24.30 (17.00–48.83)	24.00 (15.65–39.50)	28.40 (15.40–47.40)	43.60 (29.30–64.10)	<0.001
TLC	77.10 (63.53–91.50)	77.10 (64.50–87.60)	75.10 (63.80–85.70)	82.70 (69.75–90.40)	0.014
RV	96.05 (75.15–130.00)	100.60 (77.90–126.20)	100.30 (73.70–122.10)	104.40 (84.55–120.25)	0.784
DLCO	36.15 (23.30–55.38)	44.00 (30.70–62.10)	55.70 (38.58–70.83)	72.50 (59.38–83.80)	<0.001
DLCO/VA	44.70 (26.28–62.90)	53.75 (37.30–78.23)	70.15 (52.63–92.53)	91.70 (77.60–110.50)	<0.001
PAP (by Doppler cardiac ultrasound)	34.00 (30.00–44.00)	33.00 (28.00–41.00)	33.00 (28.00–40.00)	31.00 (25.00–34.00)	0.082
Times of AECOPD in 3 years	5.50 (2.00–7.25)	2.00 (1.00–3.00)	2.00 (1.00–6.00)	2.00 (1.00–5.50)	0.038
Moderate exacerbations in 3 years	0.50 (0.00–4.00)	0.00 (0.00–2.00)	0.00 (0.00–3.00)	0.00 (0.00–5.00)	0.504
Severe exacerbations in 3 years	2.00 (1.00–5.25)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (0.00–1.50)	0.003
Frequency of AECOPD per year	1.85 (0.70–2.40)	0.70 (0.30–1.00)	0.70 (0.30–2.00)	0.70 (0.30–1.85)	0.027
Length of stay of the last in-hospital	10.00 (7.25–13.75)	8.00 (7.00–12.00)	8.00 (7.00–11.00)	9.50 (8.00–12.00)	0.177
The total dosage of systemic corticosteroid	280.00 (130.00–510.00)	240.00 (160.00–360.00)	200.00 (125.00–320.00)	160.00 (90.00–420.00)	0.143

Data presented as median (IQR) unless specified. COPD, chronic obstructive pulmonary disease; BMI, body mass index; WBC, white blood cell; EOS, eosinophil; CRP, C reactive protein; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

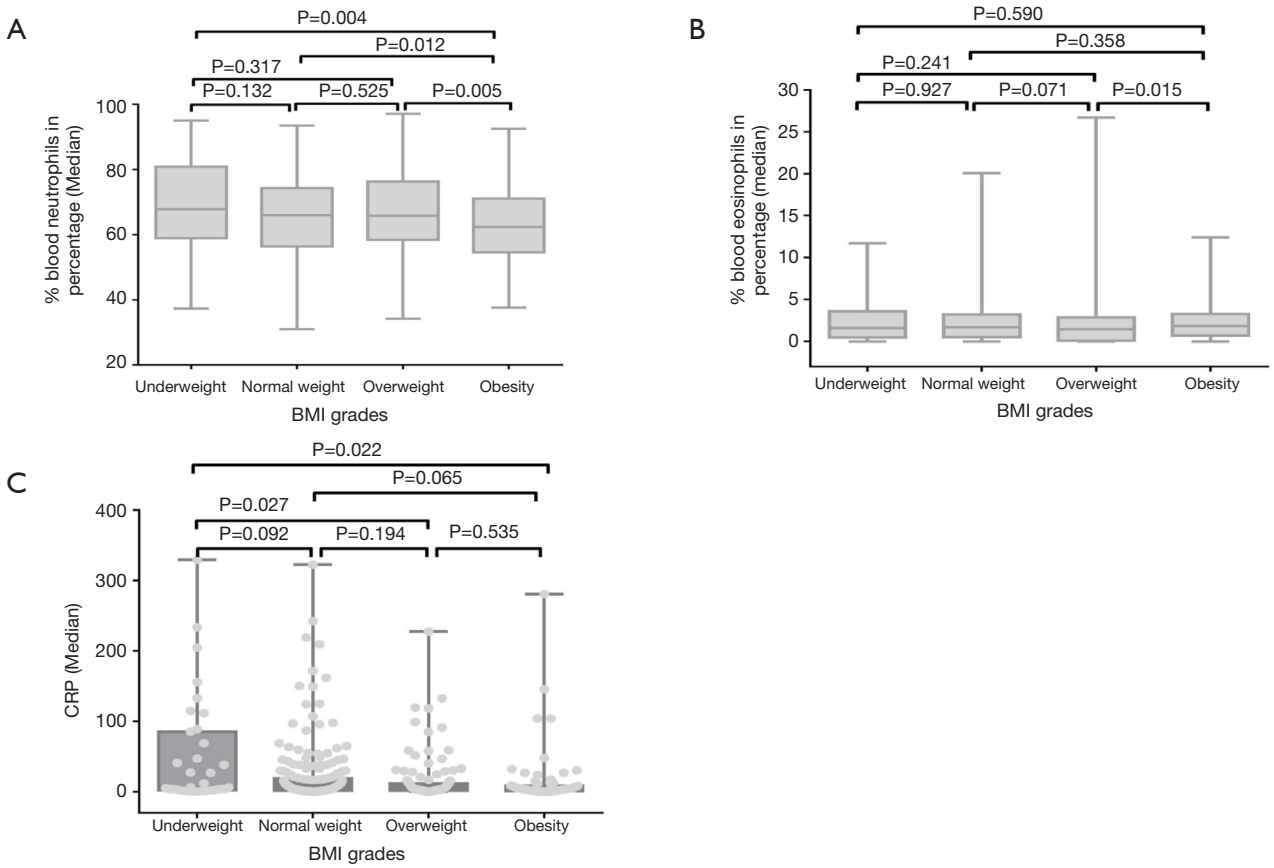

Figure 2 The association between BMI grades and inflammation level in COPD. (A) Median %neutrophils percent compared in four body mass index (BMI) grades. Box plots represent distributions of majority cases. (B) Median % eosinophils percent compared in four BMI grades. Box plots represent distributions of majority cases. (C) Median CRP compared in four BMI grades. Box plots and circles represent distributions of majority cases. BMI, body mass index; CRP, C reactive protein.

presented statistical significance. According to the results of optimization model, the Exp value was calculated. Compared with elder COPD patients, the youngers were possibly in better GOLD stages (Exp=1.052). Compared with female COPD patients, the males were possibly in worse GOLD stages (Exp=2.149). Compared with obesity class respectively, the underweight and normal weight patients were possibly in worse GOLD stages (Exp=3.297 and Exp=2.821). Compared with patients with PAP >30 mmHg (13), the patients with PAP ≤30 mmHg were possibly in better GOLD stages (Exp=0.571) (*Table* 7).

Discussion

The effect of BMI in the progression of COPD drew lots of attention (14). Our retrospectively real world research demonstrated that in patients with COPD, BMI was positively correlated with pulmonary function and negatively correlated with inflammation levels and acute exacerbations markedly.

It is generally accepted that improving nutrition status, enhancing respiratory muscles strength and reducing inflammation level are effective on long-term management of COPD (15). BMI was considered as an accurate indicator of nutrition in some degree. The prevalence of sarcopenia was common in COPD patients, especially in severe, elder or underweight patients (16). As shown in our results, compared to patients with COPD in lower BMI, those in higher BMI (overweight and obesity) had better pulmonary function, lower inflammation level (lower CRP and neutrophils) and less exacerbation. Better pulmonary function in our study were higher FEV_1%pred to show

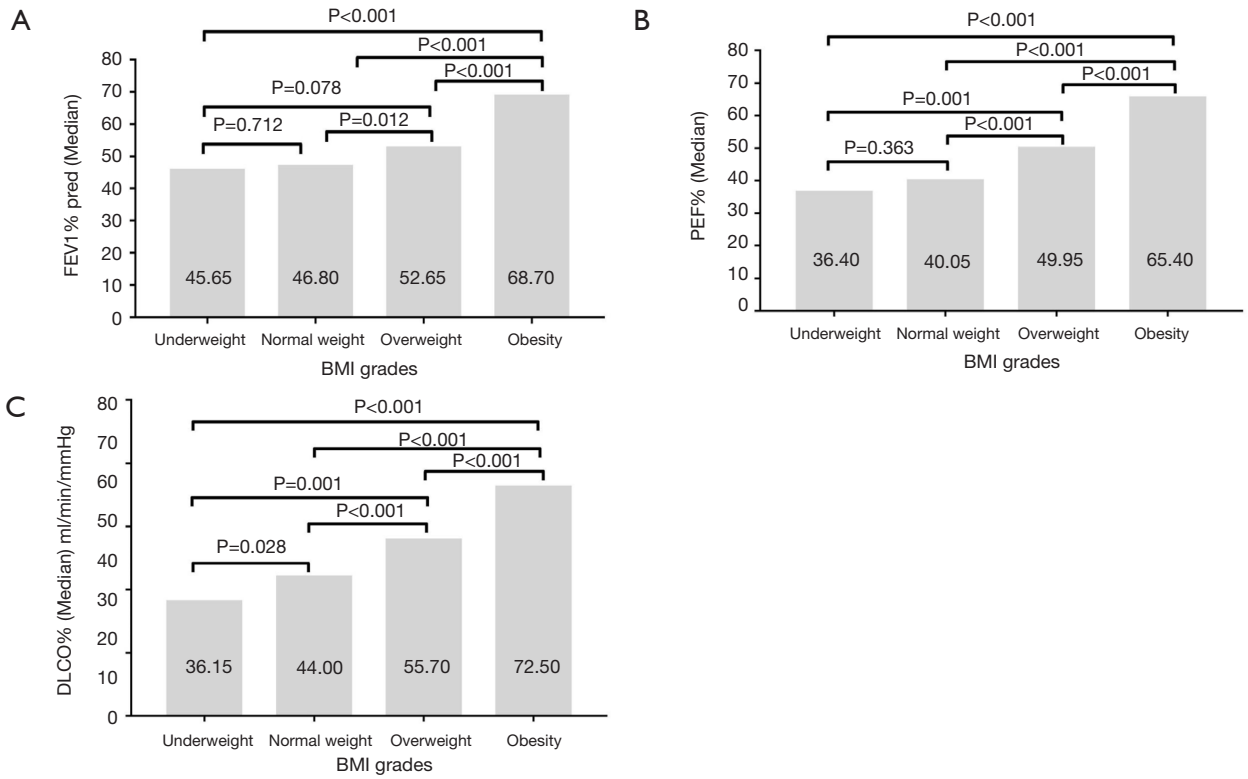

Figure 3 The association between BMI grades and lung function in COPD. (A) Median FEV_1 compared in four body mass index (BMI) grades. Values show the medians. Bars represent medians. (B) Median PEF compared in four BMI grades. Values show the medians. Bars represent medians. (C) Median DLCO compared in four BMI grades. Values show the medians. Bars represent medians. BMI, body mass index. FEV_1, forced expiratory volume in 1 second; PEF, peak expiratory flow; DLCO, diffusing capacity of carbon monoxide.

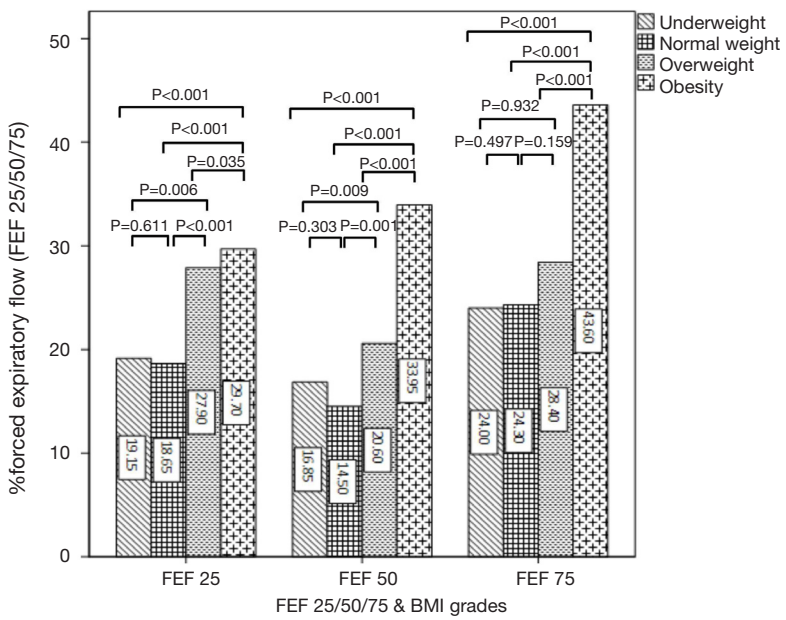

Figure 4 Median FEF25%/50%/75% compared in four body mass index (BMI) grades. Different lines style means different BMI grades. Bars represent medians. FEF25%/50%/75%, forced expiratory flow after 25%, 50%, 75%.

slighter airway obstruction, higher PEF and FEF_{25} or FEF_{50} and FEF_{75} to indicate better major or small airways function, and higher DLCO to present better lung diffusion function. In our study, no matter in total samples or subgroups divided by gender, smoking status, acute or stable COPD, the results were all consistent. All above results indicated that the overall prognosis might be better with higher BMI. We hypothesized the reasons might be: firstly, even though we did not analyze COPD patients in "blue bloater" or "pink puffer" clinical phenotypes, generally speaking, overweight and obesity COPD patients might have more nutrition intake and be in better nutrition status than underweight patients; secondly, bigger in size might let the patients have more and stronger muscles to facilitate breathing. Then, they could do more exercise and had more and stronger muscles in turn; thirdly, lower inflammation level could reduce the possibility of acute exacerbations (15,17-22). Therefore, BMI might be an important indicator to evaluate COPD patients' condition and long-term chronic diseases management.

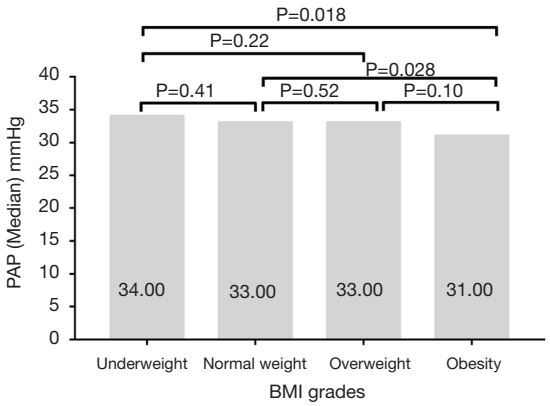

Figure 5 Median PAP compared in four body mass index (BMI) grades. Values show the medians. Bars represent medians. PAP, pulmonary arterial pressure.

Due to innate idea, some doctors think that obesity people may have glucocorticoid resistance (23), which seems that patients with COPD in obesity might need higher systemic corticosteroid doses and longer treatment for acute exacerbations. On the contrary, our research showed decreasing tendency in dose of systemic corticosteroid and length of stay with increasing of BMI grades, which also demonstrated that higher BMI might be a protective factor.

We further analyzed the effect of smoking. Different from non-smoking patients, acute moderate-severe exacerbations happened significantly less with the increase of BMI grades in smoking subgroups. In male COPD patients, the smokers were the majority and the exacerbations was significantly less with the increase of BMI. So, it would be important for male, smoking, underweight COPD patients

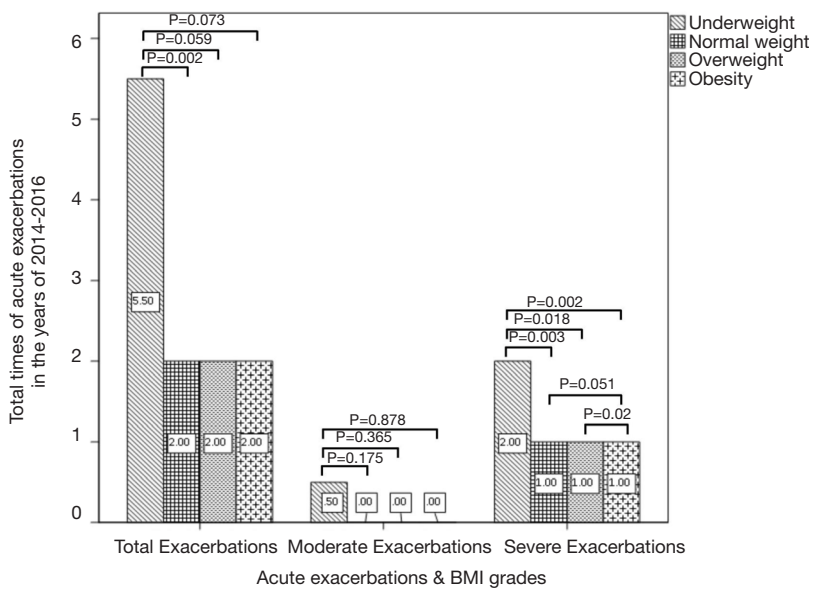

Figure 6 Different BMI grades, different lines style represents the frequency of different severity of COPD exacerbation. Values show the medians. COPD, chronic obstructive pulmonary disease; BMI, body mass index.

Table 3 Compared main indicators in male subgroup

Research indicators	Male subgroup				
	Underweight BMI <18.5 (n=47)	Normal weight 18.5≤ BMI <25 (n=276)	Overweight 25≤ BMI <30 (n=163)	Obesity BMI ≥30 (n=87)	P value
Main indicators of lung function					
FEV_1	46.10 (29.80–63.90)	44.30 (32.43–62.98)	50.30 (34.50–69.80)	68.60 (52.80-78.30)	<0.001
FVC*	72.98 (35.10–104.90)	66.26 (24.30–125.80)	66.72 (33.00–98.80)	76.89 (36.10-113.40)	<0.001
PEF	34.30 (27.10–57.80)	40.15 (27.03–56.30)	49.90 (32.90–69.80)	65.40 (51.90-79.40)	<0.001
FEF_{25}	18.60 (8.70–33.30)	18.15 (10.90–34.25)	26.80 (13.10–47.40)	29.70 (23.15-43.35)	<0.001
FEF_{50}	14.45 (8.73–32.58)	15.30 (9.60–26.58)	20.30 (11.00–38.70)	33.70 (22.80-51.20)	<0.001
FEF_{75}	24.30 (16.43–49.08)	22.85 (14.90–38.20)	25.10 (14.90–44.20)	44.45 (28.75-65.30)	<0.001
TLC	77.85 (66.28–93.63)	77.10 (64.05–87.40)	73.45 (63.20–86.60)	79.90 (69.10-86.90)	0.136
RV	99.10 (77.63–141.13)	101.50 (80.48–128.65)	101.60 (74.43–127.38)	103.00 (83.30–118.90)	0.671
DLCO*	40.79 (8.09–79.30)	45.61 (3.80–188.20)	53.36 (4.33–108.40)	72.20 (27.60–117.30)	<0.001
DLCO/VA*	47.52 (5.70–116.70)	56.32 (1.29–185.50)	71.61 (1.69–186.30)	97.03 (43.90–171.80)	<0.001
PAP (by Doppler cardiac ultrasound)	34.00 (31.00-44.00)	34.00 (28.00–41.75)	34.50 (28.00–41.25)	32.00 (28.50–34.00)	0.252
Times of AECOPD in years	6.00 (2.50–8.75)	2.00 (1.00–4.00)	2.00 (1.00–5.75)	2.00 (1.00–5.75)	0.110
Moderate exacerbations in 3 years	1.00 (0.00–4.25)	0.00 (0.00–2.00)	0.00 (0.00–2.75)	1.00 (0.00–5.50)	0.257
Severe exacerbations in 3 years	2.50 (1.00–5.25)	1.00 (1.00–2.00)	1.00 (1.00–1.75)	0.50 (0.00–1.00)	0.003
Frequency of AECOPD per year	2.00 (0.83–2.95)	0.70 (0.30–1.30)	0.70 (0.30–1.93)	0.70 (0.31–1.93)	0.080

Data presented as median (IQR) unless specified. *, data presented as mean (range). BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

to gain higher BMI in order to improve their prognosis. Interestingly, Schermer *et al.* also recently supported our results and indicated that higher BMI might be beneficial to ameliorate airway obstruction (24).

In our study, most of patients with COPD in obesity were in obesity class I (BMI 30–34.9 kg/m^2) (25), which were similar to the BMI distribution in total Chinese population (26). We found patients with COPD in BMI≥25 (overweight and obesity class I) had better pulmonary function, less exacerbations, lower PAP and lower inflammation level, compared with patients with COPD in underweight. Our results are partially opposite to some previous studies. Lambert's research showed patients with COPD in obesity were prevalent, and the increase of BMI was related to co-morbidities increasing, life quality declining, pulmonary function damaging, severe exacerbation risk rising and worse prognosis (10). Chilean researchers held the idea that CRP was weakly associated with fat mass/BMI and frequency of exacerbations (27). Weinreich *et al.* and Pekkarinen *et al.* considered lean body mass positively correlated with DLCO (28,29). The reason for this phenomenon is possibly that COPD patients in obesity in our study were all in lower obesity grade (BMI 30–34.9 kg/m^2), compared with COPD patients from western countries (nearly half of obesity patients were in BMI ≥35 kg/m^2), this phenomenon is more consistent with

Table 4 Compared main indicators in female subgroup

Research indicators	Female subgroup				P value
	Underweight BMI <18.5 (n=11)	Normal weight 18.5≤ BMI <25 (n=66)	Overweight 25≤ BMI <30 (n=45)	Obesity BMI ≥30 (n=49)	
Main indicators of lung function					
FEV_1	42.90 (36.20–63.00)	56.05 (40.93–67.55)	59.60 (43.15–84.50)	69.30 (59.05–78.70)	0.003
FVC	62.90 (49.30–69.50)	71.30 (59.73–88.63)	69.10 (57.65–90.75)	80.10 (65.80–90.15)	0.068
PEF	38.80 (23.70–51.70)	39.85 (29.15–57.48)	51.50 (34.20–77.30)	63.20 (46.20–79.95)	0.000
FEF_{25}	19.00 (13.80–25.60)	24.45 (15.30–35.43)	32.20 (17.60–64.30)	28.75 (20.78–45.18)	0.008
FEF_{50}	15.40 (8.80–18.80)	20.60 (12.35–24.88)	24.40 (12.50–51.65)	34.70 (22.90–39.95)	<0.001
FEF_{75}	29.05 (19.98–57.38)	29.30 (20.40–46.30)	32.90 (19.58–70.80)	43.60 (30.05–56.40)	0.117
TLC*	69.10 (47.40–101.60)	75.68 (3.66–119.30)	72.41 (4.58–105.90)	85.46 (45.60–138.50)	0.005
RV*	81.21 (51.40–122.90)	88.77 (1.99–174.00)	76.34 (2.60–140.80)	107.06 (50.70–212.60)	0.008
DLCO*	81.27 (49.80–132.00)	93.84 (1.64–182.00)	91.04 (1.95–217.60)	110.43 (38.00–227.40)	0.012
DLCO/VA*	31.91 (10.00–63.80)	54.42 (5.19–107.70)	63.08 (5.92–103.10)	71.90 (23.60–195.40)	<0.001
PAP (by Doppler cardiac ultrasound)	37.00 (27.00–44.00)	32.50 (29.25–37.00)	31.50 (28.25–33.25)	28.00 (22.25–37.25)	0.279
Times of AECOPD in 3 years	2.50 (2.00–5.25)	1.00 (1.00–3.00)	3.00 (1.00–7.00)	2.00 (1.00–4.50)	0.203
Moderate exacerbations in 3 years	0.50 (0.00–2.50)	0.00 (0.00–1.00)	0.00 (0.00–6.00)	0.00 (0.00–3.00)	0.943
Severe exacerbations in 3 years	1.50 (0.25–5.00)	1.00 (1.00–1.00)	1.00 (1.00–2.00)	1.00 (0.00–2.00)	0.203
Frequency of AECOPD per year	0.85 (0.70–1.75)	0.30 (0.30–1.00)	1.00 (0.30–2.30)	0.67 (0.30–1.50)	0.197

Data presented as median (IQR) unless specified. *, data presented as mean (range). BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Table 5 Compared main indicators in smokers subgroup

Research indicators	Smoker subgroup				
	Underweight BMI <18.5 (n=45)	Normal weight 18.5≤ BMI <25 (n=224)	Overweight 25≤ BMI <30 (n=118)	Obesity BMI ≥30 (n=41)	P value
Main indicators of lung function					
FEV_1	46.20 (30.35–68.40)	44.25 (32.43–60.18)	55.15 (37.95–75.00)	68.60 (52.15–76.85)	<0.001
FVC	73.20 (61.70–86.65)	64.15 (54.25–78.83)	69.05 (58.08–81.00)	77.90 (65.75–86.25)	0.001
PEF	36.90 (28.50–58.55)	39.70 (27.03–56.18)	53.65 (38.58–74.70)	65.40 (50.80–82.65)	<0.001
FEF_{25}	20.00 (11.90–41.80)	18.00 (10.80–32.45)	30.00 (14.20–53.05)	30.00 (24.00–47.90)	<0.001
FEF_{50}	14.80 (9.70–35.20)	15.30 (9.60–24.88)	23.85 (11.88–41.55)	34.00 (19.80–48.70)	<0.001
FEF_{75}	28.90 (16.70–49.35)	23.40 (15.48–37.13)	30.95 (15.35–45.43)	41.50 (27.25–65.60)	<0.001
TLC	78.10 (69.90–94.35)	78.00 (63.80–88.70)	78.10 (66.00–87.10)	76.50 (69.00–88.25)	0.297
RV	99.00 (85.30–139.30)	103.20 (79.10–131.10)	104.30 (77.15–129.05)	96.30 (79.63–118.48)	0.602
DLCO*	38.90 (24.95–58.85)	40.30 (28.90–56.00)	54.70 (38.85–70.85)	67.30 (55.73–89.13)	<0.001
DLCO/VA*	45.80 (27.25–63.30)	49.25 (35.43–72.33)	71.30 (51.40–89.75)	97.70 (79.23–118.30)	<0.001
PAP (by Doppler cardiac ultrasound)	33.00 (30.00–43.50)	33.00 (28.00–42.00)	31.00 (28.00–38.50)	31.00 (28.00–35.00)	0.434
Times of AECOPD in 3 years	6.00 (3.00–8.75)	2.00 (1.00–3.00)	2.00 (1.00–6.00)	2.00 (1.00–5.50)	0.045
Moderate exacerbations in 3 years	2.50 (0.00–4.25)	0.00 (0.00–2.00)	0.00 (0.00–3.00)	1.00 (0.00–5.00)	0.221
Severe exacerbations in 3 years	2.50 (1.00–5.25)	1.00 (1.00–2.00)	1.00 (1.00–2.00)	1.00 (0.00–1.00)	0.015
Frequency of AECOPD per year	2.00 (1.00–2.95)	0.70 (0.30–1.00)	0.70 (0.30–2.00)	0.70 (0.32–1.85)	0.031

Data presented as median (IQR) unless specified. *, data presented as mean (range). BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

the characteristics of Asians (10,25,26,30,31). Notably, in recent years, occidental researchers got the "Obesity paradox" conclusion in COPD domain. A research by Paul Stoll with 75 COPD patients showed that overweight and obesity were positive predictors of long-term survival in COPD patients (2,11).

For COPD patients in China, treatment is not standard; medication adherence is poor; and morbidity of COPD is still high (1,2). From our results, the healthy and properly body weight is good for long term management of COPD patients. This will be suitable for current Chinese condition, even Asian. The patients of this study were from Shandong Province Hospital and Shanghai Zhongshan Hospital. Their economic status, education levels and healthcare situation were similar to others from eastern China. So the conclusions of this study are representative. As we all know, obesity is a double-edged sword. In future studies, we will try to provide an optimal BMI cutoff point for patients with COPD to obtain benefits of better pulmonary function, lower level of inflammation and fewer exacerbations. There is a limitation that patients were followed-up three years frequency of AECOPD may have recall-bias in this retrospective research. Another, BMI may be not a good indicator to reflex the status of nutrition and muscles. So in next perspective study, we will pay attention to the role of body composition and fat free mass index in COPD patients.

Table 6 Compared main indicators in non-smokers subgroup

Research indicators	Non-smoker subgroup				
	Underweight BMI <18.5 (n=9)	Normal weight 18.5≤ BMI <25 (n=95)	Overweight 25≤ BMI <30 (n=68)	Obesity BMI ≥30 (n=73)	P value
Main indicators of lung function					
FEV_1	39.10 (27.20–44.50)	52.30 (37.80–70.60)	53.45 (37.98–71.83)	71.20 (56.45–79.85)	<0.001
FVC	51.60 (42.65–65.95)	69.60 (54.20–84.20)	62.00 (52.88–79.90)	80.10 (65.60–91.05)	<0.001
PEF	27.10 (23.00–43.20)	39.70 (27.90–58.30)	44.80 (30.15–64.05)	65.10 (50.15–80.20)	<0.001
FEF_{25}	14.00 (10.35–24.85)	23.40 (13.00–37.90)	26.95 (12.50–57.28)	29.60 (22.90–43.40)	0.002
FEF_{50}	12.70 (8.20–17.10)	19.90 (10.50–27.00)	20.35 (10.85–36.78)	34.80 (23.30–44.20)	<0.001
FEF_{75}	19.95 (19.68–22.78)	25.50 (15.85–44.05)	28.45 (15.95–58.33)	43.90 (32.55–64.35)	<0.001
TLC	60.30 (55.93–76.38)	73.00 (64.20–87.40)	72.00 (60.70–82.45)	83.90 (71.53–92.70)	0.001
RV	77.90 (60.18–89.28)	97.50 (75.00–114.65)	85.20 (70.20–112.75)	106.00 (87.00–118.98)	0.012
DLCO*	25.71 (8.10–63.80)	56.65 (5.19–104.60)	57.55 (5.92–103.10)	70.63 (23.60–107.90)	<0.001
DLCO/VA*	35.10 (6.60–68.20)	68.51 (1.90–185.50)	77.13 (1.75–130.30)	89.84 (29.40–171.80)	<0.001
PAP (by Doppler cardiac ultrasound)	42.00 (29.00-44.00)	33.00 (28.00–40.00)	33.00 (29.00–40.75)	30.50 (22.25–33.00)	0.235
Times of AECOPD in 3 years	2.00 (1.25–5.00)	1.00 (1.00–3.00)	2.00 (1.00–6.00)	2.00 (0.75–6.25)	0.576
Moderate exacerbations in 3 years	0.00 (0.00–0.75)	0.00 (0.00–1.00)	0.00 (0.00–3.00)	0.00 (0.00–6.25)	0.797
Severe exacerbations in 3 years	1.50 (1.00–5.00)	1.00 (1.00–1.00)	1.00 (1.00–1.00)	1.00 (0.00–2.00)	0.17
Frequency of AECOPD per year	0.70 (0.40–1.68)	0.30 (0.30–1.00)	0.70 (0.30–2.00)	0.69 (0.23–2.08)	0.615

Data presented as median (IQR) unless specified. *, data presented as mean (range). BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; FEF, forced expiratory flow; TLC, total lung capacity; RV, residual volume; DLCO, diffusing capacity of carbon monoxide; DLCO/VA, ratio of carbon monoxide diffusion capacity to alveolar ventilation; PAP, pulmonary arterial pressure; AECOPD, acute exacerbation of chronic obstructive pulmonary disease.

Table 7 The optimization model of ordinal multinational logistic regression

Factors in model	Estimate	Std. Error	Wald	df	P value	95% CI	
						Lower bound	Upper bound
Threshold							
GOLD 1	−4.208	0.989	18.12	1	0	−6.145	−2.27
GOLD 2	−2.473	0.969	6.509	1	0.011	−4.374	−0.573
GOLD 3	−0.566	0.956	0.351	1	0.554	−2.441	1.308
Location							
Age	−0.051	0.013	15.198	1	0	−0.077	−0.025
Male	0.765	0.271	7.983	1	0.005	0.234	1.296
Female[a]	0	0	0	0	0	0	0
Underweight	1.193	0.458	6.799	1	0.009	0.296	2.09
Normal weight	1.037	0.365	8.061	1	0.005	0.321	1.754
Overweight	0.634	0.385	2.705	1	0.1	−0.121	1.389
Obesity[a]	0	0	0	0	0	0	0
PAP ≤30 mmHg	−0.560	0.241	5.371	1	0.02	−1.033	−0.086
PAP >30 mmHg[a]	0	0	0	0	0	0	0

[a], this parameter is redundant; therefore it is set to zero. GOLD, global initiative for chronic obstructive lung disease; PAP, pulmonary arterial pressure; Std. Error, standard error; CI, confidence interval.

Conclusions

In our study, with the increase of BMI, the pulmonary function improved while the inflammation level and frequencies of exacerbations decreased. So, BMI might be a useful indicator to predict the prognosis of patients with COPD. This study provided a good idea for further related research and COPD long-term management.

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Footnote

Conflicts of Interest: The authors report no conflicts of interest in this work.

Ethical Statement: As there was a retrospective study, no randomization, no new treatment being explored and no potential harm to the patients. This study was approved by Shandong Provincial Hospital Medical Ethics Committee (Ethical Review of Medical Research on Human Being No. 2016-23).

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