Changes in the BODE index, exacerbation duration and hospitalisation in a cohort of COPD patients

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ABSTRACT

Introduction: We investigated the relationship between frequency of exacerbation and duration and change in functional status, as measured by the BODE index in chronic obstructive pulmonary disease (COPD) patients.

Methods: This was a longitudinal cohort study of 56 patients with moderate to severe COPD. Body mass index, spirometry, Modified Medical Research Council (MMRC) dyspnoea score and six-minute walk distance (6MWD) were measured annually when the patients were clinically stable. Data on frequency and duration of COPD exacerbations occurring in the community and requiring hospitalisation were collected prospectively. Early stage exacerbations were identified through the use of individualised patient action plans and further reinforced by fortnightly phone contact.

Results: At the two-year follow-up, the BODE index increased in 33 patients, remained stable in 18 and decreased in five patients. Patients with increased BODE index had significantly higher hospital presentation rates and longer total bed-days compared to those with stable BODE index. Among the 33 patients with increased BODE index, 20 had lower 6MWD and higher MMRC scores, indicating deteriorating functional status, and 13 had higher levels of airway obstruction. Between these two subgroups, patients with deteriorating functional status had higher exacerbation frequency, longer exacerbation duration and higher inpatient bed-days. Linear regression showed that total annual duration of exacerbation was predictive of change in 6MWD.

Conclusion: Change in the BODE index is a sensitive measure of deteriorating functional status in COPD patients. Duration of exacerbation has greater impact on functional status than frequency of exacerbation episodes.

Keywords: BODE, chronic obstructive pulmonary disease, exacerbation, functional status, hospitalisation

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the top five leading causes of death in the world, and is associated with a significant health and economic burden through hospital admission and absenteeism from work. Acute exacerbations of COPD (AECOPD) denotes a change in the patient's baseline dyspnoea, cough and/or sputum that is beyond normal day-to-day variations and is acute in onset; this may warrant a change in the regular medication of a patient with underlying COPD. AECOPD is associated with more rapid disease progression[1] and decreased quality of life in the patient.

The COPD phenotype is diverse, with individual presentation determined by the presence of a number of overlapping syndromes. These include both the extent and spectrum of lung pathology[2,3] and the presence of systemic disease manifestations such as muscle wasting.[4,5] Traditional research studies (both epidemiological and clinical trials) determine disease severity and progression by the degree of airflow obstruction alone.[6,7] However, there is no direct correlation between the measurements of lung function and functional capacity, thus suggesting that other measures of systemic manifestations of disease should be included in the study of disease progression.[2,8-10]

Celli et al developed a multidimensional staging system that includes respiratory and systemic expressions of disease known as the 'BODE' index.[11] This index uses four dimensions to classify the severity of COPD and to predict survival: body mass index (BMI) (as a measure of cachexia and muscle wasting); exercise tolerance; severity of dyspnoea; and airway obstruction (forced expiratory volume in one second [FEV_1]).[12] Population-based validation studies have demonstrated that the BODE index may be a better predictor of mortality than

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lung function alone.[11] Recent studies have also indicated that the BODE index may predict hospitalisation rates,[13] and that pulmonary rehabilitation programmes may prevent its deterioration.[14] The BODE score is primarily useful as a multifactorial measure, which captures some of the phenotypic heterogeneity of COPD, differentiating prognostic factors in patients with similar levels of airflow obstruction.[15] There is, however, limited data regarding changes in the BODE score over time,[14,15] as well as the effect of frequency and duration of exacerbation on the rate of change. In this study, we prospectively investigated a cohort of 56 patients with moderate to severe COPD over a two-year period. The relationship between change in BODE index and exacerbation frequency/duration and utilisation of acute hospital care was analysed.

METHODS

In this prospective, longitudinal cohort study, patients with moderate to severe COPD (Global Initiative for Chronic Obstructive Lung Disease [GOLD], II–IV) were recruited from the Melbourne Longitudinal COPD Cohort (MLCC). The MLCC is an open, community-based cohort of COPD patients that measures the impact of AECOPD on disease progression. The BODE index was measured annually when the patients were clinically stable, and the data on AECOPD frequency and duration, both in the community and in cases of AECOPD requiring acute hospital care, was collected prospectively.

The study population comprised 56 patients (32 male and 24 female). The inclusion criteria were a diagnosis of COPD according to GOLD criteria stage II–IV,[16] smoking history of ≥ ten pack-years, at least one inpatient admission with an episode of exacerbation of COPD in the 24 months prior to recruitment, age < 85 years and a willingness to give informed consent. Exclusion criteria were residing more than 50 km from the hospital, predominant asthma (FEV_1 reversibility ≥ 15% on spirometry),[17,18] lung cancer, chronic systemic inflammatory conditions (e.g. rheumatoid arthritis), renal failure requiring dialysis and patients identified as requiring palliative care. The Human Research Ethics Committee of Melbourne Health approved the study, and written informed consent was obtained from all subjects.

Spirometry, BMI, Modified Medical Research Council (MMRC) dyspnoea score[19] and six-minute walk distance (6MWD) were measured at recruitment and annually when the patients were clinically stable. The six-minute walk test was performed according to the American Thoracic Society guidelines.[20] The minimum clinically important difference in 6MWD was defined as a change ≥ 54 m.[21] The BODE index was calculated according to the algorithm previously published by Celli et al,[11] and the scale was constructed from 0 to 10, with 10 indicating the most severe disease with the highest mortality risk. Stable COPD was defined as no requirement for increased treatment above maintenance therapy (other than bronchodilators) for 30 days.

Table I. Baseline characteristics of patients in the cohort (n = 56).

Characteristic	Median; IQR
Gender (No.)	
Male	33
Female	23
Age (yrs)	71; 65–76
Smoking status (No.)	
Current smoker	20
Ex-smoker	25
BMI (kg/m^2)	26; 22–29
FEV_1 (L)	0.85; 0.70–1.18
FEV_1 (% predicted)	40; 30–53
D_{LCO} (% predicted)	43; 34–58
D_{LCO}/V_A (% predicted)	68; 46–83
MMRC dyspnoea score*	3; 3–4
6MWD (m)	250; 200–320
BODE index score	6; 4–7
Charlson Comorbidity Index	4; 3–5

Values are presented as median; IQR unless otherwise indicated.
* Scores can range from 0 to 4, with a score of 4 indicating that the patient is too breathless to leave the house or becomes breathless when dressing or undressing.
IQR: interquartile range; BMI: body mass index; MMRC: Modified Medical Research Council; 6MWD: six-minute walk distance

The frequency and duration of AECOPD occurring both in the community and requiring hospitalisation were collected prospectively. AECOPD was defined by the Anthonisen criteria.[22,23] Resolution of an exacerbation was defined as completion of treatment with antibiotics/increased steroids or return of symptoms to baseline levels for 48 hours. The identification of exacerbations at an early stage was achieved through the use of individualised patient action plans that included information about symptoms and instructions to contact the study team when key symptoms developed (i.e. increased dyspnoea, increased wheeze, decreased exercise tolerance, increased cough or change in sputum colour and symptoms of viral upper respiratory tract infection). This was further reinforced by fortnightly telephone contact.

Data on acute care presentation rates for AECOPD management was obtained prospectively, as part of the ongoing patient follow-up, and cross-checked against the hospital administrative data-set. Medical records were reviewed to obtain data on the frequency of

Table II. BODE index at baseline according to GOLD severity category.

COPD severity	Median; IQR		MMRC score		BMI (kg/m^2)	
	BODE index	Walking distance (m)	< 3	≥ 3	< 21	> 21
Stage II (n = 19)	4; 3–6	300; 175–350	3	16	2	17
Stage III (n = 23)	7; 6–7	240; 175–300	1	22	5	18
Stage IV (n = 14)	7.5; 5.8–9	230; 200–290	3	11	3	11

Stages II–IV of COPD were defined by the GOLD severity category. Stage II: 50% ≤ FEV_1 < 80% predicted; Stage III: 30% ≤ FEV_1 < 50% predicted; Stage IV: FEV_1 < 30% predicted or FEV_1< 50% predicted plus chronic respiratory failure (PaO_2 < 60 mmHg with or without $PaCO_2$ > 50 mmHg while breathing air at sea level)
COPD: chronic obstructive pulmonary disease; GOLD: Global Initiative for Chronic Obstructive Lung Disease; IQR: interquartile range; MMRC: Modified Medical Research Council; BMI: body mass index

Table III. Exacerbation and hospitalisation over the two-year follow-up in the COPD patients.

	Median; IQR
No. of hospital presentations	1; 0–4
No. of ED presentations	0; 0–0.75
No. of inpatient admissions	1; 0–3.75
Total bed-days	5; 0–15
AECOPD managed in community only	2; 1–5
Total duration of community AECOPD (days)	28.5; 6–82
Total no. of AECOPD	4; 2–7
Total AECOPD time (days)*	39; 15–98

*Includes both acute care and community.
IQR: interquartile range; ED: emergency department; AECOPD: acute exacerbations of chronic obstructive pulmonary disease

exacerbation, treatment received and length of hospital stay. To ensure that hospitalisations at other institutions were not missed, patients were asked at the regular follow-up call if they had been hospitalised elsewhere. Hospital presentation rate was defined as an unscheduled presentation to the emergency department or acute care admission primarily for the management of AECOPD. This was defined by discharge diagnostic-related group codes of E65A or E65B. To calculate length of stay for each presentation, each 24-hour period was coded as one bed-day and emergency department presentation lasting < 24 hours was coded as 0.5 bed-days. The total bed-days for all acute care presentations were then calculated for the two-year follow-up period. To adjust to variations in follow-up time, bed-days were also reported as the proportion of total follow-up time spent in acute care.

Qualitative variables were expressed as relative frequencies of its categories. Numerical values were expressed as median (interquartile range [IQR]) due to their skewed distribution. Differences between the groups were tested by the Mann-Whitney U test for numerical ones. The correlation between changes in MMRC score and 6MWD was tested by Pearson correlation analysis.

Logistic regression was used to determine whether frequency of exacerbation and utilisation of acute care (measured by presentation rate and total bed-days over follow-up) were predictive of change in the BODE score at two years. The BODE index in this paper was calculated each year, so the cumulative duration of AECOPD was used in the analysis. The distributions of hospital presentations and total bed-days were skewed and log-transformed to attain a normal distribution prior to the regression analysis. A p-value < 0.05 was considered statistically significant. All statistical analyses were performed using the Statistical Package for the Social Sciences version 12.0 (SPSS, Chicago, IL, USA) and STATA version 8.2 (Stata Corp, College Station, TX, USA).

RESULTS

In all, 56 patients were followed up from the years 2004–2006, with a mean follow-up time of 107 (IQR 84–123) weeks. The patients' baseline characteristics, including anthropometric data, FEV_1, D_{LCO} (diffusion capacity of the lung for carbon monoxide), MMRC score, 6MWD, BODE and Charlson index are shown in Table I. The median BODE index at recruitment, according to GOLD severity category, is shown in Table II. The median total number of AECOPD episodes (including community and hospital) was four, and the total AECOPD time over a two-year period was 39 days (Table III).

Pulmonary rehabilitation and maintenance exercise groups were offered to all patients in the study as part of usual care. 90% of the patients had completed pulmonary rehabilitation, 70% participated in a regular exercise session and 20% reported that they performed regular exercise at home.

Overall, a clinically significant improvement in 6MWD at two years was noted in 11 (20%) patients, while 27 (48%) had clinically stable 6MWD (change < 54 m) and 18 (32%) had a deterioration in 6MWD (change > 54 m). Change in MMRC score was significantly correlated

Table IV. Changes in 6MWD and MMRC score at two-year according to FEV_1% predicted.

	6MWD (m)			MMRC		
	Increased	Stable	Decreased	Improved	Stable	Deteriorated
FEV_1% ≥ 50 (n = 19)	2 (+55 to +89)	13 (−40 to +30)	4 (−50 to −125)	0	10	9
36 < FEV_1% < 49 (n = 14)	4 (+55 to +90)	6 (−20 to +20)	4 (−55 to −160)	2	10	2
FEV_1% ≤ 35 (n = 23)	5 (+70 to +220)	8 (−40 to 0)	10 (−55 to −125)	0	12	11

The cut off values for FEV_1 are based on the algorithm of the BODE index.
Data for 6MWD in parenthesis shows the change in the values; while the rest represent the no. of patients.
6MWD: six-minute walk distance; MMRC: modified medical research council

Table V. Comparison between patients with and without an increase in BODE index between recruitment and the two-year follow-up.

Variable	Median; IQR		p-value
	Worsening BODE (n = 33)	Stable/improved BODE (n = 23)	
Age (yrs)	71; 64–76	72; 67–74	0.783
Gender*			
Male	20 (60.6)	13 (56.5)	
Female	13 (39.4)	10 (43.5)	
GOLD severity*			
Stage II	14 (42.4)	5 (21.7)	
Stage III	15 (45.5)	10 (43.5)	
Stage IV	4 (12.1)	8 (34.8)	
BMI (kg/m^2)			
Baseline	26; 23–29	25; 21–32	0.933
Change	0	0	0.065
FEV_1 (%pred)			
Baseline	42; 33–52	37; 26–49	0.134
Change	−5; −12 to −1	1; −4 to 4	0.001
6MWD (m)			
Baseline	250; 175–335	240; 200–300	0.802
Change	−30; −80 to 0	0; −20 to 80	0.007
MMRC score			
Baseline	3; 3–3.5	3; 3–4	0.133
Change	1; 0–1	0	< 0.001
BODE index			
Baseline	6; 4–7	7; 5–8	0.071
Change	1; 1–2	0	< 0.001
No. of hospital presentations	2; 0–6	1; 0–1	0.011
Total no. of bed-days	10; 0–22	3; 0–7	0.021
Total no. of bed-days/follow-up time (%)	1.42; 0–3.83	0.34; 0–0.94	0.032
No. of community AECOPD	3; 1–6.5	2; 1–4	0.247
Duration of community AECOPD (days)	26; 10.5–107	30; 6–56	0.468
Total no. of AECOPD	5; 3–11.5	3; 1–6	0.021
Total duration of AECOPD (days)	50.5; 19–126	39; 13–63.5	0.177

*Values are presented as no. of patients (%).
IQR: interquartile range; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BMI: body mass index; 6MWD: six-minute walk distance; MMRC: modified medical research council; AECOPD: acute exacerbations of chronic obstructive pulmonary disease

with change in 6MWD (pairwise correlation coefficients 0.32). Changes in 6MWD and MMRC dyspnoea scale are summarised according to FEV_1% predicted in Table IV.

Patients were subsequently grouped according to change from baseline BODE score at the two-year follow-up (Table V). 33 patients had worsening BODE score and 23 had no significant change in BODE over the follow-up period. Comparing the baseline characteristics of these two groups, patients who demonstrated a change in BODE score had slightly better baseline lung function,

Table VI. Comparison between patients with and without change in severity of airway obstruction category on the BODE index

Variable	Median; IQR		p-value
	No change in FEV_1% (n = 20)	Change in FEV_1% (n = 13)	
Age (yrs)	71; 63–76	73; 66–78	0.456
Gender*			
Male	12 (60.0)	8 (61.5)	
Female	8 (40.0)	5 (38.5)	
GOLD severity*			
Stage II	6 (30.0)	7 (53.8)	
Stage III	10 (50.0)	5 (38.5)	
Stage IV	4 (20.0)	1 (7.7)	
BMI (kg/m^2)			
Baseline	27; 22–30	24; 23–29	0.501
Change	0	0	0.478
FEV_1 (%pred)			
Baseline	35; 30–52	48; 41–64	0.074
Change	−2.5; −5 to 1.50	−12; −19 to −8	< 0.001
6MWD (m)			
Baseline	250; 181–315	280; 150–350	0.986
Change	−67; −118 to −18	0; 0 to 25	< 0.001
MMRC score			
Baseline	3; 3–3	3; 2.5–4	0.986
Change	1; 0.25–1.00	0; 0 to 1	0.033
BODE index			
Baseline	6; 4.25–7	5; 3.5–6.5	0.221
Change	1; 1 to 2	1; 1 to 2	0.676
No. of hospital presentations	4; 1 to 8.5	1; 0 to 3	0.048
Total no. of bed-days	13.75; 2.25–36.00	1.50; 0–16.75	0.048
Total no. of bed-days/follow-up time (%)	1.77; 0.15–4.87	0.10; 0–2.02	0.048
No. of community AECOPD	5; 1–8	1; 1–3	0.033
Duration of community AECOPD (days)	90; 14.5–145.5	17; 6.5–30	0.022
Total no. of AECOPD	7; 5–14.25	3; 1.5–3.5	0.001
Total duration of AECOPD (days)	105.75; 37.13–151.75	19; 15–37.25	0.001

*Values are presented as no. of patients (%).
IQR: interquartile range; GOLD: Global Initiative for Chronic Obstructive Lung Disease; BMI: body mass index; 6MWD: six-minute walk distance; MMRC: modified medical research council; AECOPD: acute exacerbations of chronic obstructive pulmonary disease

as measured by FEV_1% predicted and the proportion of patients in GOLD categories II–IV in each group. The two groups were similar in their baseline 6MWD, MMRC dyspnoea score and BMI, but the stable BODE group had a higher baseline BODE index (p = 0.071). At the two-year follow-up, there were significant differences between the two groups with regard to change in 6MWD (p = 0.007), MMRC dyspnoea scale (p < 0.001) and decline in FEV_1% predicted (p = 0.001). The group with an increase in BODE score had significantly more hospital presentations (p = 0.011), longer total hospital length of stay (measured by bed-days) over the two-year follow-up (p = 0.032) and more total episodes of AECOPD (p = 0.021).

To analyse whether frequent hospitalisation had the most impact on severity of airway obstruction (measured by FEV_1% predicted) or functional status (6MWD and MMRC), the subgroup of patients with increased BODE index at the two-year follow-up were assessed (Table VI). 13 patients had a significant fall in FEV_1% predicted, with a median decline of 12% of predicted (IQR 8%–19%). In contrast, 20 patients had a significant decrease in 6MWD (median 67 m) and an increase in MMRC dyspnoea scale (median increase was one category) without substantial change in FEV_1% predicted. The results demonstrated functional decline without worsening airflow obstruction over the two-year follow-up. Comparing the exacerbation rates and acute care utilisation between these two groups, the group with more rapid functional decline had a greater number of acute care presentations (p = 0.048) and total hospital bed-days (p = 0.048) over the two years than those with predominantly FEV_1 decline.

Statistical modelling with linear regression was used to determine whether AECOPD frequency and duration were predictive of a change in BODE index over the two

years, as well as to control for factors that would modify this change, such as participation in maintenance exercise programmes, age and comorbidities. Linear regression showed that the total AECOPD rate (community and hospital AECOPD) was not predictive of changes in individual factors measured by the BODE index, but was predictive of change in total BODE score (coefficient 0.37, 95% confidence level [CI] 0.04–0.71, p = 0.03). AECOPD duration, rather than frequency, had the greatest impact on the rate of functional decline. After adjusting for comorbidities using the Charlson index, the total annual AECOPD duration (community and hospital) was predictive of change in 6MWD (coefficient –0.22, 95% CI 4.75–39.18, p = 0.013), accounting for 9% (adjusted R^2 0.09). Duration of community-managed AECOPD was also predictive of decrease in 6MWD (coefficient –0.26, 95% CI 8.93–43.44, p = 0.004) (adjusted R^2 0.17).

DISCUSSION

This study revealed several key findings: (1) The BODE staging system, which includes FEV_1% and other physiologic/clinical variables, was sensitive to changes caused both by a decline in FEV_1% and functional decline (6MWD and dyspnoea severity) in our COPD patients during the two-year period; (2) The duration of acute exacerbation of COPD had a greater impact on functional status than the frequency of exacerbation; (3) Among the components of the BODE index, 6MWD had a greater impact on the deterioration of the BODE index than FEV_1% predicted.

Although COPD is mainly characterised by the presence of airflow obstruction, the many systemic manifestations that accompany this disease partly affect the prognosis of COPD. The BODE index that captures the multidimensional manifestations of COPD is a valuable tool in the assessment of progression of disease.[12] The multidimensional staging system of the BODE index has already been shown to be a superior predictor of the risk of death and hospitalisation in patients with COPD compared to the FEV_1-based staging system. Our study demonstrates that the BODE index is sensitive to changes in patients' functional status (6MWD and dyspnoea severity) even when there is no significant decrease in FEV_1% predicted (Table VI). According to FEV_1% predicted (Table IV), the more severe the airflow obstruction, the greater the decrease in 6MWD. In patients with severe airway obstruction, particularly those with FEV_1 < 35% predicted, deterioration in exercise capacity is an important indicator of disease progression. Our results are in agreement with those of Casanova et al's study, which showed that although the 6MWD declines over time, the decline is significant only in patients with severe airflow limitation (FEV_1 < 50% predicted).[21]

Previous studies have shown that there exists a strong association between the BODE index and hospitalisation, and that the BODE scoring system is a better predictor of hospitalisation for COPD than the GOLD staging criteria based largely on FEV_1.[13] Table V compares patients with and without changes in the BODE index over the two-year period. Patients with stable BODE index had a significantly lower AECOPD rate and shorter hospital stay (total bed-days over two years) compared to those with deteriorating disease, as measured by an increased BODE index.

As mentioned earlier, the BODE index integrates BMI, airflow limitation (FEV_1), dyspnoea and 6MWD. Among the 33 patients with a worsening BODE index, 20 (60%) patients reported a change in their BODE index due to functional decline, as demonstrated by lower 6MWD and higher MMRC scores (Table VI). In our study, we found that the duration of AECOPD was the most important determinant of decline in exercise capacity over the two-year period. Importantly, it is the duration of AECOPD outside of the hospital setting rather than the number of bed-days in hospital that is the most predictive of change in walking distance and increase in BODE index over the two years. Therefore, hospitalisation rate may underestimate the impact of mild and moderate AECOPD managed in the community settings on functional decline and disease progression. Therefore, community care is as important as acute care in hospital for patients with COPD.

Our results also show the positive correlation between a change in MMRC score and 6MWD. Thus, we speculate that the major cause of increased MMRC score in the COPD patients in our study was a decline in exercise capacity. The 6MWD declined in 18 (32%) of our patients, remained stable in 11 (20%) and improved in 27 (48%) patients (Table IV). This could be due to the shorter duration of AECOPD or our patient's participation in pulmonary rehabilitation and maintenance exercise programmes.

The reason why the decline of 6MWD manifested more in patients with deteriorating BODE index over the two-year period is highly speculative. It could simply be due to the deconditioning as a result of a more sedentary lifestyle, as more severe COPD is associated with worse dyspnoea. However, it is also possible that the decline results from the prolonged duration of AECOPD, leading to more advanced systemic involvement such as muscle wasting and systemic inflammation. This finding, which is similar to that in Puhan et al's study,[24] can be clinically important,

as the therapy could change depending on the reason for the decline. The present study has several limitations, including the small sample size; thus, larger future studies are required. Furthermore, our results did not completely address the issue of individual patient variability, since we interpreted the BODE index as a median value of the group. The actual change for an individual may be more or less than the median reported here.

In summary, this study showed that the change in the BODE index over time is sensitive to changes in the FEV_1 as well as functional decline. Our results also suggest that the duration of AECOPD has a greater impact on change in the BODE index than the frequency of AECOPD events. In addition, exacerbation occurring in the community deserves more attention, as it also has important effects on changes in BODE index.

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