

Identification of relevant variables and construction of a multidimensional index for predicting mortality in COPD patients

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Background and objective: The Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index is a well-known metric for chronic obstructive pulmonary disease (COPD), but it is inadequate for predicting mortality. This study proposed a new index that combines inspiratory muscle training with the BODE index and verified its ability to predict mortality in patients with COPD.

Methods: Cox regression identified predictors of mortality, which were then included in the new index. The receiver operating characteristic (ROC) curve verified the ability of the new index to predict mortality. The Kaplan-Meier curves compared the survival rates of patients with different scores on the new index.

Results: Among the 326 patients, 48 died during follow-up (1–59 months). Cox regression showed that the fat-free mass index (FFMI), forced expiratory volume in one second/the predicted value (FEV₁%), modified Medical Research Council (mMRC) score, six-minute-walk test (6MWT) distance, and maximal inspiratory pressure were predictors of mortality ($P < 0.05$); these variables were included in the FODEP index. The AUC of the FODEP index (0.860, 95% CI: 0.817–0.896) was greater than that of the BODE index (0.778, 95% CI: 0.729–0.822). The Kaplan-Meier curves suggested that as the FODEP score increased, so did the risk of mortality in patients with COPD. The cumulative survival in the group with the highest FODEP-value was significantly lower than that in the other groups ($P < 0.01$).

Conclusion: The FODEP index was more effective than the BODE index at predicting the risk of mortality in patients with COPD.

Keywords: inspiratory muscle training, FODEP, BODE

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Introduction

Chronic obstructive pulmonary disease (COPD), with its high prevalence, mortality, and disability rates and poor treatment response, not only seriously affects patient quality of life but also imposes large societal burdens.¹ COPD is heterogeneous and is mainly characterized by respiratory symptoms, although there are also extrapulmonary effects, such as malnutrition^{2,3} and muscle dysfunction.⁴ The prognosis of patients with COPD is affected by multiple factors, such as the patients' symptoms, nutritional status,⁵ exercise tolerance⁶ and muscle function.⁴ A multidimensional evaluation is therefore needed.

The Body mass index, airflow Obstruction, Dyspnea, and Exercise (BODE) index, proposed by Celli et al⁷ as a multidimensional assessment, is widely used to evaluate COPD.⁸ It consists of the body mass index (BMI), airflow obstruction

(forced expiratory volume in one second/the predicted value ($FEV_1\%$)), dyspnea (measured by the modified Medical Research Council (mMRC) scale), and exercise capacity (measured by the six-minute-walk test (6MWT)).⁷ Compared with spirometry or the ABCD assessment tool from the Global Initiative for Chronic Obstructive Lung Disease (GOLD),⁹ the BODE index more comprehensively reflects the characteristics of COPD by evaluating the patient's disease manifestations, nutrition, exercise, and pulmonary function and better predicts mortality¹⁰ and hospitalization.¹ It is a pioneering tool for the multidimensional comprehensive assessment of COPD.

However, limitations still exist in the BODE index. First, in the BODE, $FEV_1\%$ is classified according to the three stages identified by the American Thoracic Society (ATS), which is based on a spirometry test and can not directly reflect the severity of the disease.¹¹ However, the GOLD classification system is associated with the severity of COPD¹² and its cut-off values tend to be simpler. Furthermore, nutrition is an important factor that affects the prognosis of patients with COPD,¹³ and the mortality rate is lower in overweight patients than in normal-weight or low-weight patients.¹⁴ Among patients with COPD, weight loss mainly results from the loss of skeletal muscle.¹³ Muscle atrophy in COPD is caused by dyspnea, inadequate nutritional intake, insufficient exercise, and inflammation.¹⁵ The fat-free mass index (FFMI)¹⁶ has been shown to be better than BMI for assessing the nutritional status of patients with COPD.⁵ Finally, in addition to limb muscle weakness, respiratory muscle dysfunction is also frequently observed. Inspiratory muscle weakness is not only an important cause of acute exacerbation¹⁷ but also a significant predictor of death in patients with COPD.¹⁸ However, the BODE index does not include any indicator of respiratory muscle function.

In summary, this study aimed to develop a new index by modifying the BODE index and verifying the ability of the modified index to predict the mortality of patients with COPD to provide a new tool for clinicians when evaluating patients with COPD.

Materials and methods

Patients

From January 1, 2013 to January 1, 2014, 326 outpatients (63 females) with COPD were recruited from Zhujiang Hospital for this prospective cohort study. The inclusion

criteria were as follows: age ≥ 40 years and diagnosis of COPD according to spirometry ($FEV_1/FVC < 0.70$ after inhaling 400 μg of salbutamol aerosol). All patients were clinically stable and received appropriate therapy. Patients with bronchial asthma, advanced tuberculosis, bronchiectasis, severe cardiovascular disease, malignant tumors and those who had suffered a respiratory infection in the previous 4 weeks or participated in a rehabilitation program in the previous 3 months were excluded.

Data collection

The data collected at the baseline from all patients include age; sex; pack-years of smoking; pulmonary function, BMI, FFMI, mMRC, 6MWT, maximal inspiratory pressure (MIP), maximal expiratory pressure (MEP), exacerbations in the previous year and COPD assessment test (CAT) score.

Spirometry was performed with a spirometer (Pony FX229; Cosmed, Rome, Italy) at intervals of 20 mins before and after inhalation of 400 μg of salbutamol aerosol.¹⁹ The collected parameters of pulmonary function included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), FEV_1/FVC and $FEV_1\%$. The predicted values of FEV_1 and FVC are calculated by using ECSC regression equations with appropriate conversion factors.²⁰

FFMI was measured with multifrequency electrodes (Inbody720; Biospace, Seoul, Korea). Each patient was measured twice and the average was calculated and used in subsequent analyses. BMI was calculated using the following formula: $\text{body mass}/(\text{height})^2$ (kg/m^2). FFMI was calculated using the following formula: $\text{fat-free body mass}/(\text{height})^2$ (kg/m^2).

The 6MWT was conducted under the supervision of an experienced clinician. During the test, the oxygen saturation level was maintained at above 90%. The tests were performed twice with an interval of at least 1 hr between the two tests. The maximum test result was used in the subsequent analyses.

MIP and MEP were assessed with a digital manometer (AZ-8205; AZ Instruics, Taiwan). Quality control was conducted according to the ATS and the European Respiratory Society (ERS) protocols, and the maximum value out of three measurements was selected.²¹

Follow-up

Subjects were followed every 3 months for at least 2 years or until death. Acute exacerbations requiring hospital

management (emergency visits or admissions), if any, were recorded during the follow-up. The follow-up methods included telephone calls, clinic appointments and home visits. Subjects who were lost to follow-up were excluded from the analysis. One researcher identified and recorded the cause of death listed on the hospital record.

Written informed consent was obtained from all subjects. The protocol, which was in accordance with the Declaration of Helsinki, was approved by the ethics committee of Zhujiang Hospital, Southern Medical University, Guangzhou.

Identification of factors predicting mortality

Univariate Cox regression was used to identify the factors that significantly predicted mortality. The variables included were age, sex, pack-years of smoking, FVC, FEV₁, FEV₁/FVC, FEV₁%, BMI, FFMI, 6MWT, mMRC score, MIP, MEP and number of exacerbations in the previous year. Those factors that were statistically significant were included in multivariate Cox regression.

Construction of FODEP, the new index

The following modifications were made to the BODE index: (1) the reclassification of lung function according to the GOLD guidelines; (2) the substitution of the FFMI for BMI; and (3) the addition of MIP. The newly constructed index was named the FODEP index.

The FODEP index scores range from 0 to 15, as shown in Table 1. According to the classification of airflow limitation based on the GOLD guidelines,¹² the threshold for FEV₁% ranged from 0 to 3. The value of FFMI ranged from 0 (FFMI ≥ 21.7 kg/m² for males or FFMI ≥ 18.2 kg/m² for females) to 3

(FFMI ≤ 16.6 kg/m² for males or FFMI ≤ 14.5 kg/m² for females), based on the ATS statement.²² As recommended,²³ a MIP > 60 cmH₂O is considered normal. The value of MIP was 0 when MIP was > 60 cmH₂O; otherwise, it was 3. The ranges of mMRC and 6MWT were the same as in the BODE index.

Verification of the FODEP index

A receiver operating characteristic (ROC) curve analysis was performed to compare the abilities of the BODE index and the FODEP index to predict mortality in patients with COPD. Patients were categorized into quartiles according to their FODEP scores. Then, Kaplan–Meier curves were plotted for all four groups to compare the differences in survival among the groups.

Statistical analysis

Continuous variables are presented as the mean \pm SD, unless otherwise stated. Associations between factors and mortality were evaluated using Cox regression. ROC curve analysis was performed to compare the overall performances of the FODEP index and the BODE index with regard to the prognostic prediction and to determine the optimal threshold. Kaplan–Meier curves were constructed to determine the differences in survival among patients grouped according to their FODEP score quartile. Pearson correlation analysis was used to evaluate the relationship between FODEP and hospitalization. $P < 0.05$ was considered statistically significant. Except for the ROC curve analyses, which were performed with MedCalc Statistical Software version 15.2.2 (MedCalc Software, Ostend, Belgium), all other analyses were conducted with SPSS v. 20 (IBM Corporation, Armonk, NY, USA).

Table 1 Construction of the fat-free mass index, degree of airflow obstruction, Dyspnea, exercise capacity, and maximal inspiratory pressure (FODEP) index and the number of subjects in each of the 4 stages for each component of the FODEP index

Variables/N		0	1	2	3
FEV ₁ % (%)/N		$\geq 80/31$	50–79/146	30–49/108	$< 30/41$
6MWT (m)/N		$\geq 350/251$	250–349/41	150–249/25	$\leq 149/9$
mMRC/N		0–1/151	2/88	3/55	4/32
FFMI (kg/m ²)/N	For males	$\geq 21.7/5$	19.8–21.6/12	16.7–19.7/99	$\leq 16.6/148$
	For females	$\geq 18.2/4$	16.8–18.1/10	14.6–16.7/31	$\leq 14.5/17$
MIP (cmH ₂ O)/N		$> 60/140$			$\leq 60/186$

Abbreviations: FEV₁%, forced expiratory volume in one second/the predicted value; 6MWT, the six-minute-walk test; mMRC, the modified Medical Research Council; FFMI, fat-free mass index; MIP, maximal inspiratory pressure; N, number.

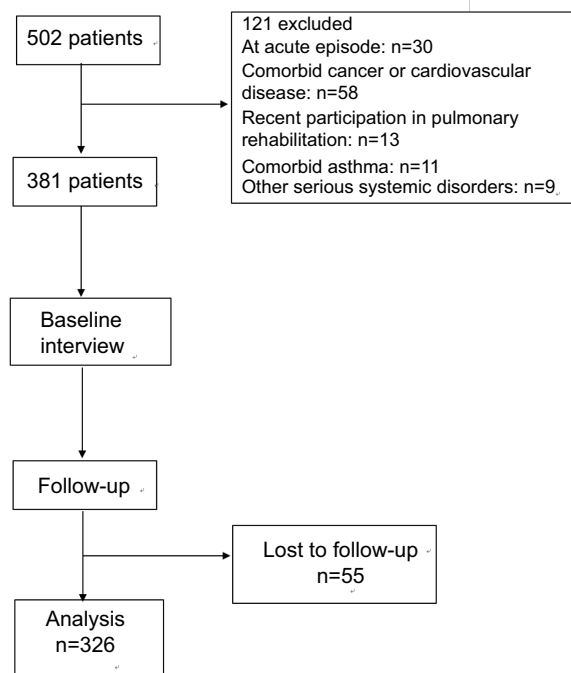


Figure 1 Flow chart of the study.

Note: We excluded such patients who were at acute episode at the time of enrollment, accompanied by more severe dyspnea and other symptoms, for they were unable to take the lung function test and six-minute-walk test in this study.

Results

Patient characteristics

In total, 502 patients were initially enrolled, of whom 121 patients were excluded. Then, the remaining 381 patients were

followed until the end of the study or death, while 55 patients were lost to follow-up. Thus, 326 patients (63 females; median age: 67.6 years [range: 41–92 years]) were included in the analysis (Figure 1). In this study, patients were followed for a median of 34 months (range: 1–59 months). The baseline characteristics of the survivors and nonsurvivors are shown in Table 2. During follow-up, 19 subjects (5.8%) died in the first 24 months, and 48 (14.7%) died in the first 59 months. Figure 2 shows the change in mortality of the subjects in two different periods. The majority of patients (56 percent) died of respiratory failure, 15 percent died of cardiogenic shock, 10 percent of cerebrovascular accident, and the rest of miscellaneous causes.

Identification of factors predicting mortality

Univariate Cox analysis suggested that the following factors were significantly associated with mortality (Table 3): age, FFMI, FEV₁%, mMRC score, 6MWT distance, MIP, FEV₁, FVC, MEP, and the number of exacerbations in the previous year. Interestingly, the association between BMI and mortality was not significant ($P=0.069$). Incorporating the above factors into multivariate Cox analysis revealed that the following factors were still significantly associated with mortality (Table 4): FFMI ($P=0.001$), FEV₁% ($P<0.001$), mMRC score ($P=0.025$), 6MWT distance ($P=0.001$), and MIP ($P=0.001$).

Table 2 Baseline characteristics of 277 survivors and 48 nonsurvivors

Baseline characteristics	Survivors (n=277)	Nonsurvivors (n=48)	P-value
Female/Male	56/221	8/40	
Age	66.87±10.42	71.81±9.30	<0.01
Pack-years smoked	24.67±28.86	24.35±22.86	0.943
BMI (kg/m ²)	22.26±3.80	21.36±3.57	0.129
FFMI (kg/m ²)	16.53±2.334	14.32±2.01	<0.001
FEV ₁ (L)	1.31±0.55	1.09±0.51	<0.05
FEV ₁ % (%)	54.89±19.34	33.65±13.10	<0.001
FVC (L)	2.49±0.83	2.19±0.78	<0.05
FEV ₁ /FVC	52.91±12.20	50.41±13.09	0.195
mMRC	1.54±1.04	3.00±1.24	<0.001
6MWT (m)	436.70±105.26	327.00±127.74	<0.001
MIP (cmH ₂ O)	59.17±19.38	41.67±12.21	<0.001
CAT	15.23±7.62	19.71±8.70	<0.001
Exacerbations in the previous year	0.93±1.10	1.33±1.26	0.041

Notes: Data are presented as the mean ± SD unless otherwise indicated.

Abbreviations: BMI, body mass index; FFMI, fat-free mass index; FEV₁, forced expiratory volume in one second; FEV₁%, forced expiratory volume in one second/the predicted value; FVC, forced vital capacity; mMRC, the modified Medical Research Council; 6MWT, the six-minute-walk test; MIP, maximal inspiratory pressure; CAT, COPD Assessment Test.

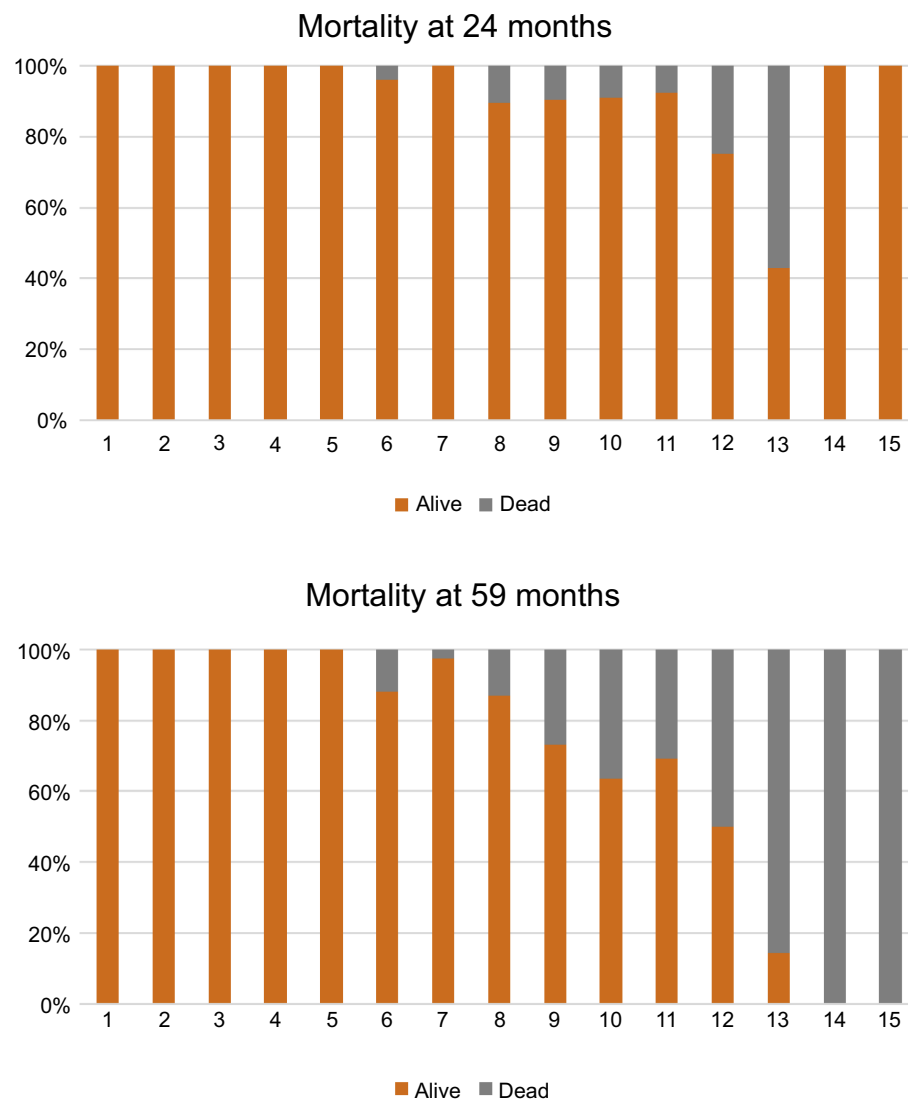


Figure 2 FODEP scores and mortality rates over time. For each unit of the FODEP score, the bars show the proportion of subjects alive and dead at the end of 24 months and 59 months.

Evaluation of the ability of the FODEP index to predict mortality

The ROC curves for the BODE index and the FODEP index are shown in [Figure 3](#). The AUCs for the BODE index and the FODEP index were 0.778 (95% CI: 0.729–0.822) and 0.860 (95% CI: 0.817–0.896), respectively. The AUC of the FODEP index was significantly different from that of the BODE index ($P<0.001$ by Delong's method).²⁴ The Youden index of the FODEP index was 0.577, with a sensitivity and specificity of 81.25% and 76.45%, respectively. The Youden index for the BODE index was 0.427, with a sensitivity and specificity of 72.92% and 69.78%, respectively.

Patients were categorized into quartiles according to their FODEP scores as follows: 0–4, 5–8, 9–12, and 13–15. The Kaplan-Meier curves are presented in [Figure 4](#). The survival

rate decreased as the FODEP index increased; the association was more significant with a higher FODEP index ($P<0.001$ by the log-rank test).

Correlation between the FODEP index and the number of hospitalizations

The FODEP index has a moderate correlation with the number of hospitalizations ($r=0.384$, $P<0.001$). However, as shown in [Figure 5](#), the ROC curves showed there was no significant difference in predicting the risk of rehospitalization between the BODE index and the FODEP index ($P=0.7046$). The AUC of the FODEP index was 0.632 (95% CI: 0.577–0.684), and the AUC of the BODE index was 0.624 (95% CI: 0.569–0.677). The Youden index of the FODEP index was 0.238, with a sensitivity

Table 3 Univariate Cox regression analysis of independent predictors of death in COPD patients

Predictor	B	HR (95% CI)	p-value
Sex	0.231	1.259 (0.589, 1.693)	0.552
Age	0.052	1.054 (1.021, 1.088)	0.001
Pack-years smoked	0.003	1.003 (0.993, 1.013)	0.595
FFMI (kg/m ²)	-0.383	0.681 (0.605, 0.767)	<0.001
BMI (kg/m ²)	-0.74	0.929 (0.857, 1.006)	0.069
FEV ₁ % (%)	-0.083	0.920 (0.898, 0.943)	<0.001
mMRC	0.945	2.574 (1.925, 3.441)	<0.001
6MWT (m)	-0.007	0.993 (0.991, 0.995)	<0.001
FEV ₁ (L)	-0.784	0.457 (0.254, 0.822)	0.009
FVC (L)	-0.416	0.659 (0.458, 0.950)	0.025
FEV ₁ /FVC	-0.018	0.982 (0.960, 1.004)	0.110
Number of exacerbations in the previous year	0.249	1.283 (1.019, 1.615)	0.034
MIP (cmH ₂ O)	-0.054	0.948 (0.930, 0.966)	<0.001
MEP (cmH ₂ O)	-0.22	0.978 (0.964, 0.992)	0.002

Abbreviations: B, beta; HR, hazard ratio; FFMI, fat-free mass index; BMI, body mass index; FEV₁%, forced expiratory volume in one second/the predicted value; mMRC, the modified Medical Research Council; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; 6MWT, the six-minute-walk test; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

Table 4 Multivariate Cox regression analysis of independent predictors of mortality in COPD patients

Predictor	B	HR (95% CI)	p-value
FFMI (kg/m ²)	-0.268	0.765(0.657,0.891)	0.001
FEV ₁ % (%)	-0.049	0.952(0.929,0.975)	<0.001
FEV ₁ (L)	0.596	1.815(0.502,6.559)	0.36
FVC (L)	0.155	1.168(0.545,2.505)	0.69
Number of exacerbations in the previous year	-0.053	0.948(0.710,1.226)	0.72
Age	-0.006	0.994(0.957,1.032)	0.74
mMRC	0.340	1.404(1.050,1.878)	0.02
6MWT (m)	-0.006	0.994(0.990,0.997)	0.001
MEP (cmH ₂ O)	0.012	1.012(0.991,1.034)	0.259
MIP (cmH ₂ O)	-0.046	0.955(0.928,0.982)	0.001

Abbreviations: B, beta; HR, hazard ratio; FFMI, fat-free mass index; FEV₁%, forced expiratory volume in one second/the predicted value; FEV₁, forced expiratory volume in one second; FVC, forced vital capacity; mMRC, the modified Medical Research Council; 6MWT, the six-minute-walk test; MIP, maximal inspiratory pressure; MEP, maximal expiratory pressure.

and specificity of 72.12% and 51.69%, respectively. The Youden index of the BODE index was 0.186, with a sensitivity and specificity of 63.46% and 55.08%, respectively.

Discussion

This study has shown that the FODEP index, consisting of FFMI, FEV₁%, the mMRC score, the 6MWT distance and MIP, is a significant and independent predictor of mortality, with every one point increase in the FODEP index score associated with a 1.55-fold increased risk of death.

Univariate Cox regression showed that age, FFMI, FEV₁%, mMRC score, 6MWT distance, MIP, FEV₁, FVC, MEP, and the number of exacerbations in the previous

year were independent predictors of the risk of mortality in COPD patients; these findings were in line with the results of other studies such as DOSE,²⁵ which indicated that smoking status and exacerbation frequency (as well as dyspnea and airflow obstruction) were important predictive factors, or ADO,²⁶ which included age (plus dyspnea and airflow obstruction). However, we found that only five factors (FFMI, FEV₁%, mMRC score, 6MWT distance and MIP) were still significantly correlated with mortality in the multivariate Cox regression, which is the reason those variable were chosen for inclusion in the FODEP index.

BMI was used to assess nutritional status in the BODE index; however, it does not reflect the status of skeletal muscle in patients with COPD.²⁷ Compared with BMI,

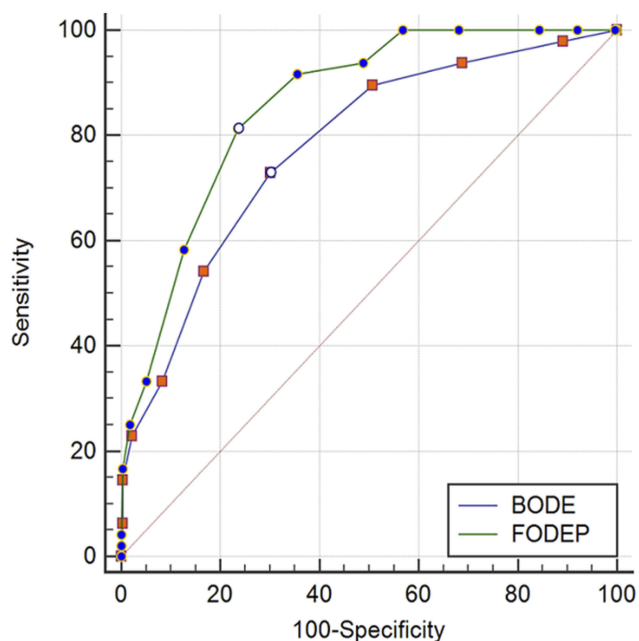


Figure 3 ROC curves of the BODE and FODEP index for the prediction of mortality in COPD patients.

Note: The AUC of FODEP: 0.860 (95% CI: 0.817–0.896), BODE: 0.778 (95% CI: 0.729–0.822). Difference of ROC curves was significant between FODEP and BODE ($P < 0.001$ by Delong et al (1988)).²⁴

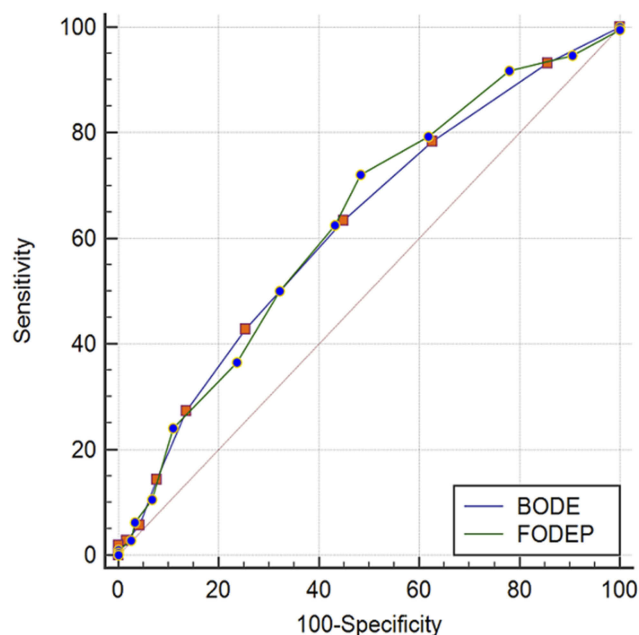


Figure 5 ROC curves of the BODE and FODEP indexes for the prediction of the risk of COPD-related hospitalization.

Note: The AUC of FODEP: 0.632 (95% CI: 0.577–0.684), BODE: 0.624 (95% CI: 0.569–0.677). Difference of ROC curves was not significant between FODEP and BODE ($P = 0.7046$ by Delong et al (1988)).²⁴

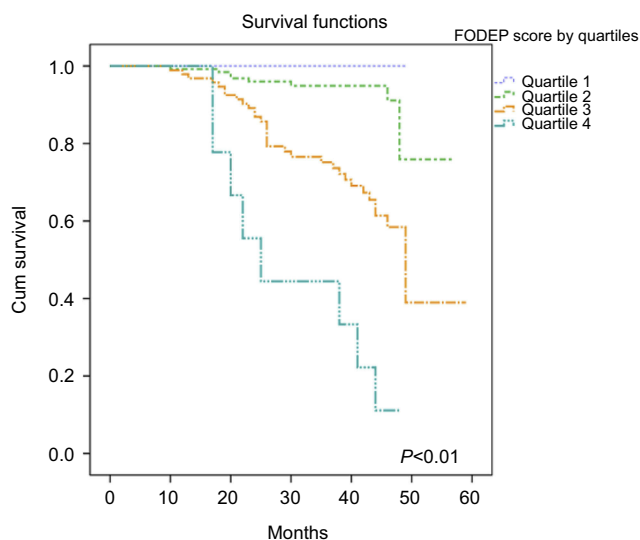


Figure 4 Kaplan-Meier survival curves for patients stratified by quartiles of FODEP scores.

Note: Quartile 1: scores of 0 to 4; Quartile 2: scores of 5 to 8; Quartile 3: scores of 9 to 12; Quartile 4: scores of 13 to 15. Survival differed significantly among the 4 groups: $P < 0.01$ by the log rank test.

FFMI seems to be more related to muscle atrophy, exercise capacity, and quality of life. FFMI was also found to be a predictor of overall mortality in subjects with normal BMI.²⁸ Thus, replacing BMI with FFMI could more accurately reflect the nutritional status of COPD patients.

Inspiratory muscle strength is commonly reduced in COPD patients, and the degree of reduction is related to the severity of disease.¹⁵ Previous studies reported that respiratory muscle weakness is observed in 20–50% of patients, with the reduction ranging from 15% to 30%.²⁹ In 2010, Hill et al²³ proposed that respiratory muscle strength is closely linked to dyspnea and exercise capacity. Inspiratory muscle strength, as assessed by MIP, has been shown to be an independent predictor of survival in COPD patients,¹⁸ which was consistent with the findings of this study. In addition, as it is less affected by external factors, MIP provides a convenient metric for inspiratory strength. Therefore, MIP was included in the FODEP index.

The ROC curve suggests that the FODEP index may be a better predictor of mortality than the BODE index, although it remains to be confirmed by further study. Kaplan-Meier survival analysis revealed that the FODEP score was closely related to the risk of mortality in patients with COPD, and the cumulative survival rate of patients with the highest FODEP score was significantly lower than that of patients with lower scores.

Exacerbations of COPD are key events in COPD management,³⁰ making exacerbation frequency a marker of disease severity.³¹ Preventing exacerbations of COPD,

especially hospitalizations, is a major goal in the management of patients with COPD. Previous studies have suggested that the BODE index is a better predictor of hospitalization for COPD than is GOLD staging based on FEV₁,¹ while our study suggested that the FODEP index has a similar ability to predict COPD-related hospitalization as that of the BODE index. Thus, the FODEP index may be helpful in predicting hospitalizations in COPD patients.

This study has certain limitations. The cohort was relatively small, and the observation duration was not long enough. Second, previous studies have shown that image-based COPD classifications can indicate degrees of dyspnea and acute exacerbations.³² Van Tho et al suggested that COPD patients with different phenotypes on imaging examinations may present with different clinical manifestations.³² However, imaging-based phenotypes of COPD were not included in the multidimensional indicators in this study.

Conclusion

Compared with the BODE index, the FODEP index is better able to predict the prognosis of COPD patients. Moreover, the FODEP index provides further insights into the comprehensive assessment and management of COPD patients.

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Author contributions

Xin Chen is the guarantor of this research. Chunquan Ou and Xin Chen were responsible for the study concept and design. Limei Xu, Tiaofei Ye and Jiahui Li contributed to patient recruitment and patient follow-up. Yuhe Hu and Wenhui Xu acquired the data. Kai Wang analyzed the data. All authors contributed to the data analysis and manuscript drafting and revision, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

Disclosure

The authors report that there are no conflicts of interest related to this work.

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