CHEST

Survival of Lung Transplant Candidates With COPD

BODE Score Reconsidered

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BACKGROUND: The BMI, obstruction, dyspnea, and exercise capacity (BODE) score is used to inform prognostic considerations for lung transplantation for COPD, but it has not been validated in this context. A large proportion of mortality in COPD is attributable to comorbidities that could preclude transplant candidacy. We hypothesized that patients with COPD who are selected as transplant candidates experience better survival than traditional interpretation of BODE scores might indicate.

METHODS: We performed a retrospective analysis of survival according to the BODE score for patients with COPD in the United Network of Organ Sharing (UNOS) database of lung transplantation candidates (n = 4,377) compared with the cohort of patients with COPD in which the BODE score was validated (n = 625).

RESULTS: Median survival in the fourth quartile of BODE score was 59 months (95% CI, 51-77 months) in the UNOS cohort and 37 months (95% CI, 29-42 months) in the BODE validation cohort. In models controlling for BODE score and incorporating lung transplantation as a competing end point, the risk of death was higher in the BODE validation cohort (subhazard ratio, 4.8; 95% CI, 4.0-5.7; $P < .001$). The risk difference was greatest in the fourth quartile of BODE scores (SHR, 6.1; 95% CI, 4.9-7.6; $P < .001$).

CONCLUSIONS: Extrapolation of prognosis based on the BODE score overestimates mortality risk in lung transplantation candidates with COPD. This is likely due to a lower prevalence of comorbid conditions attributable to the lung transplantation evaluation screening process.

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KEY WORDS: BODE index; COPD; lung transplantation; prognostication

ABBREVIATIONS: BODE = BMI, obstruction, dyspnea, and exercise capacity; LAS = lung allocation score; SHR = subhazard ratio; UNOS = United Network of Organ Sharing

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COPD remains a leading indication for lung transplantation worldwide,[1] accounting for approximately one-third of all lung transplantations performed.[2] COPD is characterized by slow disease progression such that patients with even very severe COPD can experience survival without transplantation that is similar to the survival expected following lung transplantation.[3] To inform the decisions of timing of referral to a transplantation center and timing of listing for transplantation, COPD-attributable prognostic estimates are necessary. Multiple factors independently influence survival in the natural history of COPD. In a landmark paper, Celli et al[4] demonstrated that a score incorporating measures of BMI, airflow obstruction, dyspnea, and exercise capacity (BODE score) predicted survival better than FEV_1 alone. Importantly, the survival observed in the patients with COPD in the highest quartile of BODE scores (indicating most severe disease) was clearly worse than survival observed after lung transplantation. Consequently, guidelines for the referral and timing of lung transplantation incorporated the BODE score as a key prognostic factor informing transplant decision-making.[5] This emphasis on BODE score for transplantation decision-making was reiterated in the most recent consensus statement by the Pulmonary Transplantation Council of the International Society for Heart and Lung Transplantation,[6] as well as in the COPD Global Initiative for Chronic Obstructive Lung Disease guidelines.[7] The BODE score has also been referenced as a survival benchmark against which posttransplantation outcomes have been compared to suggest a transplantation survival benefit for patients with COPD.[6,8]

A substantial proportion of mortality in COPD is attributable to comorbid conditions. Cardiovascular disease and cancer in particular result in more deaths than does respiratory failure in many COPD cohorts.[9,10] In evaluation for transplantation, patients undergo rigorous testing to identify and exclude those with an excessive burden of comorbid conditions.[6,11] As such, patients who are considered candidates for lung transplantation have fewer comorbidities than an otherwise unselected COPD population. Additionally, active tobacco abuse generally precludes consideration for transplantation and conveys increased risk of mortality. Because of this selection process, it is unclear whether BODE survival predictions are generalizable to this population.

We hypothesized that survival in patients with advanced COPD who are candidates for lung transplantation is better than predicted by their BODE scores. To assess this, we compared BODE-adjusted survival of patients with COPD listed for lung transplantation with that of the original cohort in which the BODE score was validated.

Methods

We compared adult (age ≥ 18 years) patients with COPD in the cohort in which the BODE score was originally validated[3] against those in a cohort comprised of lung transplantation candidates with a primary diagnosis of COPD listed in the UNOS database. Criteria for inclusion in the UNOS cohort required a diagnosis of COPD and age > 40 years, with FEV_1, 6-min walk test, and BMI data available for analysis. Patients receiving life support at the time of listing or those listed for repeated transplantation were not included. After inspection of the data for outliers and implausible values, we excluded those with a BMI > 40 or < 15. Transplantation candidate data were extracted from the Standard Transplant Analysis and Research files provided by UNOS. These files were compiled from individual centers and entered by data entry personnel using an electronic system with built-in data validation processes. The data set comprises a prospectively collected open cohort of US transplantation candidates spanning the period from October 1989 through December 5, 2014. The study was conducted with approval from the Institutional Review Board of the University of Maryland (HP-00052346).

Our primary outcome was the difference in survival between cohorts according to BODE classification. Transplantation was treated as a competing end point and right-censored in survival analyses. To prevent the possibility of bias in favor of improved outcomes in the UNOS cohort attributable to waitlist removal of patients with impending death, waitlist removals listed as "medically unsuitable," or "too sick to transplant" were treated conservatively as having died at the time of waitlist removal. Consequently, the date of waitlist removal was analyzed as the date of death, but a proportion of patients in reality lived longer, as the condition for which they were removed was not immediately fatal.

BODE scores ranging from 0 to 10 were calculated based on FEV_1, 6-min walk test, BMI, and New York Heart Association data or Modified Medical Research Council dyspnea measures (Table 1).

TABLE 1] Modified BODE Score Calculation

Variable	Points on BODE Index		
	0	1	2
FEV_1, % predicted	≥ 65	50-64	36-49
Distance walked in 6 min, m	≥ 350	250-349	150-249
MMRC dyspnea scale	0-1	2	3
NYHA class	1	2	3
BMI, kg/m^2	≥ 21	≤ 21	…

BODE "quartiles" were defined as quartile 1 (0-2 points), quartile 2 (3-4 points), quartile 3 (5-6 points), and quartile 4 (7-10 points). BODE = BMI, obstruction, dyspnea, and exercise capacity; MMRC = Modified Medical Research Council; NYHA = New York Heart Association.

Missing dyspnea measures were addressed through multiple imputation. To assess for any potential bias introduced by these steps taken regarding measures of dyspnea, we performed a sensitivity analysis excluding dyspnea measures from both cohorts. For the purpose of presentation, we classified BODE scores according to the quartiles from the BODE derivation cohort,[4] which were as follows: quartile 1 (BODE score 0-2), quartile 2 (BODE score 3-4), quartile 3 (BODE score 5-6), and quartile 4 (BODE score 7-10). As transplantation decision-making is framed on the survival observed in quartile 4, findings are presented with emphasis on this quartile.

Statistical Analysis

Continuous data are expressed as median (interquartile range), and categorical data are presented as counts and percentages. Unadjusted survival is presented graphically using a Kaplan-Meier curve with right censoring at transplantation in deference to the influential role that the original Kaplan-Meier curve has played in transplantation decision-making. Missing dyspnea measures were addressed in the primary analysis by imputing the mean of 20 imputations generated using an ordered logistic regression model including FEV_1, 6-min walk test, BMI, sex, and age. Transplantation as a competing end point was addressed using the methods of Fine and Gray,[12] and survival analysis is presented as subhazard ratio (SHR) values. To assess for a difference in outcomes corresponding to implementation of the lung allocation score (LAS) in May 2005, analyses were repeated to include direct comparisons made between subdivisions of the UNOS cohort according to pre-LAS and post-LAS status. As sex distribution was considerably different between the BODE validation and the UNOS cohorts, an interaction factor between sex and BODE score was evaluated to assess for effect modification. Analyses were performed using Stata statistical software, version 14 (Stata Corp LLC).

Results

The BODE validation cohort was composed of 625 patients (93% men), whereas the UNOS cohort included 4,377 patients (49% men). Although patients in the BODE validation cohort were relatively evenly distributed across the quartiles defined by the BODE derivation cohort, the UNOS cohort was skewed toward advanced disease with < 1% of patients categorized in quartile 2 vs 61% in quartile 4 (Table 2). Only 0.05% of the UNOS cohort were current smokers.

When assessed with Kaplan-Meier plots, waitlist survival censored at transplantation suggested favorable survival in the UNOS cohort compared with the BODE validation cohort (Fig 1). Median survival in quartile 4 of the BODE validation cohort was 37 months (95% CI, 29-42 months) vs 59 months (95% CI, 51-77 months) in the UNOS cohort. Favorable survival in the UNOS cohort compared with the BODE validation cohort was confirmed in survival models controlling for BODE score and incorporating transplantation as a competing end point by an SHR of 4.8 ($P < .001$) (Table 3). The SHR remained robust in a sensitivity analysis in which dyspnea scores were excluded. Analysis stratified by BODE quartile demonstrated survival in quartile 4 to be markedly worse in the BODE validation cohort compared with the UNOS cohort (SHR, 6.8; $P < .001$).

TABLE 2] Cohort Characteristics

Characteristic	BODE Validation Cohort	UNOS Cohort
Age, y	66 (60-73)	60 (56-64)
Male sex, %	93	49
BODE quartile, No.		
1	27	0.5
2	30	3
3	21	35
4	22	61

Data are expressed as median (interquartile range) or percentage. UNOS = United Network of Organ Sharing. See Table 1 legend for expansion of other abbreviation.

In light of the major changes in waitlist management that accompanied the implementation of the LAS, we performed additional analyses examining the UNOS cohort to evaluate for differences between the pre-LAS and post-LAS periods. The pre-LAS subset was approximately contemporaneous (1996-2005) with the BODE validation cohort (1997-2002) and consisted of 624 participants (14%) in the UNOS data set. The remaining 3,753 (86%) in the UNOS cohort constituted transplantation candidates from the post-LAS era. In a competing-risk regression controlling for BODE score, the observation of better survival compared with the BODE validation cohort was observed in both the pre-LAS (SHR, 0.18; 95% CI, 0.14-0.25; $P < .001$) and the post-LAS subset (SHR, 0.21; 95% CI, 0.18-0.26; $P < .001$). An interaction factor between BODE score and transplantation era was not significant ($P = .4$). When post-LAS survival was directly compared against pre-LAS survival in competing risk regressions controlling for BODE score, no difference was detected ($P = .4$).

In recognition of the differences in distribution of sex between the BODE validation cohort and the UNOS cohort, we examined for differences in outcomes according to sex. In a competing risk regression controlling for BODE score as well as cohort (BODE validation vs UNOS), female sex was associated with a higher risk of death (SHR, 1.25; 95% CI, 1.04-1.51; $P = .02$). An interaction factor between sex and BODE score introduced into this model was not significant ($P = 1.0$).

Respiratory failure was the primary reported cause of death in both cohorts, accounting for a greater proportion of deaths in the UNOS data set (73%) than in

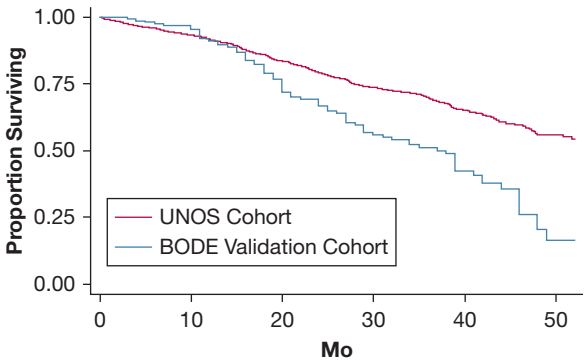

Figure 1 – *Kaplan-Meier survival curve in patients with COPD in BODE quartile 4. BODE = BMI, obstruction, dyspnea, and exercise capacity; UNOS = United Network of Organ Sharing.*

the BODE validation cohort (61%). Cardiovascular deaths were observed in similar proportions in each data set (UNOS, 12%; BODE validation, 14%), whereas deaths attributed to malignancy were notably less common in the transplantation candidates (UNOS, 1%; BODE validation, 12%).

Discussion

In this study involving 5,002 patients with COPD, we found that patients selected as candidates for lung transplantation survive considerably longer than would be predicted by prognostic estimates extrapolated from the BODE validation cohort. Furthermore, respiratory failure was a more frequent cause of death in transplantation candidates with COPD compared with patients with COPD in the BODE validation cohort.

TABLE 3] Subhazard Ratio Models for Risk of Death in BODE Validation Cohort vs UNOS Cohort

Model	SHR	95% CI	*P* Value
Model 1: Imputed data set controlled for BODE score	4.8	4.0-5.7	< .001
Model 2: Imputed data set, stratified			
BODE quartile 1	1.0	0.2-4.3	.99
BODE quartile 2	4.7	2.0-10.8	< .001
BODE quartile 3	3.5	2.3-5.3	< .001
BODE quartile 4	6.1	4.9-7.6	< .001
Model 3: Dyspnea scores removed	5.0	4.1-6.0	< .001

SHR assessed using methods of Fine and Gray. All models assess the subhazard risk of death associated with the BODE validation cohort compared with the UNOS cohort while controlling for BODE score. SHR = subhazard ratio. See Table 1 and 2 legends for expansion of other abbreviations.

Available epidemiologic data demonstrate that a significant proportion of mortality in patients with COPD is attributable to comorbid conditions, particularly cardiovascular disease and cancer.[9,10] We observed much lower rates of cancer deaths in the UNOS cohort but unexpectedly similar rates of cardiovascular deaths. We expected lower rates of cardiovascular death in the UNOS cohort due to extensive screening procedures that would preclude many patients with a high burden of coronary disease from transplantation candidacy; there was also a lack of active smoking among the transplantation candidates. The observed similarity may reflect differences in ascertainment between the cohorts. Sudden death is known to be variably misattributed to cardiac causes depending on the assessment methods.[13]

Although between-study comparisons of mortality can be difficult due to differences in ascertainment of cause of death, certain patterns emerge in the published literature. Notably, the proportion of mortality attributable to nonrespiratory comorbidities appears inversely related to the severity of COPD in the cohort studied. In the Towards a Revolution in COPD Health (TORCH) study, a large randomized controlled trial of patients with COPD, only a minority of deaths resulted from respiratory failure.[14] Notably, there were significant differences from the lung transplantation candidate cohort regarding active smoking (43% vs 0%) and severity of obstruction (mean 44% vs 22% predicted). Deaths were carefully adjudicated, and only 35% were attributed to respiratory disease. Cardiovascular disease (27%) and cancer (21%) were the leading two nonrespiratory causes of death, and only 40% of all deaths were considered definitely or probably related to COPD.[10,14] Although cause of death was not rigorously captured in our UNOS cohort, respiratory deaths represented a strong majority (> 70%), with far fewer deaths attributed to cancer and cardiovascular disease than in previously reported COPD cohorts. It should be emphasized that there is a significant possibility that nonfatal cardiovascular events and incident cancer in patients on the waitlist could result in removal from the waitlist without a corresponding cause of death indicated in the data. As such, conclusions regarding cause of death in the UNOS cohort should be made cautiously in light of the unknown details of these waitlist removals.

Our study bears several strengths and limitations that should be considered in the interpretation of results. The case definition of death for our analysis included waitlist

removal for reason of death and being "medically unsuitable" or "too sick to transplant." The date of waitlist removal was analyzed as the date of death, but in reality a proportion of patients lived longer. A conceptual example would be a patient who was removed from the waitlist due to the development of a new diagnosis of cancer, precluding transplantation but not immediately fatal. In our data set, such a patient would be treated as having died on waitlist removal. Because this conservative analytical approach truncates true survival in the UNOS cohort, our results likely underestimate the true survival difference between the cohorts and should be interpreted as a bookend estimate reflecting a worst-case scenario for the UNOS cohort. This strengthens confidence in the observation of comparatively favorable survival in the UNOS cohort.

Conclusions

Survival of patients with COPD who are considered candidates for lung transplantation is significantly better than would be predicted by extrapolation of survival from the cohort in which the BODE score was validated. This is likely due to a lower prevalence of comorbid conditions attributable to the lung transplantation evaluation screening process. Although BODE mortality predictions are used to inform prognosis surrounding transplantation decision-making, our study would support reconsideration of this practice.

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