ORIGINAL RESEARCH

CODEXS: A New Multidimensional Index to Better Predict Frequent COPD Exacerbators with Inclusion of Depression Score

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Purpose: Depression is reported in association with chronic obstructive pulmonary disease (COPD). However, to date, no multidimensional indices have taken depression into consideration to predict COPD patients' prognosis. This study aimed to determine whether a new multidimensional index named CODEXS, based on comorbidities, airflow obstruction, dyspnea, previous exacerbation and depression assessed by Self-Rating Depression Scale (SDS), could predict 1-year exacerbations.

Methods: This was a prospective study, patients with stable COPD were used to develop CODEXS at the first visit, and followed up in the 3rd, 6th, and 12th months. After the last visit, patients were divided into frequent and infrequent exacerbators. Another cohort of COPD patients was used for validation. The SDS scoring system in the multidimensional indices ranged from 0 to 4 based on the modified SDS value, representing no depression (25–39 [0], 40–49 [1]), mild depression (50–59), moderate depression (60–69), and severe depression (≥70). Comorbidity, dyspnea, airflow obstruction, and severe exacerbations were calculated according to CODEX thresholds.

Results: Two sets of 105 and 107 patients were recruited in the development and validation cohorts, respectively. Depression was demonstrated as an independent risk factor for frequent exacerbators (odds ratio (OR)= 1.14, 95% confidence interval (CI) = 1.06–1.23, $P < 0.001$). The prevalence of depression in frequent exacerbators (35.09%) was higher than that in infrequent exacerbators. CODEXS was significantly associated with exacerbation (OR =2.91; 95% CI, 1.-89–4.48, $p<0.001$). Receiver operating characteristic (ROC) curve comparison showed that CODEXS was superior to BODEX(BMI, airflow obstruction, dyspnea, previous exacerbation), BODE (BMI, airflow obstruction, dyspnea, exercise), and updated ADO (age, dyspnea, and airflow obstruction) indices, confirmed by the validation cohort with sensitivity at 85.94% and specificity at 76.74%.

Conclusion: Depression is an independent risk factor for COPD exacerbation. CODEXS is a useful predictor for predicting frequent exacerbators within 1 year and is superior to other previously published indices.

Keywords: COPD, depression, Self-Rating Depression Scale, exacerbation, CODEXS

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Introduction

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease which is characterized by persistent respiratory symptoms and persistent airflow limitation, and is currently the fourth leading cause of mortality worldwide. Acute exacerbation of COPD (AECOPD) is an event defined as acute worsening of respiratory symptoms that result in additional therapy.[1] It can accelerate deterioration of the disease,[2,3] lead to

a heavy economic burden,[4] and increase mortality.[5] Recently, there is an increasing recognition that COPD is a complex and heterogeneous disease.[6] In the review we published in 2017,[7] we concluded that there are different phenotypes in the exacerbation stage, one of which is called the "frequent exacerbator" phenotype. The frequency of AECOPD is variable among patients; a proportion of COPD patients seldom exacerbate, but others do so frequently.[8] As such, identifying those patients who are at high risk and intervening in a timely manner is a clinical priority. Many variables are proved to be related to outcome in patients with COPD; the most recognized variables are postbronchodilator FEV_1, dyspnea, and historical exacerbations.[5,9] GOLD (Global Initiative for Chronic Obstructive Lung Disease) recommendations have taken all these variables into consideration for grading COPD severity.[10] The use of multidimensional indices, such as CODEX (comorbidity, airflow obstruction, dyspnea, previous severe exacerbations),[11] BODE (BMI, airflow obstruction, dyspnea, and exercise capacity),[12] BODEX (BMI, airflow obstruction, dyspnea, and previous severe exacerbations), and updated ADO (age, dyspnea, and airflow obstruction),[13] have improved the prognostic capacity beyond individual variables.

Depression is a recognized complication of many chronic diseases, including COPD.[14,15] Some studies have found that depression is common in COPD, with the prevalence increasing with the severity of disease, from 19.6% in the mild-to-moderate group to 25% in the severe group.[14] Patients with severe COPD are at increased risk of developing depression to increase the frequency of exacerbations.[16] The Self-Rating Depression Scale (SDS) is a 20-item self-report questionnaire that can be used to screen for and assess depression.[17] It consists of four common characteristics of depression: the pervasive effect, physiological equivalents, other disturbances, and psychomotor activities. There are 10 positive and 10 negative questions. Each question is scored on a scale of 1–4 (a little of the time, some of the time, a good part of the time, most of the time), and the total score ranges from 20 to 80. The raw score is then converted to an index score by dividing the raw score by the maximum score (80) and either expressing this as a decimal or multiplying by 100 to express it as a whole number with an index score range of 25 to 100. An index score of 25 to 49 indicates no depression, 50–59 indicates mild to moderate depression, 60–69 indicates moderate to severe depression, and a score of 70 or over indicates severe depression.[18]

In this study, we investigated the relationship between depression and the outcome of patients with COPD, and determined whether the inclusion of SDS could improve the predictive value of the previously established multidimensional indices ADO, BODEX, BODE, and CODEX.

Patients and Methods

This research was approved by the local Ethics Committee of the First Affiliated People's Hospital of Shaoyang College and conducted in accordance with the Declaration of Helsinki and its amendments, and all subjects gave written informed consent to participate in the study. The study was registered in the Chinese Clinical Trial Registry (ChiCTR-ROC-16009087; http://www.chictr.org.cn/).

Study Subjects

Two cohorts of patients diagnosed with stable COPD were recruited at the outpatient department of the First Affiliated People's Hospital of Shaoyang College during different time periods from September 2015 to August 2018. One was used to develop updated multidimensional indices which included the SDS score for predicting frequent exacerbators; the other was collected to validate the new multidimensional indices. The diagnosis of COPD was based on the latest GOLD document.[1] Patients with a history of diagnosis of asthma, bronchiectasis, lung fibrosis, upper airway obstruction, or tuberculosis were excluded. Patients in the exacerbation stage were excluded. Patients who could not understand the SDS questionnaire or refused to complete the questionnaire were also excluded.

Study Design

This was a prospective study. All the patients in this study accepted four visits. At the first visit, all participants signed a written informed consent and provided the following information: age, sex, smoking history, career, education, comorbidities, BMI, COPD assessment test (CAT), modified Medical Research Council Dyspnea Scale (mMRC), Clinical COPD Questionnaire (CCQ), SDS, 6 min walk distance, history of exacerbations in the previous year, and lung function. Before using the SDS report, the researchers explained the content of the questionnaire to the patients in detail, making sure the patients understand the meaning of each item. Then, the patients were asked to rate each of the 20 items as to how it applied to them at the time of testing. If the patients forgot the meaning of any item in completing the form, the researcher could explain again without any intervention and guidance. Comorbidity was quantified according to the Charlson index.[19] CAT, mMRC, and CCQ were collected as described previously.[20,21] The 6-mins

walk test was performed according to the guideline.[22] The BODE, BODEX, CODEX, and ADO scores were calculated based on previous studies.[11–13,23] The SDS score included in the multidimensional indices ranged from 0 to 4 based on the severity of depression, representing 25–39, 40–49, 50–59, 60–69, and ≥70, respectively. Then, the SDS value was added into BODE, BODEX, ADO, and CODEX to develop the updated multidimensional indices, named BODES, BODEXS, ADOS, and CODEXS, respectively. After the baseline visit, every participant was followed up in the 3rd, 6th, and 12th months, respectively, to record the occurrence of exacerbations and the treatment therapy during 1 year of follow-up.

Definition of Exacerbations

Exacerbations were diagnosed based on event-based definition: worsening or new onset of any respiratory symptoms (cough, sputum volume or purulence, wheezing, or dyspnea) for at least 3 days that led to any of the following situations: 1. requiring prescription change under the guidance of a physician in the outpatient department; 2. requiring hospitalization or an emergency room visit with the diagnosis of AECOPD. Exacerbations separated by ≥14 days were considered distinct events. The frequent exacerbators were those who had at least two exacerbations or one hospitalization per year.

Statistical Analysis

Adjusted multiple logistic regression models were performed to determine the association between variables and COPD exacerbations. The variables age, gender, BMI, smoking status, exacerbation history, GOLD stage, CCQ, CAT, mMRC, and SDS were taken into consideration. Comparison of mean SDS score and GOLD stage was performed with one-way ANOVA. The Student t test or Mann–Whitney U-test was used to compare means difference for continuous variables and the chi-squared test was used for categorical variables. All statistical analyses above were performed using SPSS 25. Receiver operating characteristic (ROC) analysis was used to determine the predictive capacity of different multidimensional indices. Comparisons between the area under the curves (AUC) were made using the Hanley–McNeil test through Medcalc software, and a P value of <0.05 was considered statistically significant.

Results
Patient Demographic Characteristics

A flow chart of the study is shown in Figure 1. Initially, a total of 180 subjects with a primary diagnosis of COPD were screened. Among them, 57 patients were excluded

because of exacerbation (n = 15), asthma (n = 23), fibrosis (n = 9), or bronchiectasis (n = 10). Ten patients refused to perform the 6-mins walk test and dropped out. During the 1-year follow-up period, eight patients dropped out: one of them died because of extrapulmonary disease and seven of them could not be reached. Finally, 105 patients were recruited into the final analysis. Demographic and clinical data are presented in Table 1. The mean age of the patients was 67.97 ± 8.91 years, with 94.29% males and 5.71% females. The mean FEV_1/FVC and predicted $FEV_1\%$ were 49.90 ± 9.33% and 49.56 ± 15.42%. The average mMRC, CAT, CCQ, and SDS scores were 1.43 ± 0.85, 13.63 ± 7.10, 3.11 ± 3.88, and 40.59 ± 14.42, respectively. The average number of exacerbations was 1.10 ± 1.25 per year.

Depression Is an Independent Risk Factor for COPD Exacerbation

After 1 year of follow-up, 57 (54.29%) patients were grouped as frequent exacerbators. A logistic regression model was used to evaluate the prognostic value of each variable. Univariate analysis showed that several factors, including $FEV_1\%$, CAT, mMRC, SDS, comorbidities, treatment, and history of exacerbations contributed to frequent exacerbations (Table 2). These factors except CAT were then further analyzed by multivariate analysis. The multivariate model showed that SDS (odds ratio (OR) = 1.14, 95% confidence interval (CI) = 1.06–1.23, $P < 0.001$) and history of exacerbations (OR = 2.33, 95% CI = 1.20–4.51, $P < 0.001$) were independent indicators of frequent exacerbations; regular treatment (OR = 0.03, 95% CI = 0.01–0.14, $P < 0.001$) could decrease exacerbation significantly (Table 2).

Depression Severity Is Correlated with GOLD Stage and Symptom Severity

The prevalence of depression in the frequent exacerbators (35.09%) was higher than that in infrequent exacerbators (12.5%) (Figure 2). The SDS score in patients at GOLD stage IV was significantly higher than that in other stages. The average SDS score of patients at GOLD stages I, to IV was 28.33 ± 2.89, 32.73 ± 10.96, 43.50 ± 11.51, and 63.91 ± 8.76, respectively (Figure 3). The SDS score was positively correlated with the GOLD stage (rho = 0.641, $P < 0.001$), CAT score (rho = 0.528, $P < 0.001$), and mMRC (rho = 0.425, $P < 0.001$).

180 patients with primary diagnosis of COPD were screened

57 patients were excluded due to：
Exacerbation (n=15)
Asthma (n=23)
Cystic fibrosis (n=9)
Bronchiectasis (n=10)

123 patients were included

10 patients were excluded due to: without 6-minute walk test data

113 patients were finally recruited at the first visit：collect age, sex, smoking history, career, education, co-morbidity, BMI, CAT, mMRC, CCQ, SDS, 6-minute walk distance, history of exacerbations in the previous year, and lung function data

8 patients dropped out
At the first telephone interview: death (n=0), lost (n=0)
At the second telephone interview: death (n=1), lost (n=1)
At the third telephone interview: death (n=0), lost (n=6)

Following up visit: at 3rd, 6th.12th month

Collect exacerbation and treatment therapy information

105 patients were successfully recruited for final analysis

Set up updated multidimensional indexes taking SDS into consideration

Recruited another cohort of patients with the same inclusion and exclusion criteria to validate the new multidimensional indexes
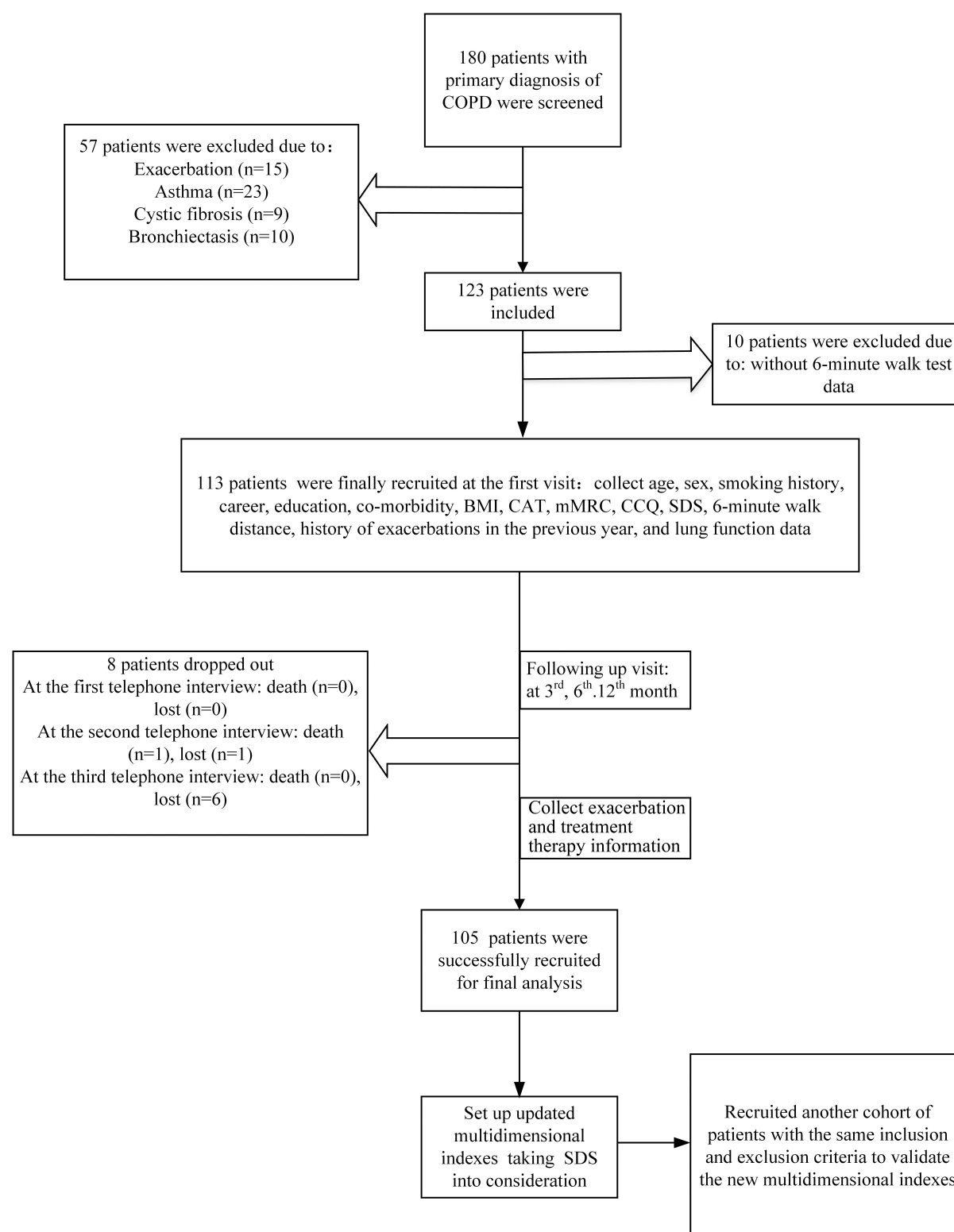
Figure 1 Study flow chart. A total of 180 subjects with a primary diagnosis of COPD were screened; 57 patients were excluded because of exacerbation (n = 15), asthma (n = 23), fibrosis (n = 9), or bronchiectasis (n = 10). Ten patients refused to perform the 6-mins walk test and dropped out. Seven of them could not be reached. During the 1-year follow-up period, eight patients dropped out; one of them died because of extrapulmonary disease and seven of them could not be reached. After developing the updated multidimensional indices, another cohort of patients was recruited to validate the indices.

Table 1 Demographic and Clinical Characteristics of Patients

Variables	Characteristics	Cohort 1		Cohort 2		p
		n	%/Mean ± SD	n	%/Mean ± SD	
Age		105	67.87 ± 8.91	107	68.48 ± 8.43	0.61
Sex	Male	99	94.29%	99	92.5%	0.61
	Female	6	5.71%	9	7.5%	
BMI		105	21.70 ± 5.86	107	21.22 ± 2.28	0.44
Smoking	Ex-smoker	14	13.33%	20	18.69%	0.29
	Current smoker	91	86.67%	87	81.31%	
FEV$_1$/FVC		105	49.90 ± 9.33%	107	47.38 ± 9.40%	0.68
FEV$_1$%		105	49.56±15.42%	107	48.31 ± 16.12%	0.57
CAT		105	13.63 ± 7.10	/	/	
mMRC		105	1.43 ± 0.85	107	1.52 ± 0.93	0.44
CCQ		105	3.11 ± 3.88	/	/	
SDS		105	40.59 ± 14.42	107	41.42 ± 12.08	0.65
GOLD stage	Mild	3	2.86%	3	2.80%	0.79
	Moderate	45	42.86%	39	36.45%	
	Severe	46	43.80%	54	50.47%	
	Very severe	11	10.48%	11	10.28%	
Comorbidities		26	24.76%	39	36.45%	0.17
		79	75.24%	68	63.55%	
6 min walk distance (m)		105	331.72 ± 91.09	/	/	
Location	Urban areas	72	68.57%	/	/	
	Rural areas	33	31.43%	/	/	
Education	Uneducated	9	8.58%	/	/	
	Primary school	40	38.10%	/	/	
	Junior school	32	30.48%	/	/	
	High school	16	15.24%	/	/	
	University	8	7.62%	/	/	
Occupation	Farmer	42	40%	/	/	
	Worker	38	36.19%	/	/	
	Other	25	23.81%	/	/	
History of exacerbations		105	1.10 ± 1.25	107	1.15 ± 0.99	0.42

Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; CAT, COPD assessment test; mMRC, modified Medical Research Council test; CCQ, Clinical COPD Questionnaire score; SDS, Self-Rating Depression Scale; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

Comparison of the Predictive Value of Different Multidimensional Indices

The ADO, CODEX, BODE, and BODEX indices could predict the frequent exacerbators effectively: the OR were 2.0, 2.79, 1.91, and 2.17, respectively. Comparison of the ROC curves showed that CODEX had a better predictive capacity for the frequent exacerbators compared with ADO ($P = 0.008$) and BODEX ($P = 0.03$); the AUC were 0.82, 0.71, and 0.79, respectively (Table 3 and Figure 4).

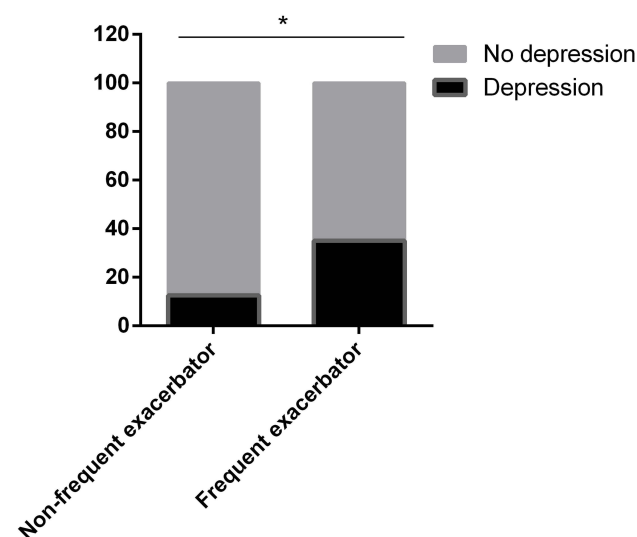## Combined Variables Improve the Predictive Value for Frequent Exacerbators

With respect to the combined variable (SDS value), all indices reached statistical significance for predicting frequent exacerbators (Table 4). ROC curve comparison showed that the inclusion of SDS value improved the predictive capacity of all the previously established indices (ADOS vs ADO, 0.80 [0.71], $P = 0.0002$ [Figure 5A];

Table 2 Univariate and Stepwise Multivariate Analysis of Risk Factors for Frequent Exacerbators
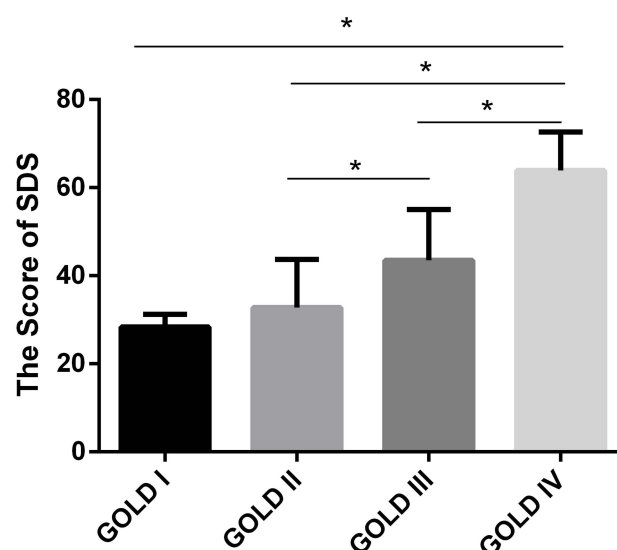
	Univariate Analysis		Multivariate Analysis	
	OR	95% CI	OR	95% CI
Age (years)	1.0	0.96–1.05	0.99	0.92–1.06
Gender (male)	1.2	0.23–6.24	–	
BMI	1.02	0.95–1.10	–	
FEV$_1$/FVC	0.94	0.89–0.98*	Not selected	
FEV$_1$%	0.94	0.91–0.97*	0.99	0.93–1.05
CAT	1.11	1.04–1.18*	Not selected	
mMRC	2.67	1.51–4.73*	1.27	0.53–3.05
CCQ	1.05	0.93–1.18	–	
SDS	1.12	1.07–1.17*	1.14	1.06–1.23*
6 min walk distance	0.99	0.98–1.00	–	
Location (city)	0.60	0.26–1.37	–	
Comorbidities	2.92	1.15–7.40*		
Job	1.23	0.75–2.01	–	
History of exacerbations	1.96	1.25–3.09*	2.33	1.20–4.51*
Smoking history	1.22	0.40–3.76	–	
Standardized treatment	0.07	0.03–0.20*	0.03	0.01–0.14*

Note: *Means $P < 0.05$.
Abbreviations: BMI, body mass index; FEV$_1$, forced expiratory volume in 1 s; FVC, forced vital capacity; CAT, COPD assessment test; mMRC, modified Medical Research Council test; CCQ, Clinical COPD Questionnaire score; SDS, Self-Rating Depression Scale.

Figure 3 SDS score for different GOLD stages. The SDS score increased with disease severity. The average SDS score of patients at GOLD stages I to IV was 28.33 ± 2.89, 32.73 ± 10.96, 43.50 ± 11.51, and 63.91 ± 8.76, respectively. *Means $P < 0.05$.
Abbreviations: SDS, Self-Rating Depression Scale; GOLD, Global Initiative for Chronic Obstructive Lung Disease.

CODEXS vs CODEX 0.88 [0.82], $P = 0.02$ [Figure 5B]; BODES vs BODE 0.83 [0.79], $P = 0.03$ [Figure 5C]; BODEXS vs BODE 0.85 [0.79], $P = 0.004$ [Figure 5D]). The cut-off point for all the multidimensional indices to differentiate frequent exacerbators was 3.5. ROC comparison showed that CODEXS had a better capacity to predict exacerbations than ADOS ($P = 0.005$), BODES ($P = 0.01$), and BODEXS ($P = 0.007$) (Figure 6).

Validation of Multidimensional Indices

In order to validate these new indices, we recruited 107 patients with COPD from the First Affiliated People's Hospital of Shaoyang College. The demographic characteristics are shown in Table 1. No significant statistic changes of the variables were found between the two

Figure 2 Prevalence of depression in COPD patients. The prevalence of depression in the frequent exacerbators (35.09%) was higher than that in infrequent exacerbators (12.5%). *Means $P < 0.05$.
Abbreviation: COPD, chronic obstructive pulmonary disease.

Table 3 Predictive Value of Different COPD Multivariate Indices for Frequent Exacerbators

Index	OR	95% CI	AUC	95% CI	P
CODEX	2.79	1.83–4.26	0.82	0.74–0.90	< 0.001
ADO	2.0	1.38–2.91	0.71	0.61–0.81	< 0.001
BODEX	2.17	1.55–3.04	0.79	0.70–0.87	< 0.001
BODE	1.91	1.42–2.57	0.79	0.70–0.87	< 0.001

Abbreviations: CODEX, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation; ADO, age, dyspnea, airflow obstruction; BODE, body mass index, airflow obstruction, dyspnea, exercise; BODEX, body mass index, airflow obstruction, dyspnea, previous severe exacerbation; OR, odds ratio; CI, confidence interval; AUC, area under the curve.
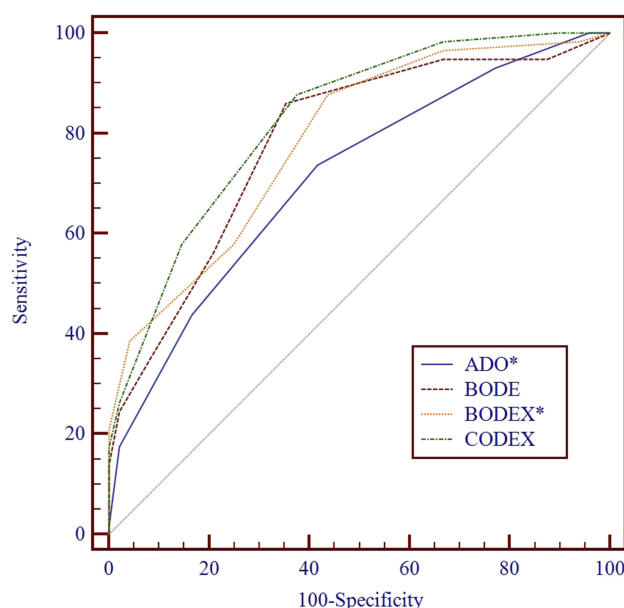
Figure 4 ROC comparison between previously established multidimensional indices for predicting frequent exacerbators. CODEX had a better predictive capacity for frequent exacerbators compared with ADO (*P* = 0.008) and BODEX (*P* = 0.03); the AUC were 0.82, 0.71, and 0.79, respectively. *Means *P* < 0.05.
Abbreviations: ROC, receiver operating characteristic; CODEX, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation; ADO, age, dyspnea, airflow obstruction; BODE, body mass index, airflow obstruction, dyspnea, exercise; BODEX, body mass index, airflow obstruction, dyspnea, previous severe exacerbation; AUC, area under the curve.

cohorts of patients. After 1 year of follow-up, 64 patients had frequent exacerbations (59.81%). Taking 3.5 as the cut-off point for CODEXS, BODEXS, and ADOS, the sensitivity to identify frequent exacerbators was 85.94%, 82.81%, and 84.38%, respectively, and the specificity was 76.74%, 60.47%, and 53.49%, respectively (Table 5).

Discussion

In this study, we found depression was an independent risk factor for frequent exacerbation in patients with COPD.

Table 4 Predictive Value of Updated COPD Multivariate Indices for Frequent Exacerbators

Index	OR	95% CI	AUC	95% CI	*P*
CODEXS	2.91	1.89–4.48	0.88	0.81–0.94	< 0.001
ADOS	1.97	1.48–2.63	0.80	0.72–0.89	< 0.001
BODEXS	2.15	1.58–2.94	0.85	0.78–0.92	< 0.001
BODES	1.80	1.41–2.30	0.83	0.75–0.90	< 0.001

Abbreviations: CODEXS, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation, depression; ADOS, age, dyspnea, airflow obstruction, depression; BODES, body mass index, airflow obstruction, dyspnea, exercise, depression; BODEXS, body mass index, airflow obstruction, dyspnea, previous severe exacerbation, depression; OR, odds ratio; CI, confidence interval; AUC, area under the curve.

The combination of SDS score with the existing indices BODE, BODEX, CODEX, and ADO improved the predictive value for frequent exacerbators significantly. We named these new indices BODES, BODEXS, CODEXS, and ADOS. We found CODEXS was superior to the other three multidimensional indices, and validated the finding in another cohort of patients with COPD. To our knowledge, no multicomponent indices took depression into consideration in previous studies. In our study, we developed and validated a new multidimensional index to predict frequent exacerbators among patients with COPD, which can be easily applied to clinical practice.

Depression is the leading cause of increased disability and impaired quality of life in older people worldwide. Many studies have reported a high rate of depression among patients suffering from COPD.[16,24,25] The prevalence of depression in COPD varies from 6% to 57% due to different sample size, age group, and depression screening tool.[26] There are many questionnaires used to study depression in COPD patients, including the Center for Epidemiologic Studies Depression Scale (CES-D), Geriatric Depression Scale (GDS), Hospital Anxiety and Depression Scale (HADS), SDS, and the Structured Clinical Interview for DSM-I. CES-D was designed to cover most depression symptoms, with emphasis on affective components; GDS was designed for screening depression in older populations, HADS was designed for screening depression in the general medical population, and SDS can screen for depression, as well as classify its severity.[27] In our study, we wanted to include the SDS score in a multidimensional index, so we chose SDS to assess the severity of depression and assigned a different value, ranging from 0 to 4 based on the SDS score, to the previously reported indices BODE, BODEX, ADO, and CODEX. We found the percentage of COPD patients with depression was 25.71%, similar to a previous study.[28] The prevalence of depression (35.09%) was much higher in frequent exacerbators compared with infrequent exacerbators (12.50%), indicating that depression is related to exacerbations in COPD patients. More severe depression was found in patients at a higher GOLD stage. A possible reason for this result may be that COPD and depression are deeply interrelated. It is well known that depression plays a role in the initiation and maintenance of smoking, that smoking is a critical risk factor for the development of COPD, and that COPD, in turn, contributes to the worsening of depression.[29,30]

Through logistic regression analysis, we found that depression is an independent risk factor for predicting
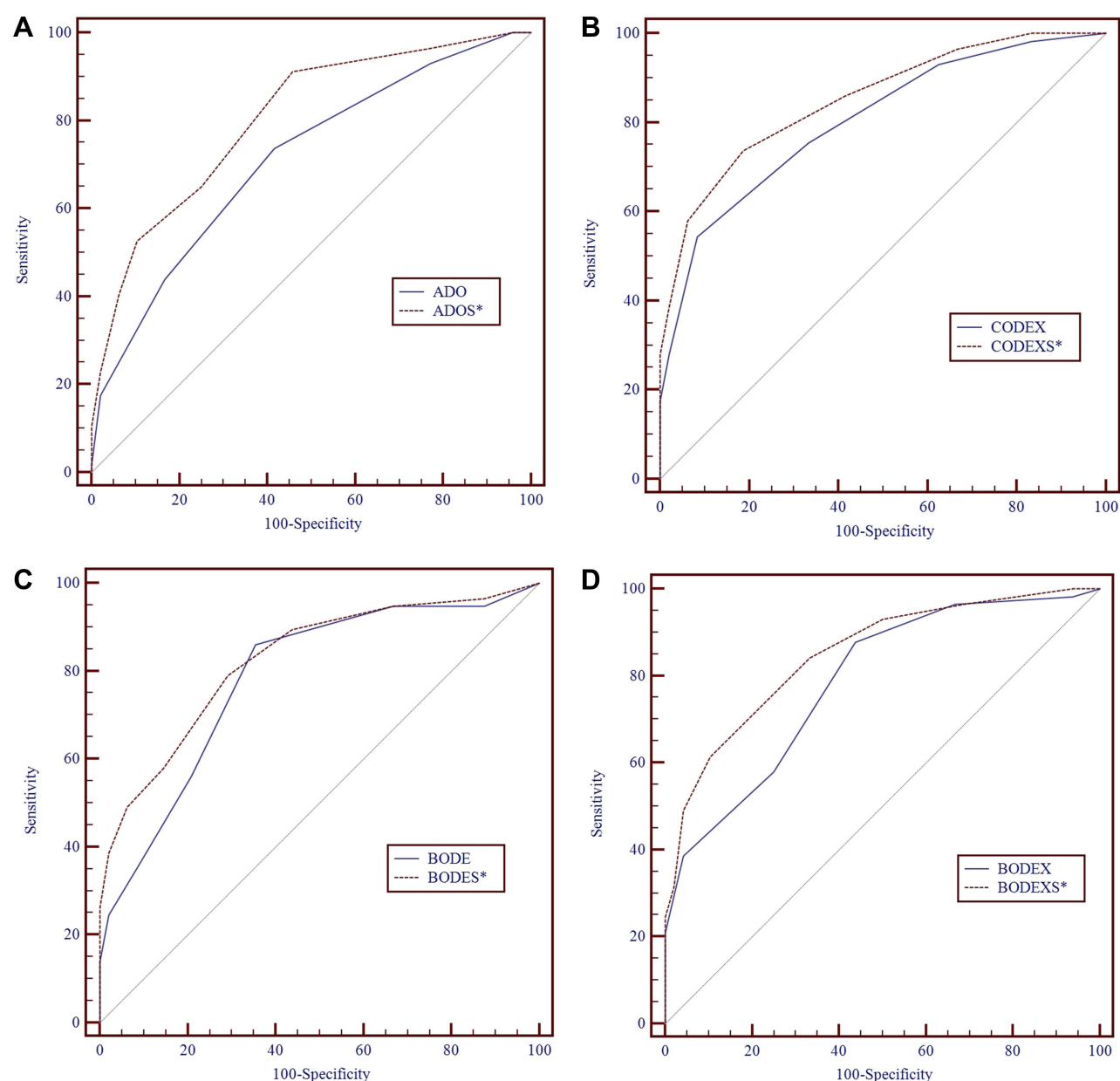
Figure 5 ROC comparison between updated multidimensional indices and previous indices. The updated multidimensional indices improved the predictive capacity of all the previous indices (**A**) (ADOS vs ADO, 0.80 [0.71], $P = 0.0002$; (**B**) CODEXS vs CODEX 0.88 [0.82], $P = 0.02$; (**C**) BODES vs BODE 0.83 [0.79], $P = 0.03$; (**D**) BODEXS vs BODEX 0.85 [0.79], $P = 0.004$). *Means $P < 0.05$.
Abbreviations: ROC, receiver operating characteristic; ADOS, age, dyspnea, airflow obstruction, depression; ADO, age, dyspnea, airflow obstruction; CODEXS, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation, depression; CODEX, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation; BODES, body mass index, airflow obstruction, dyspnea, exercise, depression; BODE, body mass index, airflow obstruction, dyspnea, exercise; BODEXS, body mass index, airflow obstruction, dyspnea, previous severe exacerbation, depression; BODEX, body mass index, airflow obstruction, dyspnea, previous severe exacerbation.

frequent exacerbators among COPD patients. To determine whether taking depression into consideration could improve the predictive value of a multidimensional index, we converted the SDS score into a 5-point scale, ranging from 0 to 4, representing 25–39, 40–49, 50–59, 60–69, and ≥70, respectively. The rationale for setting up this scale was based on the severity of depression. Index scores of 25 to 49 indicate no depression, 50–59 indicates mild

depression, 60–69 indicates moderate depression, and scores ≥70 indicate severe depression;[18] 0–1 represents no depression, and 2–4 represent mild, moderate, and severe depression, respectively.

The most widely recognized variables associated with exacerbations in patients with COPD are FEV_1%, dyspnea, and exacerbations in the previous year.[31–33] The first two are the basis of multicomponent indices; the number of
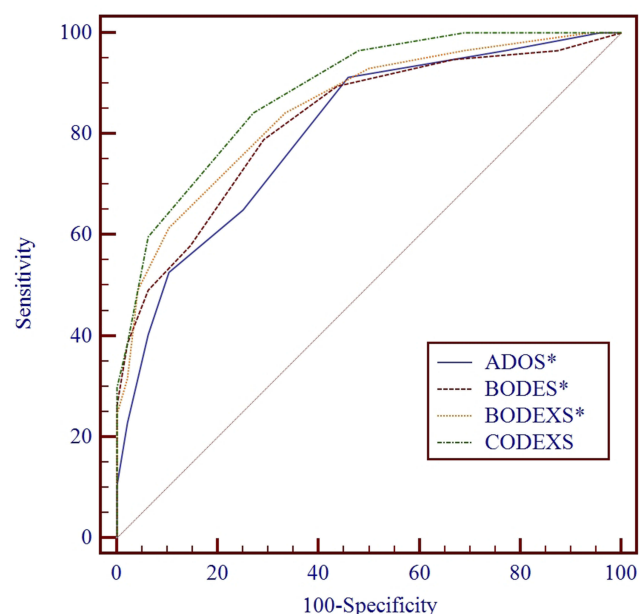
Figure 6 ROC comparison between updated multidimensional indices for predicting frequent exacerbators. CODEXS had better a capacity to predict exacerbations than ADOS (*P* = 0.005), BODES (*P* = 0.01), and BODEXS (*P* = 0.007). *Means *P* < 0.05.
Abbreviations: ROC, receiver operating characteristic; CODEXS, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation, depression; ADOS, age, dyspnea, airflow obstruction, depression; BODES, body mass index, airflow obstruction, dyspnea, exercise, depression; BODEXS, body mass index, airflow obstruction, dyspnea, previous severe exacerbation, depression.

exacerbations in the previous year has been proved to be an independent risk factor, and some indices have also included this factor. Other factors, such as age, comorbidities, BMI, and 6-mins walk test, have also been used to develop some multicomponent indices. Several multicomponent indices are widely recognized, including CODEX, BODEX, ADO, and BODE. In this study, we demonstrated that all these indices could predict 1-year exacerbations in COPD patients, which was similar to previous studies.[11,34–37] ROC comparison analysis showed that CODEX was superior to BODEX, ADO, and BODE for

Table 5 Validation of Multicomponent Indices

Follow-Up Results	CODEXS		BODEXS		ADOS		Total
	+	−	+	−	+	−	
+	55	9	53	11	54	10	64
−	10	33	17	26	20	23	43
Total	65	42	70	37	74	33	107

Note: +Means frequent exacerbators; −Means infrequent exacerbators.
Abbreviations: CODEXS, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation, depression; ADOS, age, dyspnea, airflow obstruction, depression; BODEXS, body mass index, airflow obstruction, dyspnea, previous severe exacerbation, depression.

predicting 1-year exacerbation. CODEX was first proposed by Pedro Almagro; it was an evolution of the BODE and BODEX indices, retaining their cut-offs for dyspnea, obstruction, and previous exacerbations, but replacing BMI with comorbidity measured by the original Charlson index modified by age. Although low BMI has been proved to be associated with a poor survival, the Charlson index shows a better prognostic capacity.[11] This may be why CODEX showed a better capacity for predicting frequent exacerbators.

The importance of depression in COPD is well established. However, to date, none of the COPD indices have included depression as a prognostic variable. In our study, we found that SDS score was correlated to symptoms and airflow obstruction, and confirmed that adding the SDS value into previous multicomponent indices improved their predictive value for frequent exacerbators significantly. Similar to CODEX, CODEXS is the most useful, with the highest sensitivity and specificity. As such, clinicians should pay more attention to those who are judged to be frequent exacerbators, making proper clinical interventions.

Our study has several limitations. Firstly, the population for validating the indices came from the same hospital in different time periods with the same inclusion and exclusion criteria; it would be better to validate these indices with a multicenter study, and it is worth having a longer follow-up period to assess the predictive value of CODEXS for the long-term outcome. Secondly, our study had a clear predominance of men. But this finding is similar to all studies of COPD performed in our area and it is probably to the fact that there are a higher proportion of men to smoke than that in women.[20,21,38] Finally, although we found that depression is an independent risk factor for exacerbation, we did not treat the patients with antidepressant or psychological intervention; in a future study, it would be worth determining whether proper psychological intervention improves the prognosis of patients with COPD.

Conclusion

In conclusion, depression is an independent risk factor for COPD exacerbations. CODEXS is a simple, effective tool for predicting the risk of COPD exacerbation.

Abbreviations

ADO, age, dyspnea, airflow obstruction; ADOS, age, dyspnea, airflow obstruction, depression; AECOPD, acute exacerbations of chronic obstructive pulmonary disease; AUC, area under the curve; BMI, body mass

index; BODE, body mass index, airflow obstruction, dyspnea, exercise; BODES, body mass index, airflow obstruction, dyspnea, exercise, depression; BODEX, body mass index, airflow obstruction, dyspnea, previous severe exacerbation; BODEXS, body mass index, airflow obstruction, dyspnea, previous severe exacerbation, depression; CAT, COPD assessment test; CCQ, Clinical COPD Questionnaire; CES-D, Center for Epidemiologic Studies Depression Scale; CI, confidence interval; CODEX, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation; CODEXS, comorbidities, airflow obstruction, dyspnea, previous severe exacerbation, depression; COPD, chronic obstructive pulmonary disease; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; GDS, Geriatric Depression Scale; GOLD, Global Initiative of Chronic Obstructive Lung Disease; HADS, Hospital Anxiety and Depression Scale; mMRC, modified Medical Research Council Dyspnea Scale; OR, odds ratio; ROC, receiver operating characteristic; SD, standard deviation; SDS, Self-Rating Depression Scale.

Data Sharing Statement

The authors confirm that the data supporting the findings of this study are available within the article. The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request, the authors will not share any individual deidentified participant date or other relevant study documents.

Ethics Approval and Consent to Participate

The research protocol was approved by the local Ethics Committee of the First Affiliated People's Hospital of Shaoyang College (number: C2016123) and conducted in accordance with the Declaration of Helsinki and its amendments. All subjects gave written informed consent to participate in the study.

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Author Contributions

All authors contributed to data analysis, drafting and revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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