JURNAL ILMIAH ILMU KEPERAWATAN INDONESIA
Indonesian Nursing and Scientific Journal

Volume: 14
Issue: 04
Years: 2024

Research Article

Multidimensional Index Model Development for Assessing Exacerbation Prognosis in COPD

Nuni Apriani[1*], Anggriyana Tri Widiyanti[2], Gissan Rafli Ikbari[3], Riki hermawan[4]
[1]Faculty of Health Sciences, 'Aisyiyah University Bandung, Indonesia
[*]Email Corespondent: nuni.apriani@unisa-bandung.ac.id

OPEN ACCESS
Editor: KS
Received: 07/08/2024
Accepted: 21/01/2025
Published: 25/01/2025
Available Article:
10.33221/jiiki.v14i04.3449

Conflict of interest statement: The authors have no conflict of interest.

Funding: Muhammadiyah Research Grant (RisetMu).

Abstract

Background: Acute exacerbations are a major cause of poor outcomes in patients with Chronic Obstructive Pulmonary Disease (COPD). However, attention to early recognition of acute exacerbation symptoms has been limited to FEV1 (Forced Expiratory Volume in 1 second). COPD is a complex disease that involves many dimensions, so early symptom recognition requires a more comprehensive multidimensional assessment. This study is a retrospective cohort study to develop a multidimensional index model in assessing the prognosis of exacerbations in COPD patients.
Objectives: This study aims to find a comprehensive index model in the early assessment of exacerbations to reduce mortality and morbidity in COPD patients.
Methods: This study is a retrospective cohort study by conducting non-interventional observations. A total of 28 COPD patients based on GOLD (Global Initiative for Chronic Obstructive Lung Disease) criteria were included as respondents.
Results: The Cox Regression survival analysis for the quartiles showed a significant effect of this multidimensional index on predict exacerbation prognosis.
Conclusion: The BODEX + sPO2 provided an adequate match between predicted and observed exacerbation prognosis in COPD.

Keywords:
COPD, exacerbation, multidimensional index, prognosis

Introduction

Chronic obstructive pulmonary disease (COPD) is the third leading cause of death worldwide, 90% of these deaths are in countries with middle to lower income.[1] COPD is one of a group of non-communicable diseases that is a public health problem in the world, including Indonesia.[2] COPD is characterized by airflow obstruction in the airways that is progressive and non-reversible with or without alveolar abnormalities. Both of these occur due to significant exposure to noxious particles or gases.[3] In this case, acute exacerbations are the main cause of worse disease outcomes and progression in COPD patients.[4] Acute exacerbations are characterized by worsening of the patient's respiratory symptoms, shortness of breath, and cough with or without sputum that exceeds daily symptoms. Despite the management of acute exacerbations in COPD patients, this condition still occurs frequently and is closely associated with morbidity and mortality.[5]

In an article published in 2020, it was said that there are various phenotypes in the exacerbation stage, one of which is referred to as the phenotype with frequent exacerbations, and the other phenotype shows rare exacerbations.[6] As the frequency of exacerbations varies between patients, identifying high-risk patients for timely intervention is a priority.[7] FEV1 (expiratory volume in 1 second) is currently the variable traditionally used to determine the severity of COPD according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, including in Indonesia. However, COPD is a complex disease with many dimensions involved, therefore assessment based solely on FEV1 is not effective in determining mortality and morbidity. Several studies have developed multidimensional indices that integrate various prognosis determinants, to improve the ability to better predict mortality.[8] One multidimensional index known to be effective in assessing mortality in COPD patients is BODE, which was first introduced in 2004. BODE is an acronym for Body mass index, Obstruction (measured by FEV1), Dyspnea, and Exercise which is a 4-dimensional measurement to estimate the prognosis of COPD. The BODE index is known to be more effective in predicting mortality than using only the FEV1 variable. However, the index requires a time-consuming 6-minute walking test and requires sufficient space to perform, making it difficult to perform in primary care settings. In 2023, the BODE Index was modified into BODEX by removing the 6-minute waking test and replacing it with a COPD exacerbation history component.[9] Nonetheless, the oxygen therapy dimension is still deemed necessary in assessing prognosis.

BODEX multidimensional scoring assesses 4 dimensions (BMI, FEV1%, mmRC, dyspnea scale, and number of exacerbations in the past year) in determining the prognosis of exacerbations and estimating short- and medium-term mortality. In this study, the BODEX multidimensional model will be developed by adding the oxygen demand dimension which is theoretically closely related to respiratory failure as a cause of high mortality and morbidity.

Methods

This study is a retrospective cohort study conducting non-interventional observations of COPD patients. Retrospective cohort studies are cohort studies that try to look back, data collection starts from the effects or consequences that have occurred (in this case exacerbations in COPD patients), and then the effects are traced for the causes that influence them.[10] Researchers conducted multicenter observations of hospitalized patients with study variables including measurement of body mass index (body mass index), FEV1 score from spirometry results, measurement of dyspnea score using mMRC (Modified Medical Research Council), history of exacerbation in 3 months, and measurement of oxygen saturation using a pulse oximeter. The inclusion criteria set for this study were inpatients aged more than 35 years with a diagnosis of COPD according to GOLD and in stable condition at the time of the study. The exclusion criteria set in this study are patients who have a diagnosis of chronic respiratory disease other than COPD (such as interstitial lung disease or pneumoconiosis).

Descriptive data analysis was performed by calculating the mean and standard deviation for continuous variables, while discrete variables were calculated using frequency and percentage. Comparisons between derivation and validation groups were made using Pearson's t-test or chi-square test (if required). To assess whether BODEX and SpO2 had independent values as predictors of exacerbations, regression analysis was performed.

Results

At the time of the visit, the variables recorded included age, gender, weight, and height (to determine BMI), spirometry results including FEV1 and GOLD classification, vital signs measurements especially SPO2 using spirometry, and history of exacerbations in the past year.

Table 1. Characteristics of Respondent and Mean of Each Variable

Characteristic	n	Frequency
Age		
20 – 44 Years	3	10.7%
45 – 64 Years	12	42.8%
> 65 Years	13	46.5%
Total	28	
Sex		
Male		
Female	26	21.4 %
	6	78.6%
	Mean+SD	
	21.1 ± 4.07	
BMI (B)	48.8 + 15.6	
FEV$_1$% (O)	3.18 + 1.42	
mMRC (D)	1.28 + 0.53	
Exacerbation in 1 Year (Ex)		
sPO2	96.8 +2.52	

Table 1 shows the characteristics of the study participants (n = 28). In terms of age, the majority were over 65 years old (46.5%). The gender distribution indicates that females accounted for 78.6%. The average Body Mass Index (BMI) was 21.1 ± 4.07, with a mean FEV1% of 48.8 ± 15.6, indicating moderate to severe airflow limitation. The mean mMRC dyspnea score was 3.18 ± 1.42, reflecting moderate to severe breathlessness, and the average number of exacerbations in the past year was 1.28 ± 0.53. The average oxygen saturation (sPO2) was 96.8 ± 2.52, indicating relatively stable oxygen levels among the participants.

To compare the predictive performance of the BODEX index (H_0) with its modified version (H_1), the researchers employed an analysis based on the Cox Proportional Hazard Model.

Table 2. Cox Proportional Hazard Summary Table

Model	LOG LIK	DF	AIC	BIC
H_0	-67.890	0	135.779	135.779
H_1	-64.148	5	138.296	144.957

Based on Table 2, it can be observed that the inclusion of predictor variables in the Modified Model (H_1) contributes positively to the model's performance. This suggests that gain in model fit comes at the cost of increased complexity, with only marginal improvement in overall performance. Overall, the BODEX index with SpO_2 provides more information than its original model due to the inclusion of predictors, but the improvement remains modest.

To assess whether BODEX and SpO_2 had independent values as predictor exacerbation, a Cox hazard regression analysis was carried out in the derivation cohort, to calculate Hazard Ratios (HR). We didn't use a priory sample size calculation, because there are no overall accepted methods to estimate the sample size for derivation and validation studies of risk prediction models. It has been suggested that an adequate sample size for these studies should include several participants ≥ 20.[9]

Table 3. Hazard Ratio Estimates

Model			95% CI	
H1		**Hazard Ratio**	**Lower**	**Upper**
	Column 13	0.325	0.126	0.838
	14	0.794	0.397	1.588
	15	0.797	0.466	1.362
	16	1.187	0.522	2.703
	17	1.189	0.123	11.502

Table 3 presents the coefficient estimates, hazard ratios (HR), and statistical significance for each variable in model BODEX with SPO_2, the P value indicates statistical significance. Variables such as 14,15,16 and 17 do not significantly impact survival, as their hazard ratios are not statistically different from 1. The model satisfies the proportional hazards assumption globally and for all individual variables.

Discussion

The semi-parametric survival analysis conducted using the Cox proportional Hazard Model provides critical insights into the factors influencing survival outcomes. The findings reveal both significant and non-significant variables in predicting the hazard of the event over time. This study shows that spO_2 has additional prognostic value to predict exacerbation in stable COPD. BODEX index combined with sPO2 increases the ability to predict all-cause exacerbation in this population. Predicting exacerbation is an important element in designing follow-up and treatment strategies. COPD is a multi-component disease so using the multidimensional index to predict exacerbation will give a better prediction.

The integration of SpO_2 measurements into prognostic indices for Chronic Obstructive Pulmonary Disease (COPD) has garnered significant attention in recent research. The BODE index, encompassing Body mass index, airflow Obstruction, Dyspnea, and Exercise capacity, remains a cornerstone in predicting COPD outcomes.[11] However, its reliance on the six-minute walk test (6MWT) poses practical challenges, especially for patients with comorbidities that impede physical performance.[12]

To address these limitations, researchers have proposed modifications to the BODE index. The BODEX index, which replaces the 6MWT with a history of exacerbations, has demonstrated prognostic performance comparable to the original BODE index in predicting mortality and exacerbations.[13,14] By eliminating the need for exercise testing, the BODEX index is particularly advantageous in non-specialized settings or among patients with physical limitations.

Building on this, incorporating SpO_2 into the BODEX index provides additional prognostic value. The BODEXS90 index, which integrates SpO_2 values below 90%, has been shown to significantly improve mortality prediction in stable COPD populations.[14] This highlights the importance of oxygenation status as a critical determinant of survival, particularly in severe COPD cases where SpO_2 levels are often compromised (Martinez et al., 2020). SpO_2, as a simple and non-invasive measure, adds a clinically valuable dimension to multidimensional indices, making them more accurate and practical for everyday use.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) recognizes the utility of composite indices in predicting COPD outcomes, particularly as they account for the multi-component nature of the disease. GOLD emphasizes that simplified indices, which exclude exercise testing, may serve as suitable alternatives, especially in primary care settings.[12] However, these simplified indices, such as BODEX or BODEXS90, require validation studies before they can be widely adopted in clinical practice.[15]

The survival dynamics observed in this study are consistent with prior research. The Kaplan-Meier survival curve illustrates a sharp decline in survival probability during the early observation period, underscoring the importance of early identification of high-risk patients.[11]

Conclusion

BODEX index combined with sPO2 measurement is simple and easy to obtain. The use of BODEX with sPO2 measurement might be helpful for outcome prediction in more severe cases. This study has several limitations, including a limited number of respondents and a short research time. Besides that, there were fewer patients with low sPO2 (<85%) because they had received oxygen therapy to stabilize their condition. As a consequence, we could not evaluate whether using other cut-off values for sPO2 might increase the discrimination capability of this multidimensional index. This index needs to be measured over a long period to assess exacerbation prediction. These results provide the basis for future validation studies to evaluate the effect of using such an index in direct decision-making algorithms.

Conflict of Interest Declaration

The authors have no conflict of interest.

Acknowledge

The authors thank to 'Aisyiyah University Bandung and RisetMu for all support.

Funding

Muhammadiyah Research Grant (RisetMu).

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