

Dyspnea, Obstruction, Smoking, Exacerbation Index, and Chronic Obstructive Pulmonary Disease Test Score: Correlation in Predicting Outcomes in Patients with Chronic Obstructive Pulmonary Disease Exacerbations



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ABSTRACT

Objectives: Chronic obstructive pulmonary disease (COPD) being a disease with systemic consequences necessitate the use of multidimensional indices for a comprehensive assessment of the disease's impact including the future risk of exacerbations and mortality. To study the role of dyspnea, obstruction, smoking, and exacerbation (DOSE) index as a predictor of future disease severity and its correlation with chronic obstructive pulmonary disease test (CAT) score.

Measurements and results: A total of 60 inpatients with COPD exacerbations were followed up for 6 months to record the number of exacerbations of COPD. The DOSE index and CAT score were calculated after stabilization within 48 hours of admission, at 1 week, and again at 6 months.

The mean difference between DOSE index score at admission and at 1 week was 1.382 ± 0.561 and at admission and at 6 months was 2.15 ± 0.988 , both being statistically significant ($p < 0.001$). A high DOSE index score (≥ 4) was associated with a greater risk of 2 or more exacerbations [odds ratio (OR), 12 (3.09–46.60) and risk estimate, 3.75 (1.53–9.17)]. For the prediction of exacerbations, the area under the curve (AUC) was larger for the DOSE index (0.854) than the global initiative for chronic obstructive lung disease (GOLD) stage (0.789), $p < 0.001$ for both. Furthermore, DOSE index correlated significantly with the CAT score, an established health status measure, at all stages of disease severity; at the onset of exacerbation ($r = 0.719$, $p < 0.001$), after stabilization at 1 week ($r = 0.736$, $p < 0.001$) and at 6 months ($r = 0.884$, $p < 0.001$).

Conclusion: The DOSE index is a simple, practical multidimensional grading tool for assessing current symptoms, health status, and future risk in COPD and acts as a guide to disease management as its component items can be modified by interventions. Its correlation with CAT, a well-known score is a novel observation, which further corroborates the validity of the DOSE index.

Keywords: Chronic obstructive pulmonary disease, Chronic obstructive pulmonary disease test, Dyspnea, Obstruction, smoking, and exacerbation index, Global initiative for chronic obstructive lung disease.

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ABBREVIATIONS USED IN THIS ARTICLE

ADO = Age, dyspnea, airflow obstruction; BODE = Body Mass Index, Airflow Obstruction, Dyspnea, Exercise Performance; COPD = Chronic obstructive pulmonary disease; DOSE = Dyspnea, Obstruction, Smoking, Exacerbation; CAT = Chronic obstructive pulmonary disease test; FEV1% = Forced expiratory volume in 1 second; GOLD = Global initiative for chronic obstructive lung disease; DALYs = Disability-adjusted life year; OR = Odds ratio; SGRQ. St. George's respiratory questionnaire (SGRQ); HRQoL = Health-related quality of life; 6MWT = 6-minutes walking test; MRC = Medical Research Council; mMRC = Modified Medical Research Council.

INTRODUCTION

Chronic obstructive pulmonary disease, as defined by GOLD is characterized by persistent airflow limitation that is usually progressive and associated with an enhanced chronic inflammatory response in the airways and the lung to noxious particles or gases. Exacerbations and comorbidities contribute to the overall severity

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in individual patients. Chronic obstructive pulmonary disease is currently the fourth leading cause of death in the world but is projected to be the third leading cause of death by 2020.¹ The prevalence of COPD is higher in smokers and ex-smokers than in

non-smokers, higher in people aged more than 40, and higher in men. India contributes very significantly to mortality from COPD [102.3/100,000 and 6.7 million disability-adjusted life year (DALYs) out of a world total of 28 million DALYs].²⁻⁶

COPD is often aggravated by acute periods of increased symptoms called exacerbations which lead to deterioration in the patient's quality of life.^{7,8} These are the most common reason for emergency department visits, hospital admissions, and deaths.⁹ Also, studies have shown that exacerbations generate a large impact on health systems,^{9,10} thus being an important milestone in the natural history of the disease.

To visualize the social impact, amount of DALYs, and quality of life alteration in COPD, various questionnaires are used such as CQC and CAT scores. The CAT score consists of eight items, each presented as a semantic 6-point differential scale, providing a score out of 40 indicating the impact of the disease. It is completed by the patient and the result is immediately available without the need for any investigation. The CAT score being a short, comprehensive, and easy-to-use questionnaire can also be used in various research trials attributed to population-based studies. It has a very good correlation with the St. George's respiratory questionnaire (SGRQ)¹¹⁻¹³ considered the GOLD standard of specific health-related quality of life (HRQoL) questionnaires for COPD.

Around a decade ago, COPD severity was classified based on lung function assessed by spirometry. However, as per 2019 GOLD guidelines, there has been a shift from lung function to current symptoms and future risk of exacerbations. Numerous indices have been validated over years but none seem to be perfect. An ideal index should use items that are easy to obtain, valid, and provide better associations than individual components. Thus, it should identify patients at increased risk for future events including exacerbations, hospital admissions, and mortality.¹⁴

The GOLD strategy referred to three multi-component indices that assess COPD severity, the BODE, ADO, and DOSE indices, but preferred a new system of GOLD categories based on current symptoms and future risk.¹⁵⁻¹⁷ The three multi-component indices were statistically derived and validated, whereas the GOLD categories were designed by an expert committee without statistical derivation. Subsequent studies have observed that the GOLD categories do not accurately predict future risk.¹⁸⁻²⁰ The BODE index requires the 6-minutes walking test (6MWT), which limits its use in routine clinical settings as it takes time, supervision, and space and ADO has the disadvantage that it is affected by age.

The DOSE index is a simple multidimensional grading system that incorporates four factors, Medical Research Council (MRC) dyspnea scale, predicted FEV1% value (GOLD), current smoking status, and the exacerbation rate in the previous year. It was derived as a predictor of health status,²¹ but also reflects mortality, future exacerbations, and decline in health status.²²⁻²⁴ DOSE index may be the one index to meet all the criteria required of an index for use in routine primary care clinical practice, one which would provide healthcare professionals with a measure of current status and future risk in their patients with COPD.¹⁴

Against this background, we planned to evaluate the DOSE index for future outcomes in patients with COPD and the correlation between DOSE and CAT scores.

MATERIALS AND METHODS

This study was a prospective observational study carried out in the Department of Medicine, Maulana Azad Medical College and

associated Lok Nayak Hospital, New Delhi, India, from February 2017 to January 2018 which included 60 inpatients with COPD with acute exacerbation. Prior data indicates that the prevalence of patients with COPD in India is 4-6%,^{25,26} but the exact prevalence of patients with COPD with exacerbation is unknown due to heterogeneity in the definition. Thus, it is very difficult to predict the sample size required for our study. Hence, we enrolled 60 patients with COPD with exacerbation for this study (sample of convenience). This was a pilot study conducted in India and as far as we are aware, no follow-up study has been conducted in the Indian population to study the course of health status during exacerbation in patients with COPD using DOSE index and the role of the DOSE index as a predictor of current and future disease severity. The study was conducted after being approved by the Institutional Ethical Committee and obtaining informed consent from the patients.

Patient Selection

The patients aged above 40 years diagnosed with COPD with acute exacerbations defined as "an event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to change in medication of patient with underlying COPD" were included in the study,²⁷ while excluding known cases of bronchial asthma, bronchiectasis, tuberculosis, malignancy, connective tissue disease, arthritis or inflammatory bowel disease.

We included 60 patients with acute exacerbation and followed them up for 6 months. All patients were assessed by history and physical examination and were subjected to a baseline laboratory workup. Patients with acute exacerbation were prescribed a standardized treatment regimen consisting of antibiotics, corticosteroids, nebulized bronchodilators, and oxygen.

The DOSE index and CAT scores were calculated in all patients at admission and 1 week, and again at 6 months. Dyspnea in DOSE scoring was calculated using a modified MRC scale. A pulmonary function test (PFT) was performed thrice, at admission after stabilizing the patient, at 1 week and again at 6 months. The instrument used was SCHILLER SPIROVIT SP-1, a spirometry machine.

The number of exacerbations experienced by the patients (self-reporting or documented visits to the emergency) was recorded during the follow-up period of 6 months.

We aimed to derive a cutoff value of the DOSE index in COPD patients with exacerbations to predict the course of health status.

Statistical Analysis

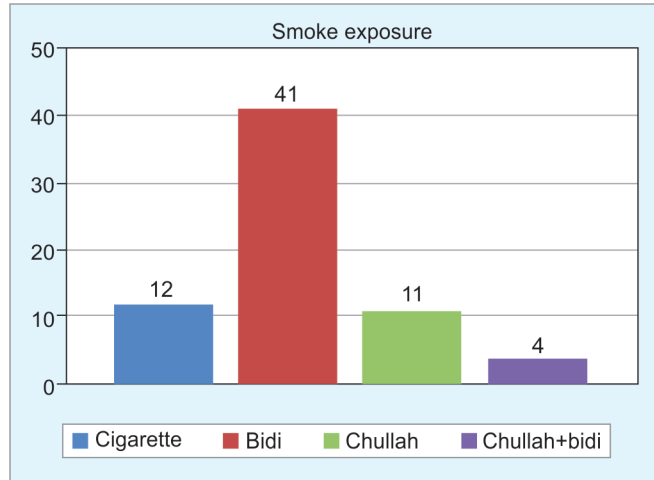
The data were analyzed on the SPSS software, version 25. The quantitative data were summarized using mean, and SD and were compared using an independent *t*-test while the qualitative data were summarized using proportions. The association between two quantitative variables was done using the Pearson correlation test. A comparison of quantitative variables between the two groups was performed using the Wilcoxon sign rank test or paired Student's *t*-test, depending on the distribution of the data. A $p < 0.05$ was considered significant.

RESULTS

Among the 60 inpatients with COPD enrolled in the study, 5 patients expired due to the severity of their illness, three patients were lost to follow-up. Thus, 52 patients completed the study. The mean age of the study group was 59.55 ± 7.44 years with male predominance (80% males). The descriptive characteristics of the study group by

Table 1: Age distribution of the study population

Age (years)	Males	%	Females	%	Total	%
40–49	7	14.58	1	8.33	8	13.33
50–59	15	31.25	5	41.67	20	33.33
60–69	20	41.67	4	33.33	24	40
70–79	6	12.5	2	16.67	8	13.33
TOTAL	48		12		60	

**Fig. 1:** Smoking preferences of the study group

age and gender are given in Table 1. The mean BMI of the study group was 23.05 kg/m².

Smoking Habit

All 60 patients with COPD in our study were exposed to smoke. A total of 53 patients had a history of inhalation of tobacco, of which 41 were bidi smokers, and 12 were cigarette smokers. 11 patients gave the history of exposure to “chullah,” out of which 4 patients also smoked bidi. Figure 1 describes the smoking preferences of the study group.

Smoking habits varied among the study population; 37 patients (61.67%) were active/current smokers. With active counseling, 7 patients stopped smoking over the course of the study duration.

Past Number of Exacerbations

We found that 38.3% had 1 exacerbation over the last year, 26.67% had 2, 23.3% had 3, 8.3% had 4 and 3.3% had 5 exacerbations over the last 12 months. The mean number of exacerbations in the study group was 2.12 ± 1.12 at admission. The etiology of the previous exacerbations could not be elicited.

Arterial Blood Gas Test Analysis and Pulmonary Function Test

The mean PCO₂ of the study population was 59.08 + 14.16 while the mean SpO₂ was 91.84 + 4.78. The PFT was performed thrice in the study subjects, at admission after stabilizing the patient, at 1 week, and again at 6 months. The PFT could not be performed in 5 patients who expired. The mean FEV1 in the study population at admission, 1 week, and 6 months were 40.53 + 17.63, 49.95 + 17.08, and 47.52 + 16.74, respectively. Patients were divided into GOLD stages according to the FEV1 at admission. The majority of

the patients in the study population at admission (47.27%), 1 week (47.27%), and 6 months (46.51%) were having GOLD stage 3.

Change in DOSE Index from Exacerbation to Stabilization

The mean DOSE index score in this study was recorded to be 5.05 at exacerbation onset, 3.67 at 1 week, and 2.88 at 6 months, respectively. This shows that the patients experienced a statistically significant improvement in the DOSE index score by 1.38 points after stabilization at 1 week. The mean difference between the DOSE index score at exacerbation and 6 months was 2.15 ± 0.988.

Exacerbations among the Study Population during Follow-up Period of 6 Months

Out of 55 patients, 3 patients were lost to follow-up; 52 patients were followed up for a period of 6 months to look for several exacerbations; 13.46% had no exacerbation, 32.69% had 1 exacerbation, 32.69% had 2, 19.23% had 3, and 1.92% had 4 exacerbations during follow-up. The commonest cause of exacerbation was infections of the respiratory tract, comprising 89% of all exacerbations while the cause could not be deciphered in the rest 11% of the cases. The mean number of exacerbations during 6 months in the study group was 1.63 + 1.01.

Role of DOSE Index as Predictor of the Number of Exacerbations during the Follow-up Period of 6 Months

The study population was divided into two groups according to the number of exacerbations, 0–1 and 2 or more. Out of 52 patients, 32 patients (61.54%) had more than or equal to 2 exacerbations and 20 patients (38.46%) had below 2 exacerbations. For patients with a DOSE index score more than or equal to 4, a total of 24 patients (75%) had more than or equal to 2 exacerbations and 8 patients (25%) had below 2 exacerbations. The risk for exacerbations was calculated using Pearson’s Chi-squared test and the resultant value was statistically significant with a $p < 0.001$ suggesting a correlation between the DOSE index score and exacerbations. The OR was 12.00 which showed that the risk of having more than or equal to 2 exacerbations was 12 times higher in patients with a DOSE index score more than or equal to 4 than in patients with a DOSE index score below 4.

Receiver Operating Characteristic Curves

Receiver operating characteristic curves were constructed for the DOSE index score at 1 week, GOLD stage at 1 week, and a past number of exacerbations for assessing their predictive capacity for more than or equal to 2 exacerbations during 6 months. The AUC value for prediction of exacerbations was 0.854 for DOSE index which was significant with a p -value of < 0.001 , for the GOLD stage,

was 0.788 ($p < 0.001$), and for the previous exacerbation rates was 0.826 ($p < 0.001$).

Change in CAT Score from Exacerbation to Stabilization

In this study, the mean CAT score was recorded to be 31.85 at exacerbation, 20.93 at 1 week, and 13.12 at 6 months, respectively. The mean difference between the CAT score at exacerbation and 1 week was 10.93 ± 3.56 , which was statistically significant with a $p < 0.001$. The mean difference between the CAT score at exacerbation and 6 months was 18.75 ± 4.76 .

The DOSE Index and CAT Scores

The DOSE index and CAT score were calculated at admission, 1 week, and at 6 months as tabulated in Table 2. The mean DOSE index was 5.05, 3.67, and 2.88 at admission, 1 week, and 6 months, respectively. The mean CAT scores at the same intervals were 31.85, 20.93, and 13.12.

Correlations between DOSE Index and CAT Scores

We studied for the correlation between DOSE index and CAT scores at admission, after 1 week, and at 6 months, a significant correlation was observed at all the 3 intervals as shown in Table 3 and Figure 2.

The change in DOSE index from admission to 1 week and admission to 6 months was also calculated and it correlated significantly with the CAT score as listed in Table 4 and depicted in Figure 3.

DISCUSSION

DOSE Index

The mean DOSE index score in this study was recorded to be 5.05 at exacerbation onset, 3.67 at 1 week, and 2.88 at 6 months, respectively. The mean difference between the DOSE index score at exacerbation and on stabilization (at 1 week and at 6 months)

Table 2: DOSE index and CAT scores at admission, 1 week, and 6 months

	Scores	Mean	Standard deviation (SD)
At admission	DOSE index	5.05	1.433
	CAT	31.85	4.953
At 1 week	DOSE index	3.67	1.516
	CAT	20.93	4.71
At 6 months	DOSE index	2.88	1.745
	CAT	13.12	6.504

Table 3: Correlation between DOSE index and CAT scores at admission at 1 week and 6 months

	DOSE index score	CAT score	Pearson correlation coefficient (r)	(R ²)	p-value
At admission (mean)	5.05	31.85	0.719	0.517	<0.001
At 1 week (mean)	3.67	20.93	0.736	0.541	<0.001
At 6 months (mean)	2.88	13.12	0.884	0.782	<0.001

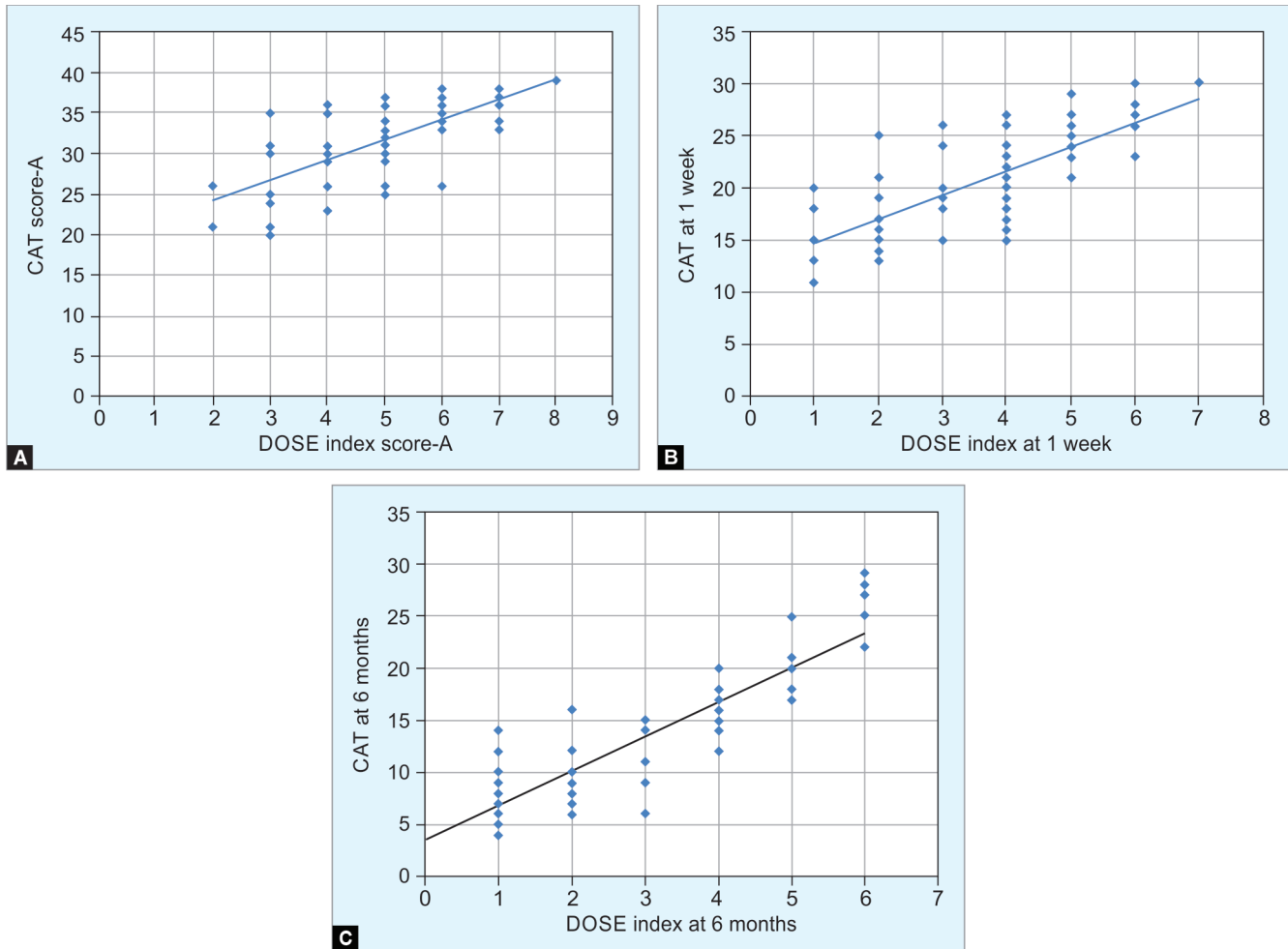
shows that the patients experienced a statistically significant improvement in the DOSE index score. The components of the DOSE index also showed improvement from exacerbation to stabilization. Thus, these results demonstrate that the DOSE index score is a good predictor of health status as there is a statistically significant reduction of the DOSE index score after stabilization from acute exacerbation episode which can be used to monitor the course of recovery of inpatient COPD exacerbations. Motegi et al.,²³ in their 2-year prospective cohort study, enrolled stable patients with COPD, and the DOSE index score was calculated at the end of the first year based on the exacerbation frequencies during the first year of the study period. They observed that the patients who experienced exacerbations during the second year had higher DOSE index scores (2.1 ± 1.5) than those who did not experience exacerbations (0.9 ± 1.2). The total mean DOSE index score (1.3 ± 1.4) was lower than our study because of a large number of patients in GOLD stages 1 and 2. In a study by Wang et al. included severe and very severe patients with COPD, the mean DOSE was $3.26 + 1.79$. In our study, the mean dose at a stable state at 6 months was 2.88 ± 1.745 .²⁸ Zhang et al. concluded in their study that the DOSE index stays significant when comparing the change between the outcomes between the periods of the study. They demonstrated the relative predictability of the DOSE index as a measure of health outcomes among a group of Chinese patients.²⁹

The DOSE Index as Predictor of Future Disease Severity (Exacerbations/Hospitalizations)

The mean number of exacerbations during the follow-up period of 6 months in the study group was 1.63. The mean annual exacerbation rates were 0.57 and 1.22 in studies conducted by Motegi et al.²³ and Jones et al.,²¹ respectively. The study of Kerkhof et al.³⁰ showed a mean annual exacerbation rate of 0.8 in mild COPD and 1.2–2.0 in moderate to very severe COPD. Mean exacerbations were higher in our study due to a higher percentage of people with GOLD stage 3.

In our study, we found that the DOSE index was a significant predictor of future risk of exacerbations. The risk for more than or equal to 2 exacerbations for DOSE index more than or equal to 4 and below 4 was calculated using Pearson's Chi-squared test and the resultant Pearson Chi-squared value (14.981) was statistically significant with a $p < 0.001$ suggesting a correlation between DOSE index and exacerbations. The OR was 12 [95% confidence interval (CI) 3.090–46.601] and the risk estimate was 3.75 (95% CI 1.527–9.174).

The AUC value for the prediction of exacerbations was calculated. The DOSE index had the highest value compared to the other two variables (GOLD stage at 1 week and past number of exacerbations) in predicting future exacerbations, while all of these were found to be significant in predicting exacerbations ($p < 0.001$). The role of the DOSE index in predicting exacerbations in patients with COPD has been assessed in various previous studies, and has shown similar results. In the study conducted by Jones and colleagues,²⁷ a high DOSE index score (>4) was associated with a greater risk of hospital admission (OR, 8.3). The DOSE Index cutoff of 4 predicted emergency department attendance at a near-significant level ($\beta = 0.10$, $p = 0.06$, $R^2 = 0.01$). The index significantly predicted exacerbations in the subsequent year ($p < 0.014$). Motegi et al.²³ studied to determine which of three multi-dimensional assessment systems the BODE index, DOSE index, or ADO index is superior for predicting exacerbations; it was found that among 183 patients who completed the study; the AUC values for prediction of exacerbations for the DOSE index, GOLD



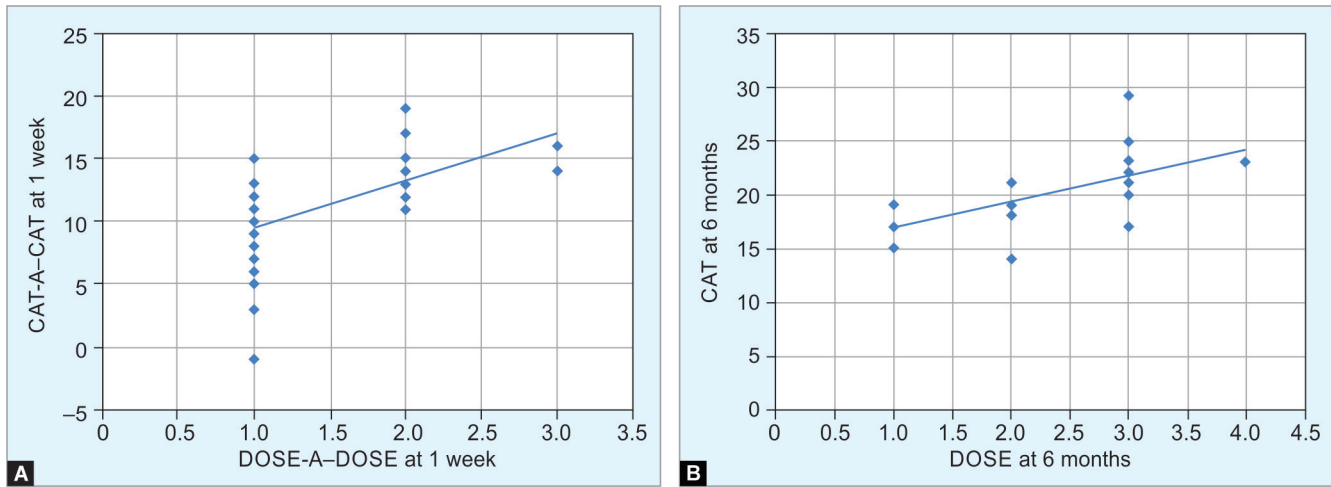
Figs 2A to C: Correlation between DOSE index and CAT score at (A) admission; (B) 1 week; and (C) 6 months. CAT, chronic obstructive pulmonary disease; CAT score-A, chronic obstructive pulmonary disease test at admission; DOSE index, dyspnea, obstruction, smoking, and exacerbation; DOSE index score-A, dyspnea, obstruction, smoking, and exacerbation score at admission

Table 4: Correlations between change in DOSE index and CAT scores from exacerbation to stabilization

		Pearson correlation coefficient (<i>r</i>)	<i>R</i> ²	<i>p</i> -value
DOSE at admission–DOSE at 1 week (mean)	1.38	0.59	0.348	<0.001
CAT at admission–CAT at 1 week (mean)	10.93			
DOSE at admission–DOSE at 6 months (mean)	2.15	0.718	0.516	<0.001
CAT at admission–CAT at 6 months (mean)	18.75			

stage, BODE index, and ADO index were 0.75, 0.66, 0.65, and 0.64, respectively. Although all of these were significant predictors, the value for the DOSE index was much greater than the values for the other assessments ($p < 0.001$). Adjusted multiple logistic regression identified the DOSE index as a significant predictor of the risk of COPD exacerbation. However, in this study, it was also found that the AUC for the previous exacerbation rate was 0.71, a finding similar to our study (AUC for previous exacerbation rates was 0.826) indicating that previous exacerbations are also a good predictor of future exacerbation risk.

Zhang et al.²⁹ in their study showed that the DOSE index was the best predictor of all COPD outcomes including patient healthcare utilization, cost of the disease, and negative clinical outcomes out of the six indices examined [DOSE, BODE, and CAT index, modified Medical Research Council (mMRC), FEV1%, and 6MWT]. Henceforth, analyzing the findings of our study as well as of other studies, we can infer that the DOSE index is a simple multidimensional index for assessing the severity of COPD, and as a measure of health outcomes. It is also a good predictor of future risk of exacerbations and hospitalizations.



Figs 3A and B: Correlation between DOSE Index and CAT score from admission to stabilization. CAT, chronic obstructive pulmonary disease; CAT-A, chronic obstructive pulmonary disease test at admission; DOSE, dyspnea, obstruction, smoking, and exacerbation; DOSE-A, dyspnea, obstruction, smoking, and exacerbation at admission

Correlations between DOSE Index Score and CAT Score

The CAT score, being a short, comprehensive, and easy-to-use questionnaire fulfills the need of facilitating communication between professionals and patients in routine practice besides aiding in the assessment of quantification of symptom burden in patients with COPD. The score correlates very closely with the SGRQ, and has been extensively documented in numerous publications.³¹ Scores of 0–10, 11–20, 21–30, and 31–40 represent mild, moderate, severe, and very severe clinical impacts, respectively.

There was a good correlation between the DOSE index score and CAT score at exacerbation onset with a correlation coefficient of 0.719 ($p < 0.001$). There was also a good correlation between the DOSE index score and CAT score at 1 week and at 6 months with a correlation coefficient of 0.736 and 0.884, respectively, with a $p < 0.001$ for both.

When changes in DOSE index scores and changes in CAT scores from exacerbation to 1 week and from exacerbation to 6 months were compared, there was an evident positive correlation with correlation coefficient being 0.590 and 0.718, respectively, with $p < 0.001$ for both.

A study was done in the Chinese population to compare the relative effectiveness of six indices (DOSE, BODE, and CAT index, mMRC, FEV1%, and 6MWT) in predicting patient healthcare utilization, cost of care, and patient health outcome. Multiple linear regression models were run on each healthcare utilization, cost, and outcome where each COPD index served as the dependent variable, and the same group of demographic variables was included for each of the respective outcomes. It was one of the first studies to indirectly compare the DOSE and the CAT. They conclude that DOSE appears to be far more effective than CAT, however, still CAT is a cheap and easy method to gauge outcomes in patients with COPD.²⁹

To the best of our knowledge, our study is the index study where the DOSE index was correlated with the CAT score to study its role as a measure of current health status and disease severity and we observed that the correlation was significant with a $p < 0.001$ both at exacerbation onset and stabilization. Thus,

DOSE index can be successfully used as a measure of health status in patients with COPD.

Our study had a few limitations as well. The statistical power of the study was low because the sample size was small. We did not have the baseline COPD scores of the patients as the patients were enrolled at exacerbation only. The patients were followed up only for 6 months. A longer follow-up would have given more concrete results. We had to rely on history and past medical records to assess previous exacerbation rates, both of which are prone to incomplete information. Only inpatients were enrolled in the study, thus the study population included patients with severe exacerbation and missed subset of patients with mild exacerbation.

CONCLUSION

Exacerbations are critical milestones in the natural history of COPD and the increased frequency of exacerbations suggests a poor prognosis. Evaluation of the risk of exacerbations is a major component of the initial assessment of a patient with COPD and reduction in the risk and prevention of acute exacerbations is a major objective of management. CAT score is a well-known, sensitive, patient-friendly questionnaire being devised to assess the health status and severity of disease in all the stages namely, stable, exacerbation and during pulmonary rehabilitation, as is reaffirmed in our study. A high DOSE index score (>4) was associated with a greater risk of 2 or more exacerbations thus identifying patients with more severe disease. The reason the DOSE index overpowers other multidimensional indices (BODE or ADO) is that it factors in the frequency of exacerbations in the previous year, which in itself is a significant predictor. Our study is the first of its kind to directly compare DOSE index and CAT scores and observed a statistically significant correlation at exacerbation onset, at 1 week, and at 6 months along with a significant correlation in a change in DOSE index and CAT score after stabilization from acute exacerbation episode at 1 week and at stable state at 6 months. The DOSE index is a practical multidimensional grading tool for assessing current symptoms, health status, and future risk in COPD and acts as a guide to disease management as its component items can be modified by interventions. The correlation with the CAT score is a novel finding

which may need large-scale longitudinal prospective studies to further consolidate the results.

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