Prognostic Validation of the Body Mass Index, Airflow Obstruction, Dyspnea, and Exercise Capacity (BODE) Index in Inoperable Non–Small-Cell Lung Cancer

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Introduction: To investigate the prognostic utility of the body mass index, severity of airflow obstruction, measures of exertional dyspnea, and exercise capacity (BODE) index in patients with inoperable non–small-cell lung cancer (NSCLC).

Methods: One hundred consecutive patients with inoperable NSCLC and performance status 0 to 3 completed pulmonary function testing, the modified Medical Research Council dyspnea scale, a 6-minute walk test, and body mass index—the multidimensional 10-point BODE index. Cox proportional models were used to estimate the risk of all-cause mortality according to the BODE index with or without adjustment for traditional prognostic factors.

Results: Median follow-up was 31.5 months; 61 deaths (61%) were reported during this period. There was a significant univariate association between the BODE index score and mortality (adjusted $p_{trend} = 0.027$). Compared with patients with a BODE index of 0, the adjusted hazard ratio for risk of death was 1.37 (95% confidence interval [CI], 0.74–2.55) for a BODE index of 1, 1.22 (95% CI, 0.45–3.25) for a BODE index of 2, and 2.44 (95% CI, 1.19–4.99) for a BODE index more than 2. The BODE index provided incremental prognostic information beyond that provided traditional markers of prognosis (adjusted $p_{trend} = 0.051$). Every one-point increase in the BODE index, the risk of death increased by 25% (hazard ratio = 1.25; 95% CI, 1.27–4.64).

Conclusions: The BODE index is a strong independent predictor of survival in inoperable NSCLC beyond traditional risk factors. Use of this multidimensional tool may improve risk stratification and prognostication in NSCLC.

Key Words: Lung cancer, Survival, Prognosis, Exercise.

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Lung cancer remains the leading cause of cancer-related death in the United States, responsible for approximately 27% of all cancer deaths in 2013.[1] More than 220,000 new cases of lung cancer are expected in 2013, with the majority being diagnosed with inoperable disease.[1] Despite advances in screening and treatment, median survival for patients with inoperable disease remains dismal at 12 to 14 months.[2–4] As such, identification of robust prognostic markers is a major clinical need in this setting.

Of the numerous prognostic markers examined, performance status (PS) scoring, either assessed by the Karnofsky Performance Scale (KPS) or Eastern Cooperative Oncology Group (ECOG) scoring systems, is one of the most consistent independent predictors of survival.[3,5] Nevertheless, PS scoring systems are subjective and do not provide a comprehensive assessment of functional performance; as a result, these tools lack sensitivity to discriminate between individuals, particularly those defined as having a score of *good* (i.e., KPS >70; ECOG 0–1) PS.[5,6] As such, our group, and others, has started to test the utility and prognostic value of alternative clinical tools that provide an objective assessment of physical functioning including maximal cardiopulmonary exercise testing (to assess peak oxygen consumption; VO_{2peak}) and 6-minute walk testing (to assess 6-minute walk distance [6MWD]) in the setting of non–small-cell lung cancer (NSCLC).[7–10] Results of these studies provide strong preliminary evidence that both VO_{2peak} and 6MWD are strong independent predictors of the risk of death even after controlling for traditional prognostic markers including PS.

VO_{2peak} and 6MWD are single-modality tools that evaluate the integrative capacity of the cardiovascular system during exercise *stress*; nevertheless they do not measure other physiologic outcomes that may also be of prognostic importance in inoperable NSCLC such as weight loss, dyspnea, and pulmonary function.[3] In the setting of chronic obstructive pulmonary disease (COPD) and other respiratory diseases, the *b*ody mass index, airflow *o*bstruction, *d*yspnea, and *e*xercise capacity (BODE) index, a composite but pragmatic multidimensional scoring system that evaluates respiratory, systemic, and whole-body functional capacity, is consistently demonstrated to be a strong independent predictor of mortality beyond traditional factors.[11–13] Despite sharing similar disease pathophysiology and symptomatology, to our knowledge, the

prognostic importance of the BODE index has not been evaluated in the setting of inoperable NSCLC.

Accordingly, in this study, we sought to investigate the prognostic importance of the BODE index in patients with inoperable NSCLC. We also investigated whether the BODE index provided additional prognostic information beyond traditional markers (e.g., PS, age, sex) in this population. We hypothesized that the BODE index would be a significant independent predictor of mortality and provide incremental information on the prediction of mortality beyond traditional markers. We also explored the prognostic value of the individual BODE index components on mortality risk prediction.

PATIENTS AND METHODS

Patients and Procedures

Patients with histologically confirmed Stage IIIB or IV (i.e., inoperable) NSCLC presenting to the Duke Cancer Institute (DCI) were considered eligible for the study. Other major eligibility criteria were: (1) KPS 50 or more, (2) life expectancy 3 months or more, and (3) attending oncologist approval. Major ineligibility criteria were: (1) uncontrolled or recent cardiac disease (unstable angina, acute myocardial infarction, heart failure), (2) uncontrolled hypertension, (3) concomitant infection or mental illness, and (4) contraindications to a 6-minute walk test according to American Thoracic Society guidelines.[14] The study was approved by the DCI and Duke University Medical Center Institutional Review Board, and written informed consent was obtained before the commencement of any study-related procedures.

BODE Index

All BODE index assessments were conducted during outpatient clinic visits at Duke University Medical Center in the following order of presentation: (1) Modified Medical Research Council (MMRC) questionnaire,[15] (2) pulmonary function tests, and (3) 6 minute walk test (6MWT). Body weight and height (used to calculate body mass index [BMI]) were measured on calibrated scales during the clinic appointment. BODE index point allocation for each variable was 0 to 3 points for forced expiratory volume in 1 second (FEV_1) (% predicted), 0 to 3 points for 6MWD, 0 to 3 points for dyspnea (MMRC scale), and 0 to 1 points for BMI. The points for each component were added to obtain the total BODE index score (for a score range, 0–10; Table 1).

TABLE 1. The BODE Index

	Points on BODE Index			
Variable	**0**	**1**	**2**	**3**
FEV_1 (% predicted)	≥65	50–64	36–49	≤35
6-min walk test (m)	≥350	250–349	150–249	≤149
MMRC dyspnea scale	0–1	2	3	4
Body mass index	>21	≤21		

BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; FEV_1, forced expiratory volume in 1 s; MMRC, Modified Medical Research Council.

Body Mass Index

Anthropometric data were used to calculate the BMI, calculated as weight divided by height squared.

Airway Obstruction

Pulmonary function tests were performed using a portable spirometer (Vitalograph micro, model 6300; Vitalograph, Lenexa, Kansas) and reference values.[16] The FEV_1, FEV_1% predicted, forced vital capacity, and forced expiratory ratio were recorded (FEV_1/forced vital capacity%). The FEV_1% predicted was used in the BODE index.

Dyspnea

The MMRC questionnaire was completed for each participant and a score (0 through 4) was recorded. A higher score represents worse breathlessness and disability. The possible scores for the MMRC are: 0 = I only get breathless with strenuous exercise; 1 = I get short of breath when hurrying on level ground or walking up a slight hill; 2 = On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace; 3 = I stop for breath after walking approximately 100 yards or after a few minutes on level ground; and 4 = I am too breathless to leave the house or I am breathless when dressing.

Exercise (Functional) Capacity

Exercise capacity was evaluated by using the 6MWT conducted according to American Thoracic Society guidelines[14] and the highest value in meters recorded. The participants were instructed to walk as far as they could in 6 minutes and received standardized encouragement from clinical staff.

Clinical Measurements

PS was assessed by using the ECOG scale at the time of study enrollment by the attending oncologist. Follow-up survival data were obtained through multiple confirmatory sources: DCI vital statistics; the social-security death index; electronic medical record; tumor registry; and clinical notes. Demographic data related to time to diagnosis, disease stage, cancer treatment, COPD diagnosis, age, and sex were extracted from the electronic medical records.

Statistical Analyses

Descriptive statistics were reported for clinical parameters and study outcomes. The Cox proportional hazards model was used to examine the relationship between BODE index score and mortality. A likelihood ratio test was used in the context of the Cox model to assess the contribution of the BODE index score to the prediction of mortality beyond that provided by PS alone and the combination of PS, age, sex, time from diagnosis to BODE assessment, stage (stage IIIB versus IV), epidermal growth factor receptor (EGFR) status, and COPD status. BODE index score was categorized by means of an unbiased quartile split (i.e., BODE = 0, 1, 2, >2). The median value of the BODE index score within each category was used as a predictor for linear trend in analyses. Our quartile split is distinct from that adopted by Celli et al.[11]

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in the original BODE index study. A Cox proportional model was also used to explore the relationship between each component of the BODE index and mortality with and without adjustment for PS and the other aforementioned covariates. Akaike Information Criteria (AIC) were used to compare model fit of the full BODE index in comparison with the individual BODE index components on mortality risk prediction. Survival time was defined as the time between assessment of the BODE index components and death; for patients remaining alive, survival was censored at the time of last follow-up. A two-sided significance level of 0.05 was used for all statistical tests. All statistical analyses were conducted by using SAS version 9.3 (SAS Institute, Cary, NC).

RESULTS

Participant Characteristics

The characteristics of participants are presented in Table 2. In brief, mean age was 62 ± 10 years and 57% were men. Sixty-six percent of patients had a diagnosis of adenocarcinoma and 14% had a concomitant diagnosis of COPD. Seventy percent of patients were currently receiving chemotherapy, 10% were receiving chemoradiotherapy, and 22% were receiving some form of molecularly targeted therapy (e.g., EGFR-targeted therapy). Seventy-two percent of patients had ECOG score of 1 (ambulatory and able to carry out light but not strenuous activities). Mean FEV_1 and 6MWD were 71% ± 16% and 424 m ± 100 m, respectively; median MMRC and mean BMI were 1 (0–4) and 27 ± 5, respectively. Median BODE index score was 1. No adverse events were observed during 6MWT.

BODE Index and Mortality

Median follow-up was 31.5 months. During this period, 61 deaths were recorded (61% of the total sample). The median time from BODE index assessment to death was 15 months (95% confidence interval [CI], 12.5–20.0).

Univariate Prediction

There was a significant association between BODE index score and mortality. Mortality rates increased across increasing BODE index score categories (unadjusted p_{trend} = 0.011; Table 3 and Fig. 1). Specifically, median months to death were 22.1, 17.2, 18.0, and 9.7 months for a BODE index score of 0, 1, 2, and more than 2, respectively. Compared with patients with a BODE index of 0, the unadjusted hazard ratio (HR) for risk of death was 1.36 (95% CI, 0.73–2.52) for a BODE index of 1, 1.28 (95% CI, 0.48–3.38) for a BODE index of 2, and 2.64 (95% CI, 1.35–5.18) for a BODE index of more than 2 (Table 3).

Multivariate Prediction

The BODE index provided incremental prognostic information beyond provided by PS alone (adjusted p_{trend} = 0.027; Table 3) and beyond other traditional markers of prognosis, including PS, age, sex, COPD diagnosis, and time from diagnosis to BODE index assessment (adjusted p_{trend} = 0.032; Table 3). Compared with patients with a BODE index of 0, the adjusted HR for risk of death was 1.66 (95% CI, 0.88–3.15)

TABLE 2. Demographic and Medical Characteristics of Participants

Variable	No. (%)	Mean ± SD
Age, yr		62 ± 10
Range		28–81
BMI, kg/m^2		27 ± 5
Range		17–46
Men	57 (57)	
ECOG		
0	22 (22)	
1	72 (72)	
2	6 (6)	
Time since inoperable diagnosis, months		27 ± 22
Histologic features		
Adenocarcinoma	66 (66)	
Squamous	11 (11)	
Other (bronchoaveolar, unclassified)	23 (23)	
EGFR mutation status		
Present	13 (13)	
Absent	22 (22)	
Unknown	65 (65)	
Current therapy		
Chemotherapy	70 (70)	
Radiation	10 (10)	
Molecularly targeted therapy	22 (22)	
Angiogenesis-inhibitor therapy (e.g., bevacizumab)	7 (7)	
EGFR-targeted therapy (e.g., erlotinib)	15 (15)	
Prior therapy for operable disease (if applicable)		
Surgery	15 (15)	
Chemotherapy	51 (51)	
Radiation	47 (47)	
Tobacco smoking—current smoker	14 (14)	
Comorbid conditions	31 (31)	
Hypertension	19 (19)	
Hyperlipidemia	9 (9)	
Diabetes mellitus	5 (5)	
Tachycardia	1 (1)	
Arrhythmias	3 (3)	
Angina	4 (4)	
COPD	14 (14)	
Other	1 (1)	
Exercise behavior[a]		
Meeting ACSM guidelines, %	4 (4)	
Reporting no exercise behavior, %	17 (17)	
Six-min walk distance (m)		424 ± 100
Range		163–645
FEV_1 (% predicted)		71 ± 16
Range		14–100
Dyspnea (MMRC scale), median		1
Range		0–4

[a]ACSM guidelines (i.e., reporting at least 150 min of moderate to vigorous intensity exercise per week).

BMI, body mass index; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; COPD, chronic obstructive pulmonary disease; ACSM, American College of Sports Medicine; FEV_1, forced expiratory volume in 1 s; MMRC, Modified Medical Research Council.

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TABLE 3. Association between BODE Index Score and Survival

Analysis	BODE Score 0		1		2		>2		Likelihood Ratio p_{trend}
No. at risk	48		27		9		16		
No. of events	24		18		5		14		
Median, BODE	0	0–0	1	1–1	2	2–2	3	3–6	
Median, Months	22.1	11.28–32.14	17.2	10.26–25.89	18.0	3.03 to -	9.7	5.82–13.85	
Unadjusted, HR	Referent		1.36	0.73–2.52	1.28	0.48–3.38	2.64	1.35–5.18	0.011
Adjusted[a], HR	Referent		1.37	0.74–2.55	1.22	0.45–3.25	2.44	1.19–4.99	0.027
Adjusted[b], HR	Referent		1.56	0.80–3.02	1.08	0.36–3.24	2.60	1.14–5.96	0.032

[a]Adjusted for performance status only.
[b]Adjusted for performance status, age, sex, COPD status, time from diagnosis to BODE index assessment, stage, and EGFR mutation.
BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; HR, hazard ratio; EGFR, epidermal growth factor receptor; COPD, chronic obstructive pulmonary disease.

for a BODE index of 1, 1.38 (95% CI, 0.48–4.01) for a BODE index of 2, and 2.18 (95% CI, 0.99–4.81) for a BODE index of more than 2 (Table 3). The fully adjusted multivariate Cox model indicated that for every one-point increase in the BODE index, the risk of death increased by 24% (HR = 1.25; 95% CI, 1.00–1.54), holding all adjusted variables constant (model p = 0.05; Table 4).

Individual BODE Index Components and Mortality

Univariate analyses indicated significant relationships with mortality for dyspnea and exercise capacity ($p < 0.05$); nevertheless, no individual BODE components were significant in adjusted analyses. AIC analyses indicated that the full BODE index has a superior model fit for mortality risk prediction in comparison with the individual BODE index components.

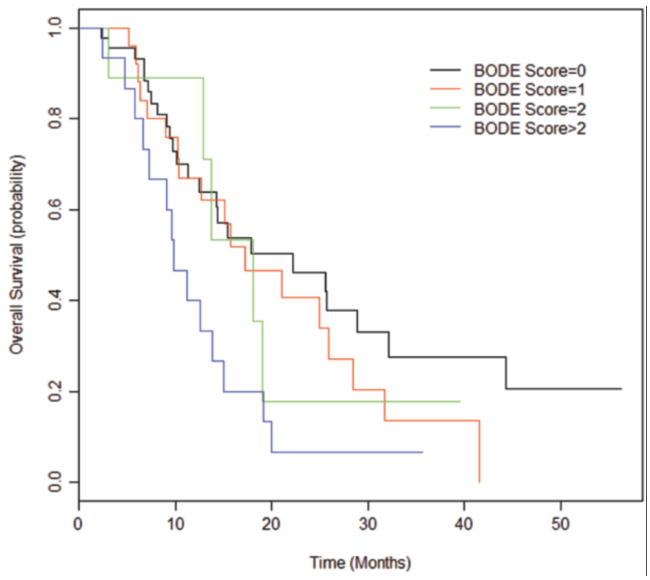

FIGURE 1. Association between BODE index and mortality *The quartile split is distinct from that adopted by Celli et al.[11] in the original BODE index study. BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity.

DISCUSSION

In this preliminary investigation, we found that the BODE index is a significant independent predictor of all-cause mortality which also provides additional information on the prediction of mortality beyond individual BODE components and selected conventional prognostic markers, including the widely utilized ECOG scoring system, in patients with inoperable NSCLC. To our knowledge, this is the first study to examine the prognostic utility of the BODE index in the setting of NSCLC. If replicated, the BODE index may provide a simple but robust multidimensional scoring system that may complement other available conventional and novel prognostic markers to optimize mortality risk prediction in the setting of inoperable NSCLC.

A vast number of biological, histological, and more recently, tumor genomic signatures have been investigated to improve mortality prognostication in patients with inoperable NSCLC.[3] In this context, and typically regardless of the prognostic marker(s) being evaluated, PS remains consistently one of the strongest markers in multivariate analyses. Despite its robust consistency, PS measures have well-documented limitations.[5,6] Hence, alternative tools without the same degree of subjectivity as current PS measures may provide superior mortality risk discriminatory information. In recent years, the prognostic value of alternative objective measures that assess physical functioning under *exercise stress* conditions has been investigated.[7–10] Utility of these measures has been investigated in other areas of respiratory medicine but have received limited attention in inoperable NSCLC.[17,18] In the first published study of this nature, we found that VO_{2peak} was a strong independent predictor of death in 398 surgical candidates with NSCLC after adjustment for KPS, age, sex, and pulmonary function (FEV_1).[9] Interestingly, the prognostic importance of VO_{2peak} was even stronger in nonresected (inoperable) patients. Each 1.0 ml/kg per minute increase in VO_{2peak} was associated with a 4% reduction in all-cause mortality. Nevertheless, VO_{2peak} can only be measured with the use of a maximal cardiopulmonary exercise test; use of cardiopulmonary exercise

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TABLE 4. Multivariate Cox Regression Model

Parameter	Parameter Estimate (SE)	HR (95% CI)	HR Wald χ^2 *p*	Likelihood ratio *p*
Age	0.0160 (0.0162)	1.02 (0.98–1.05)	0.3230	
COPD	−0.5708 (0.3972)	0.57 (0.26–1.23)	0.1508	
Time from diagnosis to BODE assessment	−0.0182 (0.0108)	0.98 (0.96–1.00)	0.0901	
Women	−0.8053 (0.2864)	0.45 (0.25–0.78)	0.0049	
EGFR mutation	−0.4348 (0.4653)	0.65 (0.26–1.61)	0.3500	
No EGFR mutation	−0.7217 (0.3701)	0.49 (0.24–1.00)	0.0511	
Stage IIIB	−1.2002 (0.3754)	0.30 (0.14–0.63)	0.0014	
ECOG	−0.0394 (0.2679)	0.96 (0.57–1.63)	0.8831	
BODE index	0.2168 (0.1113)	1.24 (1.00–1.54)	0.0515	0.0569

BODE, body mass index, airflow obstruction, dyspnea, and exercise capacity; EGFR, epidermal growth factor receptor; HR, hazard ratio; COPD, chronic obstructive pulmonary disease; ECOG, Eastern Cooperative Oncology Group; CI, confidence interval.

test in patients with inoperable NSCLC presents a number of challenges—these tests are relatively expensive, require specialized personnel and equipment and medical supervision; hence, this may limit translation into routine clinical practice, particularly in community settings.[19]

To address this issue, investigators have also evaluated the utility of alternative, pragmatic tools. 6MWT is a simple, clinically feasible, and objective tool designed to assess functional capacity in severely deconditioned clinical populations and may more closely correspond to activities of daily living.[14] Similar to VO_{2peak}, 6MWD is also a significant independent predictor of mortality in patients with inoperable NSCLC. For example, Kasymjanova et al.[10] found that relative to less than 400 m, a 6MWD of 400 m or more was associated with a 56% reduction in the risk of death in 64 patients. These findings were corroborated by our group.[8] Collectively, these findings provide strong, promising data that objective measures of physical functioning such as VO_{2peak} and exercise (functional) capacity may improve prognostication in patients with inoperable NSCLC.

Other related systemic features have known prognostic importance in inoperable NSCLC (e.g., lung function, weight loss).[3] Given the importance of evaluating multiple parameters, we hypothesized that the BODE index—a composite tool validated to be a strong predictor of mortality in respiratory diseases[11–13]— would also be a robust prognostic tool in the setting of inoperable NSCLC. Our findings support and extend prior work by demonstrating that the BODE index is a significant predictor of mortality beyond traditional factors. Specifically, compared with patients with a BODE index of 0, those with a BODE index of 1 or higher had up to an approximately 2.5-fold increased risk of death; each one-point increase in the BODE index was associated with a 25% increased risk of death. To highlight the multifactorial nature of NSCLC, and the use of multidimensional or composite tools to evaluate this complexity, we also explored the relationship between each component of the BODE index and mortality. Interestingly, only dyspnea and exercise capacity were significant univariate predictors of mortality; neither were significant predictors in multivariate analyses. Furthermore, AIC model fit indicated that the full BODE index was superior at predicting mortality than any of the individual BODE index components.

The magnitude of mortality risk prediction of the BODE index in this study is similar to that observed in noncancer clinical populations. For example, in the original BODE study, Celli et al.[11] reported that a higher BODE index was a significant predictor of mortality in 625 patients with COPD; every one-point increase in the BODE score was associated with a 34% increased risk of death from any cause and 62% increased risk of death from respiratory causes. Further work in COPD by Martinez et al.[20] found that the modified BODE index (investigators utilized the University of California, San Diego shortness of Breath Questionnaire (UCSD SOBQ) dyspnea measure as opposed to MMRC measure) was an independent predictor of death in 609 patients with severe emphysema. The powerful prognostic value of the original BODE index and modifications of the BODE index has now been demonstrated by multiple groups.[21,22]

In addition to mortality risk prediction, modification of one or more of the BODE index components may be attractive therapeutic targets to improve clinical outcomes in inoperable NSCLC. Clearly, multitargeted strategies with ability to modify one or more components would be expected to have the greatest impact. Exercise training, an intervention that exerts pleiotropic effects across a number of organ systems may modify one or more BODE index components, may be particularly efficacious. For example, Cote and Celli[23] reported that standard pulmonary rehabilitation improved components of the BODE index in 246 patients with COPD; improvements in BODE were associated with improvements in 2-year mortality. Nasis et al.[24] found that both high-intensity and conventional constant-load aerobic exercise training significantly lowered BODE scores in 42 patients with COPD. Several studies have provided promising evidence that supervised exercise training (both aerobic and resistance training) is a safe and feasible intervention strategy that is associated with favorable improvements in physiological outcomes (and quality of life) in patients with both operable and inoperable NSCLC.[25] The impact of exercise training on modification of the BODE index has not been examined in the setting of NSCLC.

Several limitations need to be considered when interpreting the findings of this study. The most important limitation is the small number of patients with a BODE index of 2 or more than 2. Relatedly, we recruited patients at any time after

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inoperable NSCLC diagnosis (27 ± 22 months since diagnosis). Consequently, we recruited a biased patient cohort, characterized by those with better physical functioning, less advanced disease, and experiencing less treatment-related complications. Cohort studies recruiting newly diagnosed patients are required to fully understand the clinical utility of the BODE index in the setting of inoperable NSCLC. Nevertheless, higher representation of patients with poor PS (BODE >2) may be challenging because these patients may be physically incapable of performing a 6MWT. It is also of importance to study the BODE index in nonsmokers with lung cancer, because there is less overlap in the etiology of the cancer compared with patients with COPD. Also, patients with oncogenic driver mutations (e.g., overexpression of EGFR) should be studied separately, because survival in this patient cohort may be less driven by BODE index components compared with smokers treated with cytotoxic chemotherapy. In general, larger studies in homogenous cohorts of inoperable NSCLC patients receiving uniform treatment and/or tumor molecular features or mutations are required to adequately evaluate the utility of the BODE index. Finally, we only had information on death from any cause; the specific cause of death in our patient cohort is unknown.

In summary, the BODE index score is a strong independent predictor of survival in inoperable NSCLC that may complement traditional markers of prognosis to improve risk stratification and prognostication.

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