Predictors of Mortality in Patients with Emphysema and Severe Airflow Obstruction

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Purpose: **Limited data exist describing risk factors for mortality in patients having predominantly emphysema.**

Subjects and Methods: **A total of 609 patients with severe emphysema (ages 40–83 yr; 64.2% male) randomized to the medical therapy arm of the National Emphysema Treatment Trial formed the study group. Cox proportional hazards regression analysis was used to investigate risk factors for all-cause mortality. Risk factors examined included demographics, body mass index, physiologic data, quality of life, dyspnea, oxygen utilization, hemoglobin, smoking history, quantitative emphysema markers on computed tomography, and a modification of a recently described multifunctional index (modified BODE).**

Results: **Overall, high mortality was seen in this cohort (12.7 deaths per 100 person-years; 292 total deaths). In multivariate analyses, increasing age ($p = 0.001$), oxygen utilization ($p = 0.04$), lower total lung capacity % predicted ($p = 0.05$), higher residual volume % predicted ($p = 0.04$), lower maximal cardiopulmonary exercise testing workload ($p = 0.002$), greater proportion of emphysema in the lower lung zone versus the upper lung zone ($p = 0.005$), and lower upper-to-lower-lung perfusion ratio ($p = 0.007$), and modified BODE ($p = 0.02$) were predictive of mortality. FEV_1 was a significant predictor of mortality in univariate analysis ($p = 0.005$), but not in multivariate analysis ($p = 0.21$).**

Conclusion: **Although patients with advanced emphysema experience significant mortality, subgroups based on age, oxygen utilization, physiologic measures, exercise capacity, and emphysema distribution identify those at increased risk of death.**

Keywords: chronic obstructive pulmonary disease; computed tomography; mortality; prognosis; pulmonary function

Chronic obstructive pulmonary disease (COPD) is associated with significant morbidity and mortality (1), and studies defining long-term survival have documented widely varied survival rates (2). Numerous factors have been reported to influence prognosis, including FEV_1 (1, 3, 4), inspiratory capacity (5), diffusion capacity for carbon monoxide ($D_{L_{CO}}$) (6–8), hypoxemia (2, 9), hypercarbia (2, 7, 8, 10), impaired exercise capacity (2, 4, 11–15), sex (16), body mass index (BMI) (4, 17–19), dyspnea (20), and health status (13, 21). The clinical phenotype of the patient with COPD may also impact prognosis (22), as early investigators suggested that emphysema is associated with a worse prognosis than chronic bronchitis or asthma (7, 23). More robust predictors of increased risk of death in advanced COPD would be useful clinically, and in investigating potential therapeutic interventions.

The National Emphysema Treatment Trial (NETT) offers a unique opportunity to define the natural history of a large group of patients with COPD with clinically and radiologically defined emphysema and severe chronic airflow obstruction (24, 25).

METHODS

Patient Selection

The study group of 609 patients includes all patients randomized to medical therapy at 17 clinics as part of the NETT (25), except for one patient who received lung volume reduction surgery outside of the NETT for whom the surgery date was unknown. A total of 35 of the 609 patients received lung volume reduction surgery outside of the NETT, and an additional 18 of the 609 patients received a lung transplant during the NETT; their mortality data are censored as of the date of surgery or transplant. The design and methods of the trial have been previously detailed, and are enumerated in the online supplement (24, 25). All patients provided written, informed consent, and the study was approved by the institutional review board at each clinic. Baseline measurements were completed after pulmonary rehabilitation but before randomization.

Clinical Assessment

Demographic data and smoking and medical history were collected by patient interview using standardized instruments. Health status was assessed using the Quality of Well-Being scale, the Medical Outcomes Study Short Form 36-item health survey, and the St. George's Respiratory Questionnaire (26). Dyspnea was quantified using the University of California, San Diego, Shortness of Breath Questionnaire (UCSD SOBQ) (27). Oxygen utilization was obtained by patient report and characterized as positive if patient was using oxygen at rest or during sleep or exercise.

Physiologic Testing

Patients underwent spirometry and plethysmographic lung volume measurement after the administration of albuterol; diffusing capacity, respiratory pressures, and arterial blood gases were also measured. The protocol used for 6-min-walk testing (6MWT) has been described in

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detail and provided the maximal distance walked (28). Maximal exercise capacity was measured on a cycle ergometer with an increment of 5 or 10 W/min after 3 min of unloaded pedaling with the patient breathing 30% oxygen.

Diagnostic Imaging Studies

The severity and distribution of emphysema were determined from chest computed tomography (CT) scans obtained during full inspiration. Data were evaluated using a standard reconstruction kernel, with image analysis performed using a custom-built software program (29). After segmentation, the image voxels within each field were labeled as being emphysema-like based upon their X-ray attenuation coefficient or Hounsfield unit. The distribution of the number of voxels at each Hounsfield unit was plotted with Hounsfield unit values less than −950 corresponding to severe emphysema. Hounsfield unit values of −910 and −850 have roughly corresponded to moderate or mild emphysema regions, respectively. Percent emphysema for the whole lung was calculated, as was the difference between the upper and lower lung regions in percent emphysema. The α value (*see* the online supplement) was calculated for the whole lung, as was the difference in α between the upper and lower lung regions. Lungs with greater proportions of small lesions have a steep slope and a large α, whereas lungs with larger lesions have a smaller α (30).

BMI, Airflow Obstruction, Dyspnea, Exercise Capacity Index

The BODE (Body mass index, airflow Obstruction, Dyspnea, Exercise capacity) index is an 11-point composite score (0–10) in which higher scores indicate poorer outcomes (4). We modified the original BODE by using the UCSD SOBQ as the dyspnea measure, as the Medical Research Council dyspnea scale was not used in the NETT. The contribution of dyspnea to the BODE score was based on quartile distribution of the UCSD SOBQ in our 609-person sample. A UCSD SOBQ score of less than or equal to 52 contributed 0 points toward the BODE score, whereas a score from 53 through 63 contributed 1 point, a score of 64 through 77 contributed 2 points, and a score of 78 or higher contributed 3 points.

Statistical Analysis

Means and standard deviations are reported for baseline characteristics. The overall mortality rate from all causes was calculated as number of deaths per 100 person-years of follow-up. Cause of death was obtained by review of death certificates in a subset of patients (*see* the online supplement). Univariate comparisons of mortality rates by risk factors were performed using Cox proportional hazards regression analysis. For continuous risk factor variables with no obvious clinical cut-off point for defining healthy versus unhealthy groups, a least-healthy group was identified as the poorest performing quintile on that measure. The reference group for these variables was then defined as the remaining 80% of the distribution. For maximal exercise capacity, the thresholds predictive of differential mortality after lung volume reduction surgery were used (25). For BMI, both upper and lower quintiles were examined, whereas the middle 60% of the BMI distribution was used as the reference. Importantly, the lower threshold was quite similar to a validated threshold (4). Kaplan-Meier mortality curves were created to display differences in mortality by selected risk factors. Differences between mortality curves were assessed using the log rank test.

Two multivariate Cox proportional hazards models were used to identify the variables that predicted mortality after adjusting for all other variables. In the first model, all variables tested with univariate analysis, except the modified BODE index, were included. The second model was the same as the first, except that the modified BODE index replaced BMI, FEV_1, dyspnea, and 6MWT distance.

RESULTS

The study cohort consisted of 609 patients. Descriptive characteristics are enumerated in Table 1. The group overall was characterized by severe airflow obstruction, hyperinflation, impaired D_{LCO}, mild hypoxemia, impaired 6MWT distance, decreased maximal wattage, impaired health status, and severe emphysema, as measured by CT.

TABLE 1. BASELINE CHARACTERISTICS FOR 609 PATIENTS WITH SEVERE EMPHYSEMA MANAGED MEDICALLY AS PART OF THE NATIONAL EMPHYSEMA TREATMENT TRIAL

Parameter	Mean ± SD or %
Age, yr	66.7 ± 5.9
Male, %	64.2
BMI, kg/m^2	24.7 ± 3.5
SF-36	
PCS	29.6 ± 7.6
MCS	54.1 ± 9.3
QWB	0.56 ± 0.11
SGRQ	53.6 ± 12.7
UCSD SOBQ	63.4 ± 18.6
Oxygen use (at rest, exercise, or sleeping), %	81.3
$FEV_{1\%}$ predicted	26.7 ± 7.0
TLC % predicted	128.5 ± 15.0
RV % predicted	223.4 ± 48.9
IC/TLC	0.22 ± 0.06
D_{LCO} % predicted	28.4 ± 9.7
Pa_{O_2}, mm Hg	64.2 ± 10.1
Pa_{CO_2}, mm Hg	43.0 ± 5.8
Hemoglobin, g/dl	14.3 ± 1.3
6MWT distance, m	371.7 ± 96.4
Maximal CPET workload, W	39.5 ± 22.2
Percent emphysema in whole lung*	15.9 ± 10.6
Perfusion ratio	0.28 ± 0.23
Cigarette smoking, pack-years	66.2 ± 32.9
Duration since stopped smoking, yr	8.8 ± 7.5
Duration of cigarette smoking, yr	41.0 ± 8.3

Definition of abbreviations: BMI = body mass index; CPET = cardiopulmonary exercise testing; D_{LCO} = diffusing capacity of carbon monoxide; IC = inspiratory capacity; MCS = mental component scale; PCS = physical component scale; QWB = Quality of Well-Being scale; RV = residual volume; SF-36 = Medical Outcomes Study 36-item Short Form health survey; SGRQ = St. George's Respiratory Questionnaire; 6MWT = 6-min-walk test; TLC = total lung capacity; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

* At the −950 Hounsfield unit cutoff.

The median follow-up time as of September 2005 was 3.9 yr, with an observed mortality rate of 12.7 per 100 person-years. Figure 1 illustrates survival characteristics of the cohort segregated by age. Table 2 presents the results of univariate mortality analyses. Associated with reduced survival were: greater age, lower BMI, oxygen utilization, lower hemoglobin, lower Quality of Well-Being score, higher St. George's Respiratory Questionnaire

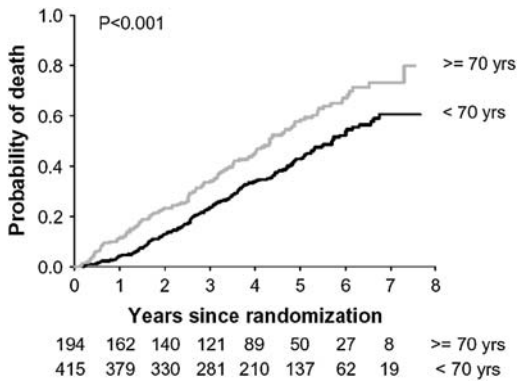

Figure 1. Kaplan-Meier estimates of the probability of death as a function of number of years after randomization for medically treated patients segregated by age. The p value was derived from the log rank test for the comparison between subgroups over a median follow-up period of 3.9 yr.

TABLE 2. UNIVARIATE MORTALITY MODEL IN 609 PATIENTS WITH SEVERE EMPHYSEMA

Variable	n	Hazard Ratio (*95% CI*)	p Value
Demographic/Clinical			
Age, yr			
70–83	194	1.56 (1.23–2.32)	< 0.0001
40–69	415	Reference	
Sex			
Male	391	0.94 (0.63–1.19)	0.60
Female	218	Reference	
Race			
Non-white	35	1.06 (0.66–1.68)	0.82
White	574	Reference	
Annual income			
< $15,000	112	1.04 (0.77–1.39)	0.82
⩾ $15,000	496	Reference	
BMI, kg/m^2			
High (⩾ 28.1)	123	0.77 (0.56–1.06)	0.11
Medium (reference)	362	Reference	
Low (⩽ 21.4)	123	1.48 (1.13–1.95)	0.005
Oxygen use (rest, exercise, or sleeping)			
Yes	495	1.80 (1.30–2.49)	< 0.001
No	114	Reference	
Hemoglobin, g/dl			
9.1–13.3	129	1.63 (1.26–2.12)	< 0.001
13.4–19.1	479	Reference	
Health status			
Quality of Well-Being (QWB)			
0.16–0.49	122	1.47 (1.13–1.93)	0.005
0.50–0.89	487	Reference	
SGRQ			
65.3–88.8	122	1.62 (1.24–2.10)	< 0.001
18.7–65.2	487	Reference	
UCSD SOBQ			
79–109	131	1.89 (1.46–2.45)	< 0.001
9–78	478	Reference	
Physiology			
$FEV_{1\%}$ predicted			
11–21	150	1.44 (1.11–1.85)	0.005
22–54	459	Reference	
TLC % predicted			
140–203	131	1.07 (0.81–1.41)	0.65
95–139	478	Reference	
Residual volume % predicted			
262–412	124	1.41 (1.07–1.85)	0.01
97–261	485	Reference	
IC/TLC			
0.04–0.17	122	1.80 (1.39–2.34)	< 0.001
0.18–0.45	487	Reference	
$D_{L_{CO}}$, % predicted			
6–21	148	1.89 (1.48–2.41)	< 0.001
22–68	457	Reference	
$P_{I_{max}}$ % predicted			
3–17	138	1.12 (0.86–1.47)	0.39
18–57	462	Reference	
$P_{E_{max}}$ % predicted			
4–14	140	1.02 (0.78–1.34)	0.88
15–50	462	Reference	
Arterial blood gas			
Pa_{O_2}, mm Hg			
36–55	133	1.65 (1.28–2.13)	< 0.001
56–95	475	Reference	
Pa_{CO_2}, mm Hg			
47–66	131	1.35 (1.04–1.77)	0.03
29–46	477	Reference	
Exercise testing			
Maximal 6MWT distance, m			
144–288	123	2.02 (1.56–2.61)	< 0.001
289–652	486	Reference	
Maximal CPET workload, W			
Low*	271	2.20 (1.74–2.78)	< 0.001
High*	338	Reference	

(*Continued*)

TABLE 2. CONTINUED

Variable	n	Hazard Ratio (*95% CI*)	p Value
Computed tomography			
Percent emphysema in whole lung†			
25.7–48.5	111	1.14 (0.85–1.52)	0.38
0.4–25.6	441	Reference	
Missing	57	0.96 (0.65–1.41)	0.82
Difference in % emphysema (upper lung:lower lung)†			
−40.4 to −0.9	111	1.39 (1.04–1.85)	0.02
−0.8 to 63.6	441	Reference	
Missing	57	0.99 (0.68–1.46)	0.98
Alpha for whole lung†			
0.4–0.9	111	0.99 (0.73–1.34)	0.94
1.0–1.8	441	Reference	
Missing	57	0.93 (0.63–1.36)	0.71
Difference in alpha (upper lung–lower lung)†			
0.4 to 1.6	111	1.22 (0.91–1.64)	0.18
−1.6 to 0.3	441	Reference	
Missing	57	0.97 (0.66–1.42)	0.87
Distribution of emphysema (radiologist)			
Homogeneous	274	1.14 (0.90–1.43)	0.28
Heterogeneous	335	Reference	
Nuclear perfusion scan			
Perfusion ratio (upper lung:lower lung)			
0.04–0.14	136	1.28 (0.98–1. 68)	0.07
0.15–3.13	472	Reference	
Modified BODE index			
7–10	139	2.38 (1.86–3.04)	< 0.001
1–6	469	Reference	
Cigarette smoking, pack-years			
90–280	126	1.15 (0.87–1. 51)	0.34
0.15–3.13	481	Reference	
Nuclear perfusion scan			
Duration since stopped smoking, yr			
⩽ 2	127	1.14 (0.86–1. 51)	0.36
3–42	480	Reference	

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CPET = cardiopulmonary exercise testing; $D_{L_{CO}}$ = diffusing capacity for carbon monoxide; IC/TLC = ratio of inspiratory capacity to total lung capacity; $P_{E_{max}}$ = maximum expiratory pressure; $P_{I_{max}}$ = maximum inspiratory pressure; QWB = Quality of Well-Being scale; 6MWT = 6-min-walk test; SGRQ = St. George's Respiratory Questionnaire; UCSD SOBQ = University of California, San Diego Shortness of Breath Questionnaire.

* Low exercise is defined as a maximal workload at or below the sex-specific 40th percentile (25 W for females and 40 W for males); high exercise is defined as a workload above this threshold.

† At the −950 Hounsfield unit cutoff.

score, higher UCSD SOBQ score, lower FEV_1, higher residual volume (RV), lower inspiratory capacity/total lung capacity (TLC), lower $D_{L_{CO}}$ % predicted, lower Pa_{O_2}, higher Pa_{CO_2}, lower 6MWT distance, lower maximal exercise capacity, more lower–lung zone emphysema, and a higher modified BODE index.

The variables in Table 2 were used to develop two multivariate models of mortality. Table 3 displays variables that remained predictive of mortality at the $p \leqslant 0.05$ level in either model after adjusting for all of the other variables included in the model; the adjusted hazard ratios are also shown. The variables that remained predictive in the multivariate model that included all variables but the modified BODE index were age, oxygen utilization, TLC, RV, maximal wattage during cardiopulmonary exercise testing, the difference between the upper and lower lungs in percent emphysema, and the perfusion ratio of upper to lower lung zones. The predictors of mortality with the largest hazard ratios were the difference in percent emphysema between the upper and lower lung zones and age. The second model, in which the BODE index replaced BMI, FEV_1, 6MWT distance, and UCSD SOBQ score, gave similar, but not identical, results as the first model. In the second model, oxygen use and TLC were not as strong, whereas hemoglobin and $D_{L_{CO}}$ were weakly predictive, A BODE score of at least 7 was predictive, with a hazard ratio of 1.48 (95% confidence interval = 1.07–2.05; p = 0.02). Figure 2 demonstrates mortality by modified BODE index. Similar results were obtained when the six patients with α_1-antitrypsin deficiency were excluded from analysis.

DISCUSSION

In this study of patients with severe emphysema randomized to the medical arm of the NETT, we document that increased mortality was independently associated with the following: (*1*) greater age, (*2*) use of oxygen supplementation, (*3*) lower hemoglobin, (*4*) higher RV (as % predicted), (*5*) lower $D_{L_{CO}}$ % predicted, (*7*) lesser maximal exercise performance on cardiopulmonary exercise testing, (*8*) a higher modified BODE, and (*9*) greater lower–lung zone emphysema.

In this well-characterized cohort of patients with severe emphysema, multivariate analyses indicated increasing age to be associated with increased mortality. These data support the findings of others, who have suggested that increased age is associated with worsened survival (31, 32). Interestingly, no difference in mortality was noted between males and females with severe emphysema in univariate or multivariate analyses. Our data are in contrast with reports that female patients with COPD have a better prognosis compared with males (16, 33). Importantly, we confirm a weak, independent, predictive ability of a lower

TABLE 3. SIGNIFICANT PREDICTORS IN MULTIVARIATE MORTALITY MODELS IN 609 PATIENTS WITH SEVERE EMPHYSEMA*

	Model 1‡		Model 2‡	
Predictor	Hazard Ratio (*95% CI*)	p Value	Hazard Ratio (*95% CI*)	p Value§
Age, yr				
70–83	1.64 (1.23–2.18)	0.001	1.72 (1.31–2.26)	< 0.001
40–69	Reference		Reference	
BMI, kg/m^2				
High (> 28.1)	0.86 (0.62–1.21)	0.40	NA	
Medium	Reference		BODE component	
Low (< 21.4)	1.32 (0.98–1.78)	0.06		
Oxygen use (rest, exercise, or sleeping)				
Yes	1.46 (1.02–2.10)	0.04	1.40 (0.98–2.01)	0.07
No	Reference		Reference	
Hemoglobin, g/dl				
9.1–13.3	1.34 (0.97–1.85)	0.08	1.38 (1.00–1.89)	0.05
13.4–19.1	Reference		Reference	
UCSD SOBQ score				
79–109	1.39 (0.98–1.97)	0.06	NA	
9–78	Reference		BODE component	
TLC % predicted				
140–203	0.68 (0.46–1.00)	0.05	0.69 (0.47–1.01)	0.06
95–139	Reference		Reference	
RV % predicted				
262–412	1.57 (1.03–2.39)	0.04	1.56 (1.04–2.37)	0.03
97–261	Reference		Reference	
D_{LCO}				
6–21	1.34 (0.99–1.82)	0.06	1.36 (1.01–1.84)	0.04
22–68	Reference		Reference	
Maximal CPET workload, W				
Low†	1.54 (1.17–2.03)	0.002	1.48 (1.12–1.94)	0.006
High†	Reference		Reference	
Difference in % emphysema (upper lung:lower lung)				
−40.4 to −0.8	1.74 (1.19–2.57)	0.005	1.80 (1.22–2.66)	0.003
−0.7 to 63.6	Reference		Reference	
Missing	0.84 (0.55–1.28)	0.41	0.86 (0.57–1.31)	0.49
Perfusion ratio				
0.04–0.14	1.57 (1.13–2.17)	0.007	1.53 (1.11–2.12)	0.01
0.15–3.13	Reference		Reference	
Modified BODE index‡				
7–10	NA‡§	NA	1.48 (1.07–2.05)	0.02
1–6			Reference	

Definition of abbreviations: BMI = body mass index; CI = confidence interval; CPET = cardiopulmonary exercise testing; D_{LCO} = diffusing capacity of carbon dioxide; IC/TLC = ratio of inspiratory capacity to total lung capacity; NA = not applicable; RV = residual volume; TLC = total lung capacity; UCSD SOBQ = University of California, San Diego, Shortness of Breath Questionnaire.

* All variables listed in Table 2 were included in each model except as noted in the table; results are shown for those variables that were significant predictors at the $p \leq 0.05$ level in either model.

† Low exercise is defined as a maximal workload at or below the sex-specific 40th percentile (25 W for females and 40 W for males); high exercise is defined as a workload above this threshold.

‡ Includes all variables in Table 2 except components of modified BODE index: BMI, FEV_1, UCSD SOBQ score, and 6MWT distance. The Model 2 was the same as the Model 1, except that the modified BODE index replaced BMI, FEV_1, dyspnea, and 6MWT distance.

§ p Value for the four components for the modified BODE index = 0.12.

BMI, a marker for the systemic manifestations of COPD (34), for increased mortality. This supports the findings of other investigators who have noted a similar predictive ability of low BMI in COPD (4, 17–19). We extend these findings by confirming this relationship, even after adjusting for the extent of emphysema using state of the art chest computed tomographic quantification of emphysema percent. As there was an upper limit for BMI in the NETT, we cannot address whether a high BMI is associated with mortality. The importance of systemic disease is also supported by the greater mortality associated with decreased hemoglobin. Anemia has been reported to be present in patients with severe COPD (35). We demonstrate that decreased hemoglobin is independently associated with greater mortality.

Our results demonstrate the strengths and limitations of physiologic testing in predicting survival in patients with COPD. Although many investigators have suggested that FEV_1 is inversely associated with mortality (2, 3, 23, 31, 36, 37), it was not predictive in our cohort using multivariate analysis. Similarly, in contrast to others who have described a decreased D_{LCO} as strongly predictive of mortality (6–8, 36), we found that lower D_{LCO} was strongly predictive in univariate models, but its impact weakened in multivariate modeling. Both of these discrepancies may reflect the relatively severe reduction and narrow range of FEV_1 and D_{LCO} in our patients. We confirm the importance of hyperinflation by demonstrating increased mortality with a higher RV, and a trend toward lower inspiratory capacity/TLC. On the other hand, in the multivariate model, after including RV

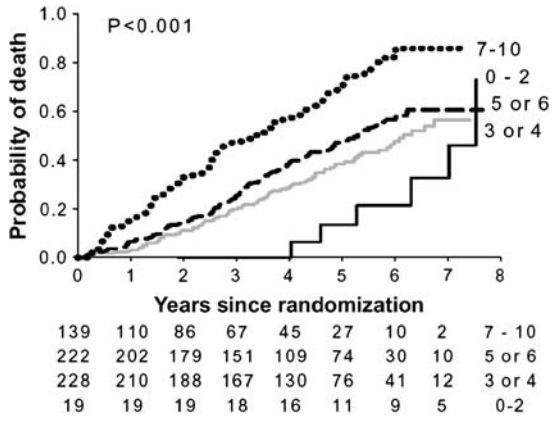

Figure 2. Kaplan-Meier estimates of the probability of death as a function of number of years after randomization for medically treated patients segregated by modified BODE index. The p value was derived from the log rank test for the comparison between subgroups over a median follow-up period of 3.9 yr.

in the model, TLC in fact is inversely associated with mortality, most likely reflecting the relative impact of chest wall compliance on vital capacity, and hence ventilatory reserve. Lower Pa_{O_2} was associated with decreased survival, although only in univariate modeling. Using multivariate modeling, this parameter had no independent influence on mortality, in contrast to the findings of others (2, 9). Intriguingly, the use of oxygen therapy was associated with impaired survival in our cohort. Whether oxygen prescription is an epimarker of more severe impairment, or truly had a negative effect on patient outcome (38), is impossible to discern from our data.

Our univariate analysis data suggest that distance walked and maximal exercise capacity are important predictors of mortality. Importantly, in multivariate analyses, 6MWT distance was no longer predictive, although maximal wattage remained a strong predictor. Although others have associated impaired exercise capacity with decreased survival (4, 11–13, 15), our data extend these findings by incorporating both 6MWT distance and maximal exercise wattage in the analyses. Our study is strengthened by the use of sex thresholds that have been demonstrated to result in differing mortality effects of lung volume reduction surgery (25). A higher dyspnea score, quantified using the UCSD SOBQ, was strongly predictive of decreased survival only in univariate analysis. This finding contrasts with that of other studies suggesting the independent value of dyspnea quantification using other symptom-specific instruments (4, 20). Similarly, we found predictive value to health status measurements only during univariate analyses. This also contrasts with the findings of other investigators (13, 21, 39), and may reflect the relatively narrow range of dyspnea and health status measurements in a more severely diseased population.

One group has recently demonstrated that a multifunctional index, incorporating BMI, FEV_1, 6MWT distance, dyspnea measurement, and the BODE index, performs better than the individual measurements in a large cohort of patients with COPD (4). Although we did not utilize the Medical Research Council dyspnea instrument, we were able to construct a modified BODE index by using the UCSD SOBQ. In our cohort, this instrument proved an independent predictor of mortality, although in multivariate analyses its predictive value was less notable than previously reported. This may represent differing operating characteristics of the dyspnea parameter in the modified BODE index, although the hazard ratio was quantitatively similar to that previously reported (4). More likely, this reflects the predominantly emphysematous population of our patients, or the greater predictive value of maximal achieved wattage during oxygen-supplemented exercise testing. Our data may have important clinical implications, as they suggest that a modified BODE index should be interpreted carefully in clinical situations that are critically dependent on accurate prognostication in patients with COPD, such as the timing of listing for lung transplantation. Additional data in this patient population are desperately required.

Surprisingly, in our patients, the overall percentage of emphysema was not associated with increased mortality in univariate or multivariate analyses. As such, our data suggest that the overall percentage of emphysema does not independently influence survival in a large cohort of patients with severe emphysema. This contrasts with a recent study showing that the percentage of emphysema is predictive of survival in α_1-antitrypsin–induced emphysema (40). The differences between those results and the findings of our study may reflect different patient population (patients with α_1-antitrypsin deficiency were a minority of our cohort), age, and disease severity. In addition, enrollment in the NETT required that patients have bilateral emphysema (identified by chest CT imaging) that was at least moderately severe, but neither too severe nor too homogeneous. Therefore, narrow clustering of emphysema severity in our dataset probably limits this variable's independent predictive value for mortality in our study. Nevertheless, the distribution of emphysema in our cohort was predictive of mortality, with improved survival in patients with greater emphysema in the upper compared with the lower lung zones. Because typical, centrilobular emphysema generally is most prominent in the upper lung zones early in disease, and becomes more diffuse as severity progresses (41), apical predominance may be a marker of reduced disease severity. Alternatively, lower-lobe emphysema may represent a phenotypic or pathobiologic variant of emphysema.

The major limitation of this study comes from its sample population. As all subjects were part of the NETT, the patient population exhibited emphysema and severe chronic airflow obstruction. In addition, selection bias was imposed by requirements for sustained smoking cessation and absence of significant comorbidities that precluded surgical therapy. As a result, the findings may not be applicable to all patients with COPD. On the other hand, the survival characteristics of our cohort are similar to those of other published series (42), including the more severe subgroups of the intermittent positive-pressure breathing trial (3) and other more recent series (4).

In summary, we show that mortality in patients with COPD with moderate to severe emphysema, as defined by high-resolution CT scan, plus severe, chronic airflow obstruction, is influenced by numerous clinical and physiologic factors. We note increased mortality in patients with greater age, lower BMI, oxygen utilization (in contrast to Pa_{O_2}), and greater hyperinflation. Exercise capacity, as quantified by cardiopulmonary exercise testing in contrast to 6MWT distance, proves a powerful independent predictor of survival. By contrast, a multidimensional index, the modified BODE index, proved a weak independent predictor in patients with severe emphysema. These data suggest that readily available clinical parameters may be useful in predicting outcome in severe emphysema.

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