Inspiratory-to-Total Lung Capacity Ratio Predicts Mortality in Patients with Chronic Obstructive Pulmonary Disease

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Static lung hyperinflation has important clinical consequences in patients with chronic obstructive pulmonary disease. We analyzed the power of lung hyperinflation as measured by the inspiratory capacity–to-total lung capacity ratio (IC/TLC) to predict mortality in a cohort of 689 patients with chronic obstructive pulmonary disease (95% males; FEV_1, 1.17 L) with a mean follow-up of 34 months. We also compared the predictive value of IC/TLC with that of the BODE (body mass index, airflow obstruction, dyspnea, exercise performance) Index. Subjects who died (183; 27%) were older; had lower body mass index, FEV_1, and IC/TLC ratio; walked less in the 6-minute walking distance; and had more dyspnea, a higher BODE Index, and comorbidity ($p < 0.001$). On the basis of logistic regression analysis, IC/TLC was found to be a good and independent predictor of all-cause and respiratory mortality. On the basis of receiver operating characteristic Type II curves, IC/TLC compared favorably with FEV_1 and predicted mortality independently of the BODE Index. We conclude that IC/TLC is an independent risk factor for mortality in subjects with chronic obstructive pulmonary disease. We propose that this ratio be considered in the assessment of patients with chronic obstructive pulmonary disease.

Keywords: chronic obstructive pulmonary disease; inspiratory capacity; outcomes

Chronic obstructive pulmonary disease (COPD) is recognized as a major cause of death in the world (1). COPD is characterized by poorly reversible airflow limitation and its severity is usually graded on the basis of the forced expiratory volume in 1 second, or FEV_1 (2–4). The loss of lung elastic recoil and development of expiratory flow limitation promote progressive air trapping with an increase in the end-expiratory lung volume and a decrease in inspiratory capacity (IC). Static lung hyperinflation, and its increase during exercise (dynamic hyperinflation), have been associated with limitations in the functional capacity of those patients (5, 6).

Although primarily a respiratory disease, COPD has been associated with important systemic consequences, and there is some debate about the use of FEV_1 as the main single evaluative parameter for patients with COPD (7, 8). Studies have shown that the 6-minute walk distance (9, 10), peak $\dot{V}o_2$ during a cardiopulmonary exercise test (11), body mass index (12, 13), and dyspnea as measured with the Modified Medical Research Council (MMRC) Scale (14) predict mortality better than does the FEV_1. In addition, we have reported the excellent predictive value of the multidimensional BODE (body mass index, airflow obstruction, dyspnea, exercise performance) Index, which incorporates these variables into a single score (15).

There have been no studies aimed at exploring the possible value of hyperinflation in predicting survival, even though it has been shown to be the most important determinant of dynamic hyperinflation with exercise (6). In the one study where it was evaluated (16), lung volume separated as an individual component in a factor analysis of a cohort of patients with COPD. Thus, we hypothesized that because there is a close relationship between IC and exercise performance in COPD, lung hyperinflation estimated by the inspiratory capacity–to-total lung capacity (IC/TLC) ratio could be a predictor of value in the natural course of the disease among patients with COPD independent of the FEV_1.

We completed this study to assess the contribution of the IC/TLC ratio in predicting the mortality and survival time of a cohort of patients with COPD monitored for 5 years, with a median follow-up of 34 months. Some of the results of this study have been previously reported in the form of an abstract (17).

METHODS

A total of 689 outpatients with COPD and a wide range of airflow obstruction, from clinics in the United States (St. Petersburg, FL; Boston, MA) and Spain (Tenerife and Zaragoza, Spain), participated in the study, approved by the institutional review boards for human subject research at each center. Patients were enrolled from December 1995 to August 2003. COPD was defined on the basis of smoking (a more than 20 pack-year history) and a postbronchodilator FEV_1/FVC ratio less than 0.7. Patients were clinically stable for at least 6 weeks and were receiving optimal medical therapy. Exclusion criteria were as follows: uncontrolled comorbidities likely to affect mortality within 3 years, such as malignant disorders or cardiovascular disease; a history of asthma; a change in FEV_1 of more than 200 ml after bronchodilator treatment; and an inability to perform the tests. A total of 525 patients who had plethysmographic determination of TLC are also part of a larger cohort, the results of which have been reported earlier (15).

The patients were evaluated within 6 weeks of enrollment. Pulmonary function tests, spirometry, and lung volumes were measured according to American Thoracic Society guidelines (18). Exercise capacity, dyspnea, body mass index (BMI), and comorbidity were determined by standard methods. The IC was measured according to the protocol described by O'Donnell and Webb (19). Because there are no current equations for normal spirometric IC values, we used IC/TLC as a measure of resting hyperinflation. We also used the best of two 6-minute walk distance tests (6MWDs) separated by at least 30 minutes (20). Dyspnea was evaluated by MMRC Scale (21). BMI was calculated as kilograms per square meter. The FEV_1 percent predicted (FEV_1%), BMI, 6MWD, and MMRC values were integrated into the BODE Index as described previously (15). The combined Charlson Index was used to determine the degree of comorbidity (22). Patients were seen every 6 months or until death. All-cause and respiratory mortalities were recorded. The information was obtained from the family and then confirmed by reviewing medical records.

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Data are expressed as means ± 1.96 SE for normally distributed variables or as median and 5th and 95th percentiles for those with nonnormal distribution. A binary logistic regression model was used to evaluate the predictive value of the different variables, using mortality as the outcome. Because this model retained IC/TLC, an ROC Type II analysis with mortality as the "gold standard" reference was used to determine the better cutoff point for IC/TLC (23). Kaplan–Meier analysis for survival due to all and respiratory causes was performed with an IC/TLC value of 25%. To evaluate the capacity of the 25% cutoff IC/TLC index to predict the risk of death we performed Cox proportional hazard regression analyses. Finally, to determine how much more precise the IC/TLC ratio is than the FEV_1 and BODE Index to predict overall mortality, we obtained ROC Type II curves and estimated the C statistics for each one. The calculations were made with SamplePower 2.0 and SPSS 11.5.1 (SPSS, Chicago, IL).

RESULTS

The cohort of 689 patients was distributed as follows: 503 (73%) from the United States (388 from Florida; 115 from Boston) and 186 (27%) from Spain (110 from Tenerife; 76 from Zaragoza). The median age was 66 years (5th percentile–95th percentile [P_5–P_{95}], 50–80 years), and most (95%) were men. At entry time their American Thoracic Society severity stage had the following distribution: 15 (2%) mild (FEV_1% ⩾ 80), 195 (28%) moderate (FEV_1% from 50 to 79), 306 (45%) severe (FEV_1% from 30 to 49), and 173 (25%) very severe (FEV_1% < 30). Their dyspnea had the following distribution: 41 patients (6%) MMRC 0, 94 (14%) MMRC 1, 252 (36%) MMRC 2, 199 (29%) MMRC 3, and 103 (15%) MMRC 4, with a median of 2 (P_5–P_{95}, 0−4). They showed a median FEV_1 of 1.17 L (P_5–P_{95}, 0.6−2.34 L), a mean Pa_{O_2} of 69.8 mm Hg (95% CI, 46.3−93.3 mm Hg), a mean IC/TLC ratio of 0.28 (95% CI, 0.10−0.46), a median 6MWD of 350 m (P_5–P_{95}, 109−556 m), a median BMI of 26 kg/m^2 (P_5–P_{95}, 18−36 kg/m^2), and a median comorbidity of 4 points (P_5–P_{95}, 1−10 points) in the combined Charlson Index.

Median follow-up time was 34 months (P_5–P_{95}, 8−56 months; range, 1−62 months), with 1,737 person-years of accumulated exposure.

During the follow-up there were 183 (27%) deaths: 134 (20%) had a respiratory cause for death, 40 (6%) were nonrespiratory deaths, and 9 (1%) died of causes not identified. We observed an absolute risk of death from any cause of 10.54×10^2 persons/year (95% CI, 8.25−12.83 persons/year), and a respiratory mortality ratio of 7.71×10^2 persons/year (95% CI, 5.72−9.70 persons/year).

Baseline characteristics of survivors and nonsurvivors are shown for individual hospitals and as a whole in Tables 1 and 2. Subjects who died were older; had a lower BMI; had more dyspnea and comorbidity; were more obstructed, hyperinflated, and hypoxic; and walked less in the 6MWD test than those who survived.

The correlation between variables considered as predictors of mortality is shown in Table 3. There was a high correlation with FEV_1, IC/TLC, MMRC, and 6MWD. Correlations were weaker with Pa_{O_2}, BMI, and Charlson Index. There was a high correlation between BMI and IC/TLC, between Charlson Index and MMRC, and between Pa_{O_2} and FEV_1.

Results of adjusting the logistic binary model over the potential predictors of death for all-cause death and for respiratory death are shown in Tables 4 and 5. The BODE Index, 6MWD, Charlson Index, and IC/TLC were the best predictors of all-cause mortality whereas the same factors plus the MMRC best predicted respiratory mortality.

We then explored the predictive power of the IC/TLC ratio, using a range from 15 to 40% at 5% intervals, and selected the cutoff point with the best sensitivity and sensitivity for all-cause mortality (Figure 1). The 25% IC/TLC cutoff point resulted in a sensitivity of 0.71, a specificity of 0.69, a positive predictive value of 0.46, and a negative predictive value of 0.87. These results are shown in Table 6.

TABLE 1. CHARACTERISTICS OF PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE ACCORDING TO SURVIVAL

Variable	Alive (*n = 506*)	Dead (*n = 183*)	p Value
Sex, M/F*	474/32	178/5	0.0830
Age, yr†	65 (48–79)	68 (54–81)	0.0001
BMI, kg/m^2†	27 (18–36)	24 (16–32)	< 0.0001
FEV_1, L†	1.29 (0.64–2.41)	0.95 (0.53–1.98)	< 0.0001
ATS–ERS staging*			< 0.0001
Mild, ⩾ 80% of predicted FEV_1, %	3	0	
Moderate, 50–79% of predicted FEV_1, %	32	17	
Severe, 30–49% of predicted FEV_1, %	46	40	
Very severe, < 30% of predicted FEV_1, %	19	43	
Pa_{O_2}, mm Hg‡	70.9 ± 23.3	67.2 ± 23.6	0.0001
6MWD, m†	396 (175–575)	240 (80–457)	< 0.0001
BODE Index‡	3.6 ± 2.1	6.3 ± 2.5	< 0.0001
IC/TLC‡	0.30 ± 0.17	0.23 ± 0.17	< 0.0001
Dyspnea, MMRC staging*			< 0.0001
0, %	8	2	
1, %	16	6	
2, %	42	22	
3, %	27	33	
4, %	7	37	
Median†	2 (0–4)	3 (1–4)	< 0.0001
Comorbidity, Charlson Index†	4 (1–9)	5 (2–12)	< 0.0001

Definition of abbreviations: 6MWD = 6-minute walk distance; ATS = American Thoracic Society; BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, exercise performance; ERS = European Respiratory Society; F = female; IC/TLC = inspiratory capacity/total lung capacity; M = male; MMRC = Modified Medical Research Council.

* Number or percentage; comparisons with Pearson χ^2 exact test.

† Median (P_5–P_{95}); comparisons with Mann–Whitney U rank exact test.

‡ Mean ± 1.96 SE; comparisons with Student *t* test.

TABLE 2. CHARACTERISTICS OF THE COHORT ACCORDING TO CENTERS

Variable	Bay Pines, Florida (*n = 388*)	Candelaria, Tenerife (*n = 110*)	St. Elizabeth, Boston (*n = 115*)	Servet, Zaragoza (*n = 76*)	p Value
Sex, M/F*	374/14	95/15	108/7	75/1	0.0020
Age, yr†	66 (51−81)	66 (45−76)	68 (51−81)	65 (53−77)	0.0141
BMI, kg/m²†	26 (18–36)	27 (20–33)	26 (18–36)	28 (21−37)	0.0042
FEV_1, L†	1.17 (0.59−2.38)	1.08 (0.60−2.13)	1.19 (0.56−2.36)	1.32 (0.63−2.42)	0.1136
ATS–ERS staging*					< 0.0070
Mild, ⩾ 80% of predicted FEV_1, %	2	3	1	4	
Moderate, 50–79% of predicted FEV_1, %	26	31	21	45	
Severe, 30–49% of predicted FEV_1, %	43	48	52	35	
Very severe, < 30% of predicted FEV_1, %	29	18	26	16	
Pa_{O_2}, mm Hg‡	71.4 ± 1.3	68.1 ± 1.8	71.5 ± 2.5	63.2 ± 2.1	< 0.0001
6MWD, m†	310 (109−502)	470 (331−619)	329 (109−498)	449 (230−582)	< 0.0001
BODE Index‡	5 ± 2.5	2.7 ± 2	4.8 ± 2.3	2.5 ± 1.9	< 0.0001
IC/TLC‡	0.28 ± 0.009	0.31 ± 0.017	0.28 ± 0.017	0.30 ± 0.020	0.0032§
Dyspnea, MMRC staging*					< 0.0001
0, %	0	30	1	7	
1, %	6	33	4	41	
2, %	39	21	44	36	
3, %	36	3	40	12	
4, %	19	13	11	4	
Median†	3 (1–4)	1 (0−4)	3 (1–4)	2 (0−3)	< 0.0001
Charlson Index†	5 (2–11)	3 (1–5)	4 (2–11)	3 (1–4)	< 0.0001
Deaths from any cause*	127 (33%)	16 (15%)	28 (24%)	12 (16%)	0.0001
Deaths from respiratory cause*	95 (25%)	10 (9%)	20 (17%)	9 (12%)	0.0011

For definition of abbreviations, *see* Table 1.

* Number or percentage; comparisons with Pearson χ^2 exact test.

† Median (P_5–P_{95}); comparisons with Kruskal–Wallis H exact test.

‡ Mean ± 1.96 SE; comparisons with analysis of variance test.

§ Difference present only between Florida and Tenerife hospitals (Bonferroni *post hoc* test, p = 0.005).

At the 25% IC/TLC cutoff point the cohort was homogeneously distributed: 286 (42%) had an IC/TLC of ⩽ 25% and 403 (58%) had an IC/TLC > 25%. At this IC/TLC cutoff point there were important differences in mortality: it was 71% in patients with IC/TLC ⩽ 25% versus 29% in those with IC/TLC > 25%. The all-cause mortality rate for IC/TLC ⩽ 25% was 18.48×10^2 persons/year (95% CI, 17.06−19.90 persons/year) and the respiratory mortality rate was 14.92×10^2 persons/year (95% CI, 10.79−19.05 persons/year).

The Kaplan–Meier analysis showed that IC/TLC ⩽ 25% was associated with significantly shorter survival time than IC/TLC > 25% for all-cause and respiratory deaths (32 months with 55% censored versus 36 months with 87% censored, respectively; p < 0.0001). These results are shown in Figure 2.

By adjusting Cox regression models with the IC/TLC at a 25% cutoff value, we obtained a hazard ratio associated with an IC/TLC ⩽ 25% for all causes of 1.970 (95% CI, 1.364−2.847), and of 2.042 (95% CI, 1.257−3.317) for respiratory failure, adjusting by all the other predictive factors.

Comparison between IC/TLC ratio, BODE Index, and FEV_1 ROC Type II curves, and under curve area C statistics with the 95% CI estimation for each of these respiratory parameters, are shown in Figure 3.

DISCUSSION

To our knowledge this is the first study reporting that static hyperinflation, as expressed by the IC/TLC ratio, is an independent

TABLE 3. CORRELATION* AMONG POTENTIAL PREDICTORS OF MORTALITY

	IC/TLC	BMI	MMRC	FEV_1	6MWD	Charlson Index
BODE	−0.61 (< 0.001)					
BMI	0.41 (< 0.001)					
MMRC	−0.41 (< 0.001)	−0.15 (< 0.001)				
FEV_1	0.67 (< 0.001)	0.26 (< 0.001)	−0.41 (< 0.001)			
6MWD	0.43 (< 0.001)	0.17 (< 0.001)	−0.73 (< 0.001)	0.39 (< 0.001)		
Charlson Index	−0.14 (< 0.001)	−0.06 (0.152)	0.29 (< 0.001)	−0.08 (0.028)	−0.41 (< 0.001)	
Pa_{O_2}	0.22 (< 0.001)	−0.10 (0.020)	−0.22 (< 0.001)	0.35 (< 0.001)	0.13 (0.002)	0.02 (0.706)

For definition of abbreviations, *see* Table 1.

* Spearman rank coefficient, except Pearson coefficient for Pa_{O_2} and BODE Index with IC/TLC. Upper values represent coefficient and values in parentheses represent the two-tailed significance.

TABLE 4. RISK OF DEATH FROM ANY CAUSE AND FROM RESPIRATORY FAILURE: UNIVARIATE LOGISTIC REGRESSION MODELING*

	Any Cause		Respiratory Failure	
For Each	Relative Risk	95% CI	Relative Risk	95% CI
Age, per 1-yr increase	1.043	1.023–1.064	1.038	1.015–1.061
BMI, 1 unit less	1.091	1.054–1.12	1.117	1.074–1.161
FEV_1, 10 ml less	3.846	2.551–5.780	8.621	4.926–14.925
Pa_{O_2}, 1 mm Hg less	1.026	1.010–1.042	1.027	1.010–1.044
6MWD, 1 m less	1.010	1.008–1.011	1.011	1.009–1.013
BODE Index, one point more	1.644	1.505–1.796	1.824	1.641–2.027
IC/TLC, 1% lower	1.112	1.087–1.139	1.142	1.109–1.175
MMRC, 1 unit increase	2.520	2.058–3.087	3.300	2.573–4.231
Charlson Index, per unit increase	1.240	1.161–1.323	1.227	1.147–1.312

Definition of abbreviations: 6MWD = 6-minute walk distance; BMI = body mass index; BODE = body mass index, airflow obstruction, dyspnea, exercise performance; CI = confidence interval; IC/TLC = inspiratory capacity/total lung capacity; MMRC = Modified Medical Research Council.

* With constant.

predictor of all-cause and respiratory mortality in patients with COPD. Using the analogy to the left ventricular ejection fraction, which so well predicts outcome in congestive heart failure (24), we propose that this ratio be named the "inspiratory fraction."

Lung hyperinflation is a frequent occurrence in patients with COPD. Studies have shown a strong correlation between static hyperinflation and the degree of dynamic lung hyperinflation during exercise (6, 25, 26). Both have been associated with the limitation of tidal volume increase during exercise and with the development of dyspnea and exercise intolerance in those patients (5, 6, 19). The resting inspiratory capacity (IC), a reflection of end-expiratory lung volume, has been correlated with exercise capacity measured by the peak $\dot{V}o_2$ (11) and with carbon dioxide retention during exercise (27), and has been used to assess the effect of inhaled bronchodilator (28, 29). In spite of the long association between COPD and hyperinflation and its role in the genesis of dyspnea, only one longitudinal study has analyzed the influence of IC on COPD prognosis. In that study, Schols and coworkers retrospectively reviewed data from 400 patients and prospectively added another 203 (12), using the percentage of normal IC as the variable reflecting lung hyperinflation. In that cohort the IC did not predict mortality. In another study, we also evaluated resting IC as a predictor of mortality in a large cohort of patients. Like Schols and coworkers, we failed to observe any predictive capacity for absolute IC, or for that matter any of the lung volumes to predict mortality (15). However, neither study related IC to TLC, which reflects not only the degree of lung hyperinflation but also the functional reserve in patients with COPD. Interestingly, another prospective study (14) showed that hyperinflation expressed as the residual volume (RV)/TLC ratio, was a powerful predictor of mortality in patients with COPD. However, in that work RV/TLC was not included in the Cox proportional hazard model and was not mentioned as an important predictor of mortality.

Our understanding about COPD is increasing. It is accepted that the FEV_1 is essential for the diagnosis and assessment of respiratory impairment (2–4). However, although in classic studies the FEV_1 was the strongest factor that predicted mortality compared with other predictive variables (30, 31), new data suggest that other parameters not explored previously, such as BMI (12, 13), dyspnea (14), walking distance (9, 10), health-related quality of life (32), and $\dot{V}o_2$ peak (11), as well as the composite BODE Index, independently predict outcome in COPD, and some are better predictors of this outcome than the FEV_1 (15). All of these observations can be explained if we conceive of COPD as primarily a respiratory disease with complex systemic consequences (7, 16, 33). The power of the multidimensional BODE Index as a predictor of survival in this cohort is once again documented. However, the IC/TLC remained an independent predictor when it was evaluated together with the BODE Index and the FEV_1. We believe that the BODE Index can be widely applied and utilized as an excellent descriptor of a patient's state of compromise. The IC/TLC adds an independent new dimension and should be the object of more research so that its true value can be weighted and determined.

The novel finding of our study is that the IC/TLC ratio is an excellent predictor of all-cause and respiratory mortality, above and beyond several of the more recently reported nonrespiratory factors such as the level of dyspnea, 6MWD, Pa_{O_2}, and BMI in our cohort. The IC/TLC is a noninvasive test that could be easily

TABLE 5. RISK OF DEATH FROM ANY CAUSE AND FROM RESPIRATORY FAILURE: MULTIVARIATE LOGISTIC REGRESSION MODELING

	Any Cause*		Respiratory Failure†	
For Each‡	Relative Risk	95% CI	Relative Risk	95% CI
BODE Index, one point more	1.457	1.314–1.617	1.609	1.425–1.817
IC/TLC, 1% lower	1.052	1.022–1.083	1.062	1.026–1.099
Charlson Index, per unit increase	1.195	1.110–1.286	1.177	1.084–1.277

Definition of abbreviations: BODE = body mass index, airflow obstruction, dyspnea, exercise performance; IC/TLC = inspiratory capacity/total lung capacity.

* With constant, using backward stepwise method and Wald's criteria adjusted at nine iterations.

† Without constant, using backward stepwise method and Wald's criteria adjusted at seven iterations.

‡ Only factors with relative risks that produce statistical significance at the 0.05 level are shown.

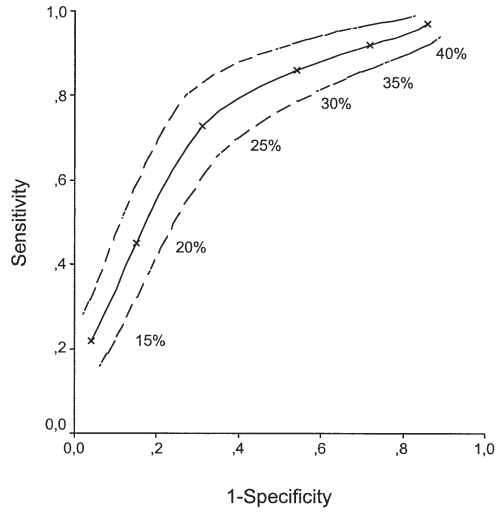


Figure 1. The receiver operating characteristic (ROC) Type II curve is a mathematical function of the sensitivity and specificity of the IC/TLC ratio. An ROC Type II curve with 95% CIs for the various IC/TLC cutoff points for death from any cause is shown. The best value for death prediction from any cause (including 183 deaths) was 25%.

TABLE 6. VALIDITY PARAMETERS FOR VARIOUS INSPIRATORY CAPACITY/TOTAL LUNG CAPACITY CUTOFF POINTS AMONG DEAD FOR ANY-CAUSE PREDICTION

Cutoff Point*	Sensitivity (95% CI)†	Specificity (95% CI)†	Positive Predictive Value (95% CI)†	Negative Predictive Value (95% CI)†
15%	0.20 (0.14–0.26)	0.97 (0.95–0.99)	0.69 (0.57–0.81)	0.77 (0.73–0.81)
20%	0.44 (0.37–0.51)	0.86 (0.83–0.89)	0.52 (0.44–0.60)	0.81 (0.77–0.85)
25%	0.71 (0.64–0.78)	0.69 (0.65–0.73)	0.46 (0.39–0.53)	0.87 (0.83–0.91)
30%	0.81 (0.76–0.86)	0.46 (0.41–0.51)	0.35 (0.30–0.40)	0.87 (0.83–0.91)
35%	0.91 (0.87–0.95)	0.27 (0.23–0.31)	0.31 (0.27–0.35)	0.87 (0.82–0.92)
40%	0.96 (0.93–0.99)	0.14 (0.11–0.17)	0.29 (0.25–0.33)	0.91 (0.84–0.98)

* Up to and greater than.
† Estimated by Hilgers's method (23).

measured in a lung function laboratory (11, 34). The observation that IC/TLC is an excellent predictor of mortality in COPD rebalances our thinking, in a way, because it provides a descriptor of the severity of lung impairment, which in some way was missing from the FEV_1. Indeed, it is tempting to speculate that this association between lung hyperinflation and mortality may explain the beneficial effect on survival seen after lung volume reduction surgery in hyperinflated patients with nonhomogeneous emphysema and limited postrehabilitation exercise capacity in the NETT trial (35). A careful review of the physiologic benefits of lung volume reduction surgery, as reported by Martinez and coworkers, shows that the improvement in exercise capacity and dyspnea was better associated with change in end-expiratory lung volume than with FEV_1 (36). How lung volume relates to mortality and, more interestingly, how its reduction may improve survival is not known and should prompt more investigation as pharmacologic therapy does result in significant lung deflation (29).

The correlation between IC/TLC and MMRC and 6MWD was significant but not superior to that obtained with FEV_1, indicating that IC/TLC does express lung function impairment. On the other hand, IC/TLC showed a stronger correlation with BMI than did BMI with FEV_1, suggesting that IC/TLC may also better reflect the overall impact of disease severity, and could have a great potential impact on the multidimensional evaluation of COPD.

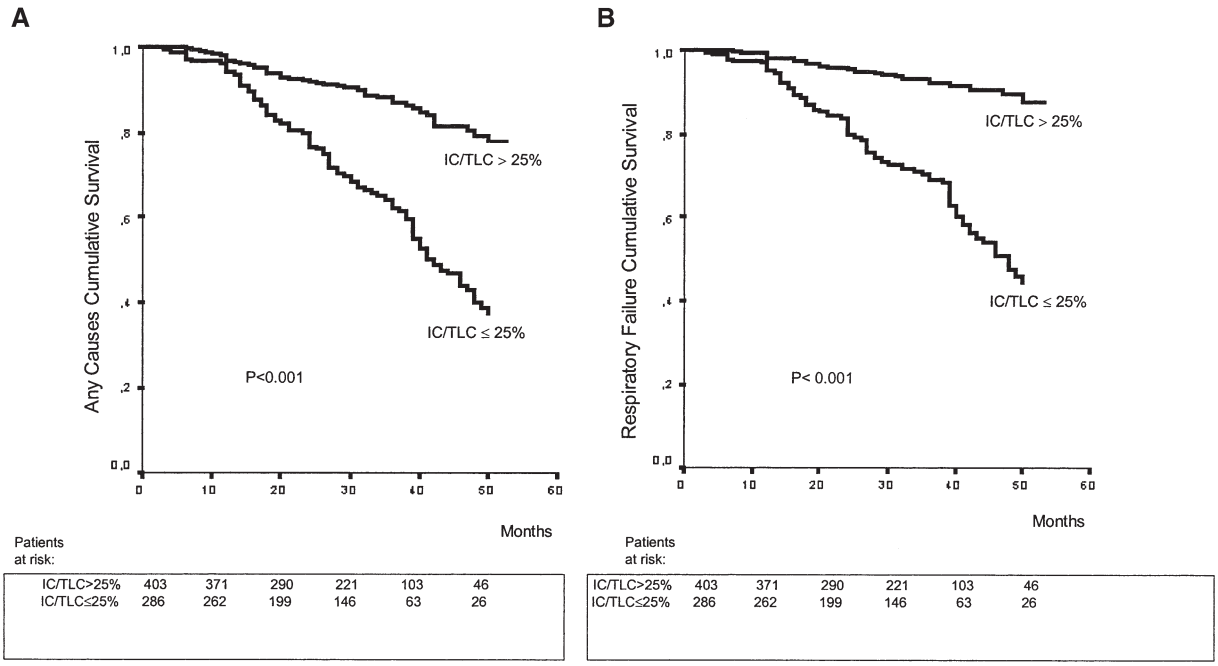
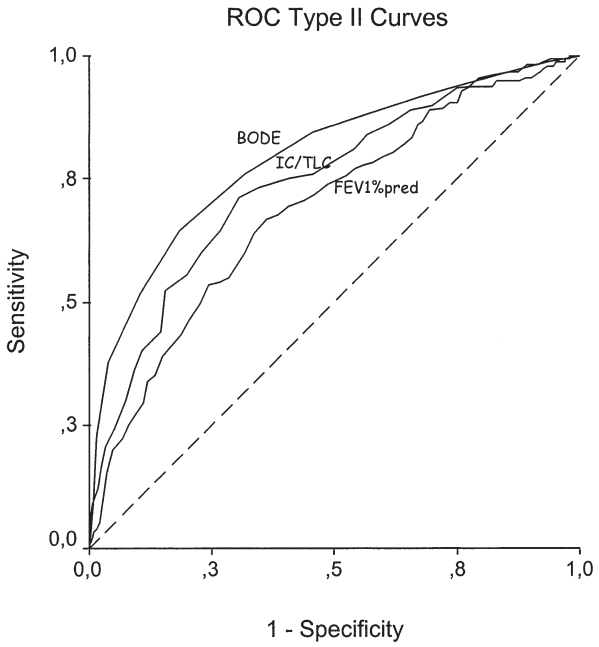


Figure 2. Static lung hyperinflation measured by the IC/TLC ratio, using a 25% value as threshold. Kaplan–Meier curves for all causes and respiratory failure cause are shown. Survival differed significantly among both groups ($p < 0.001$ by the log-rank test) as seen in (*A*) and (*B*).



C-statistics

Parameter	C	SE	p-Value	95%CI(C)
BODE	0.795	0.021	0.000	0.755–0.835
IC/TLC	0.742	0.022	0.000	0.699–0.785
FEV1% predicted	0.688	0.023	0.000	0.642–0.734

Figure 3. Comparative ROC Type II curves and C statistics value for IC/TLC ratio, FEV_1, and BODE Index as predictors of mortality in patients with COPD. The sensitivity and specificity of IC/TLC are greater than that of the FEV_1 but less than that of the BODE Index.

We calculated various sensitivity and specificity values for IC/TLC. An IC/TLC threshold of 25% provided the best power to predict all-cause and respiratory mortality. Although we acknowledge the continuum of expression of biological variables, the 25% IC/TLC value offers the best combined sensitivity, specificity, and positive and negative predictive values. This easy-to-remember value could prove useful in the risk stratification of patients.

The evaluation of patients with left ventricular dysfunction has been greatly helped by the introduction and wide clinical use of the left ventricular ejection fraction (24). This value provides a ratio that expresses the volume of blood ejected by the ventricle at the end of the systolic contraction over the total diastolic volume of the left ventricle at end diastole. We propose that the ratio of the inspiratory capacity over the total lung capacity may express an analogous concept, the volume of air inhaled during a maximal inspiration over the total volume of air available. As the left ventricular ejection fraction is expressed as a percentage, we have expressed the IC as a percentage of the TLC. We propose that this ratio be named the "inspiratory fraction." We recognize that the ejection fraction expresses the fraction ejected by the ventricle during a normal contraction whereas the inspiratory fraction expresses the value of air inhaled during a maximal inhalation. However, given its ease of calculation and its good predictive power, the term may be justified.

This study had some limitations. First, the mortality rate was slightly higher than that of other classic studies from the 1980s with a similar cohort size and follow-up time (31). However, those studies did not include patients with severe hypoxemia, perhaps indicative of the recruitment of patients with less severe disease. This is supported by the similar mortality in our patients compared with more recent studies of smaller size (11, 14, 32). Second, few women were included. This was not by design, because we offer the opportunity to join the study independent of sex. The low number probably reflects the problem of underdiagnosis of COPD in women and in Spain probably the relative late beginning of smoking among women. Third, we would have liked to monitor our patients for a longer period. Nonetheless, the size of our population and the number of deaths allowed us to obtained clinical significant differences that were unlikely to have changed over a longer time. Fourth, there were differences between the populations and in mortality rate between the four hospitals, in spite of a similar mean FEV_1; however, in the multiple regression analysis adjusted by hospitals the IC/TLC remained the strongest predictor of mortality, and the hospital influence was rejected. Fifth, these findings are applicable to patients attending pulmonary clinics, the population that we studies. Whether they can be extended to the population of COPD at large remains to be determined.

In summary, our results show that resting hyperinflation measured as IC/TLC is an independent predictor of respiratory and all-causes mortality in COPD. A threshold IC/TLC value of 25% was identified as an easy threshold to remember that could be important in the evaluation of disease. Our results emphasize that the IC/TLC ratio or inspiratory fraction should be considered in addition to other lung function parameters in the proper assessment of patients with COPD.

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