CHEST

Clinical and Prognostic Impact of Low Diffusing Capacity for Carbon Monoxide Values in Patients With Global Initiative for Obstructive Lung Disease I COPD

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BACKGROUND: The Global Initiative for Obstructive Lung Disease (GOLD) does not promote diffusing capacity for carbon monoxide (D_{LCO}) values in the evaluation of COPD. In GOLD spirometric stage I COPD patients, the clinical and prognostic impact of a low D_{LCO} has not been explored.

RESEARCH QUESTION: Could a D_{LCO} threshold help define an increased risk of death and a different clinical presentation in these patients?

STUDY DESIGN AND METHODS: GOLD stage I COPD patients (n = 360) were enrolled and followed over 109 ± 50 months. Age, sex, pack-years' history, BMI, dyspnea, lung function measurements, exercise capacity, BODE index, and history of exacerbations were recorded. A cutoff value for D_{LCO} was identified for all-cause mortality and the clinical and physiological characteristics of patients above and below the threshold compared. Cox regression analysis explored the predictive power of that cutoff value for all-cause mortality.

RESULTS: A D_{LCO} cutoff value of <60% predicted was associated with all-cause mortality ($D_{LCO} \geq 60\%$: 9% vs $D_{LCO} < 60\%$: 23%, $P = .01$). At a same FEV_1% predicted and Charlson score, patients with $D_{LCO} < 60\%$ had lower BMI, more dyspnea, lower inspiratory capacity (IC)/total lung capacity (TLC) ratio, lower 6-min walk distance (6MWD), and higher BODE. Cox multiple regression analysis confirmed that after adjusting for age, sex, pack-years history, smoking status, and BMI, a $D_{LCO} < 60\%$ is associated with all-cause mortality (hazard ratio [HR], 95% CI = 3.37, 1.35-8.39; $P = .009$)

INTERPRETATION: In GOLD I COPD patients, a $D_{LCO} < 60\%$ predicted is associated with increased risk of death and worse clinical presentation. What the cause(s) of this association are and whether they can be treated need to be determined. CHEST 2021; 160(3):872-878

KEY WORDS: clinical; COPD; D_{LCO}; mortality

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ABBREVIATIONS: 6MWD = 6-min walk distance; ATS = American Thoracic Society; BODE = BMI, airflow obstruction, dyspnea, exercise performance; CHAIN = COPD History Assessment In SpaiN; D_{LCO} = diffusing capacity for carbon monoxide; GOLD = Global Initiative for Obstructive Lung Disease; HR = hazard ratio; IC = inspiratory capacity; TLC = total lung capacity

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Take-home Points

Study Question: Does a low DLCO determine worse clinical outcomes in GOLD I COPD patients?
Results: In GOLD I COPD patients, a DLCO < 60% predicted is associated with increased risk of death and more severe clinical manifestations.
Interpretation: The identification of this "high-risk" population of "mild" COPD patients could help in their management and in trying to minimize the increased risk of death.

The Global Initiative for Obstructive Lung Disease (GOLD) document does not mention the use of the single-breath diffusion capacity for carbon monoxide (DLCO) among the physiological parameters to include in the evaluation of patients with COPD,[1] despite several studies in COPD patients that have shown that low DLCO values are associated with reduced exercise capacity,[2] increased symptoms, risk of severe exacerbations,[3] and mortality.[3] However, these studies have primarily included patients with moderate to severe airflow limitation, with none of them enrolling patients with a postbronchodilator $FEV_1/FVC < 0.70$ and an $FEV_1 \geq 80\%$, defined by GOLD as spirometric stage I COPD patients.[1,2]

Large epidemiological studies such as the National Health and Nutrition Examination survey[4] Cardiovascular Health Study and Atherosclerosis Risk in Communities cohorts[5] or the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar,[6] have shown that patients with GOLD I (mild obstruction) suffer from an increased risk of death. However, no information is available of the potential impact that the presence of an abnormal DLCO could have in their clinical presentation and prognosis, so patients with GOLD I degree of obstruction are seldom studied and certainly not included in pharmacological trials,[7] on the assumption that the labeling of "mild" diseases implicates a good prognosis.

We hypothesized that the information provided by a simple DLCO measurement could help select patients with "mild" (GOLD I) airflow limitation with worse overall COPD compromise and an increased risk of death. To test this hypothesis, we measured DLCO at baseline and followed a large cohort of GOLD I COPD patients and determined the optimal threshold value of DLCO that was associated with those outcomes.

Methods

This is a retrospective analysis from three different prospectively recruited cohorts of COPD patients followed up for a mean period of 9 years, at pulmonary clinics of tertiary university hospitals in Spain and Canada. They were recruited during the period of 1995 to 2011. They were all observational studies, with regular yearly follow-up clinical appointments at the University Hospitals clinics; the main outcome variable was all-cause mortality. The CHAIN cohort in Spain was the only study that has received supportive funding. Patients from the BMI, dyspnea, lung function measurements, exercise capacity (BODE) cohort[8] and the COPD History Assessment In SpaiN (CHAIN) study[9] shared the same methodology. Both are multicenter, observational, multidimensional, prospective evaluation of COPD patients from university hospitals, who are monitored annually. Details on the methodology of the BODE and CHAIN cohorts have been previously published.[8,9] Patients recruited in the Kingston (Canada) cohort followed a similar recruitment process, also an observational with a yearly follow-up protocol. In all cohorts, COPD was defined by smoking history ≥10 pack-years and a post-bronchodilator $FEV_1/FVC < 0.7$ after 400 μg inhaled salbutamol.[1,2] All patients from these cohorts with an $FEV_1/FVC < 0.7$ and $FEV_1 \geq 80\%$ of predicted value were included in the current study. At baseline, all patients were stable for at least 8 weeks and received optimal medical therapy according to current guidelines.[1,2]

All participants signed the informed consent approved by the ethics committees (Comité de Etica de la Investigación, Hospital Universitario la Candelaria, Tenerife; 258/2009).

Measurements

Age, sex, BMI, smoking history (pack-years history and smoking status), and pulmonary function tests were recorded. Spirometric measurements, including FVC, FEV_1, and inspiratory capacity (IC) and DLCO were measured following the European Respiratory Society/American Thoracic Society (ATS) guidelines.[10-12] Values

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were corrected for hemoglobin levels. Quality control followed accepted recommendations, for all calibrations made before each session, volume calibrations before each patient test, and biological calibrations daily. Predicted values used are those of the Global Lung Initiative values.[13,14] The 6-min walking distance (6MWD) test was conducted according to the ATS recommendations.[15] The BODE index was calculated as previously reported.[8] Exacerbations were defined by worsening of respiratory symptoms beyond normal daily variations that required the use of antibiotics, steroids, or both, medical consultation, or admission to hospital.[1,2] Comorbidities were scored using the Charlson index.[16]

Survival was determined by direct follow-up with participants, review of death certificates, or contacting their family members if needed.

Statistical Analysis

To explore the normality of the data distribution of the evaluated parameters, we used the Kolmogorov-Smirnov test. Data were summarized as relative frequencies for categorical variables and mean (SD) for normally distributed variables (only normally distributed variables were found). Comparison between those in different DLCO % of predicted categories were done by Student *t* test for continuous variables and χ^2 for categorical ones. By exploring survival curves of different DLCO % categories, adjusted for age, sex, BMI, and smoking status, we selected the highest threshold that showed a statistically significant difference in all-cause mortality. For simplicity in the message, we followed the current cutoff values of the European Respiratory Society/ATS guidelines[11,12] with cutoff at >75%, 75% to 61%, 40% to 60%, and <40% of predicted values. As shown in Figure 1, survival curves based on Cox analysis for these categories adjusted by age, sex, pack-years history, smoking status, and BMI clearly show that from category 40% to 60% predicted and lower, there is a clear survival disadvantage. Based on this, we selected 60% of predicted as the cutoff value for our analysis. A log-rank test explored differences between groups. A proportional Cox survival analysis determined the independent association of each study parameter with all-cause survival. The criteria selection for including variables in the Cox model was clinical, based on the most important variables that could determine DLCO values: age, sex, pack-years history, smoking status, and BMI. Significance level was established as a two-tailed $P \leq .05$. We used SPSS 26.0 for the statistical analysis.

Results

One hundred forty-five patients from the BODE cohort, 138 patients from the CHAIN cohort and 77 patients from the Kingston cohort were included in the study. Table 1 shows the clinical and physiological characteristics of the participants. This predominantly male population was mildly overweight, had few comorbidities, normal FEV_1 values, mild dyspnea, normal 6MWD, and very few exacerbations.

The Kaplan Meier curves in Figure 2 show that a DLCO of 60% predicted values provided a statistical significant increase in all-cause mortality over the follow-up time. The figure includes up to 120 months (10 years), a value that is slightly beyond the mean follow-up time for both cohorts. The curves separated after 12 months of follow-up.

Table 2 shows that patients with baseline DLCO < 60% predicted included a higher proportion of females, with lower BMI, higher pack-year history, same spirometric values, but lower IC/total lung capacity (TLC) values, lower distance walked in the 6MWT, higher dyspnea, similar exacerbation rate, higher BODE index, and higher mortality than patients with higher DLCO % predicted values.

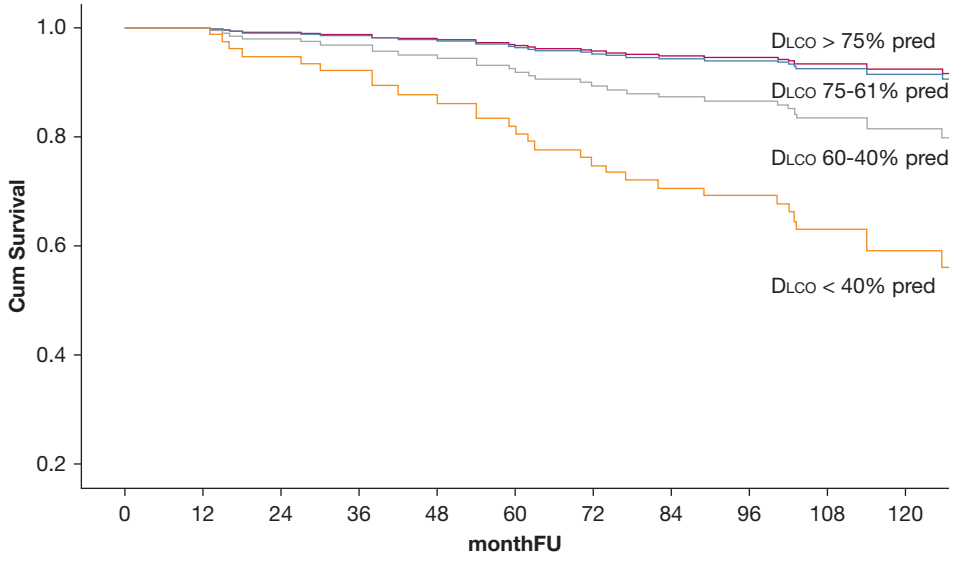

Figure 1 – *Survival curves of each of the European Respiratory Society/ATS guidelines DLCO categories (>75%, 75%-61%, 40%-60%, and <40% of predicted values) adjusted by age, sex, pack-years history, smoking status, and BMI.*

TABLE 1] Baseline Clinical and Physiological Characteristics of the Participants

Variable	N = 360
Age, y	63 ± 9
Female, %	31
Follow-up, mo	109 ± 50
BMI	27 ± 4
Pack-years history	45 ± 25
Active smoking, %	43
FEV_1, % of predicted	91 ± 10
FVC, % of predicted	114 ± 15
FEV_1/FVC	62 ± 6
IC/TLC	0.40 ± 0.08
DLCO, % of predicted	81 ± 21
Charlson score	1.2 ± 1.4
MRC	0.8 ± 0.8
6MWD, m	480 ± 112
BODE index	0.3 ± 0.6
Exacerbations, per year	0.5 ± 1.1
Exacerbation in previous year, %	27
Mortality, No. (%)	41 (11)

6MWD = 6-min walk distance; BODE = BMI, Obstruction, Dyspnea, and Exercise capacity; DLCO = diffusion capacity for carbon monoxide; IC = inspiratory capacity; MRC = medical research council; TLC = total lung capacity.

The Cox proportional analyses, shown in Table 3, shows that the 60% predicted value of DLCO was a predictor of all-cause survival in these patients after adjusting for age, sex, pack-years history, smoking status, and BMI.

Discussion

This multicenter observational study of spirometric GOLD I COPD patients attending pulmonary clinics shows that a DLCO value < 60% identifies individuals with worse clinical expressions of the disease and is also independently associated with an increased risk of death.

DLCO and Mortality

Different population-based studies have previously demonstrated that GOLD I COPD patients have an increased risk for all-cause mortality.[4-6] Mannino et al,[4] using the data from the NHANES I survey that included at least 309 active or former smokers followed up for 22 years, found that active GOLD I smokers have 1.3 times increased risk of death (95% CI, 1.01-1.7) not observed in former smokers: hazard ratio (HR) of 0.98 (95% CI, 0.7-1.5). Other population-based studies, such as the Cardiovascular Health Study and Atherosclerosis Risk in Communities,[5] including a much larger sample of GOLD I COPD patients (2,696 patients) followed up for approximately 10 years, also confirmed an adjusted increased risk of mortality (HR = 1.4; 95% CI = 1.2-1.6). This was also true in the Proyecto Latinoamericano de Investigacion en Obstruccion Pulmonar study[6] that included 323 GOLD I patients that also showed an increased risk of death for these patients (HR = 1.5; 95% CI = 1.01-2.3). However, none of these studies went further in assessing potential testing that could help select the individuals within the large population of GOLD I patients responsible for the overall increased mortality risk. This is important because GOLD I represent the largest proportion of patients with airflow limitation detected in epidemiological studies.[17,18]

To our knowledge, only one previous study has specifically explored the potential independent impact of low CO transfer values on COPD mortality. Boutou et al[19] studied 604 COPD patients that were followed up for 80 ± 49.8 months, and showed that carbon monoxide transfer factor was an independent risk factor for all-cause mortality. However, the study only included 14 GOLD I COPD patients, with more than 70% of patients having GOLD III and IV obstruction. In addition, they classified patients according to carbon monoxide transfer factor quartiles, starting from a 50% threshold to explore the relationship with mortality. Our study extends the information provided by these authors by only including patients with GOLD I obstruction and expanding the evaluation to include variables different from lung function, as we shall discuss. The careful characterization of the patients allowed adjustment for the most important confounders. Even after this adjustment (Table 3), a DLCO value lower than 60% predicted tripled the risk of death in these patients. Our study was conducted in multiple centers in two continents, proving that standardized DLCO obtained in clinics is feasible and useful.

The reasons a low DLCO determine a higher mortality rate in COPD patients with mild obstruction are unclear and were not the main goal of the current work. Unfortunately, we only have

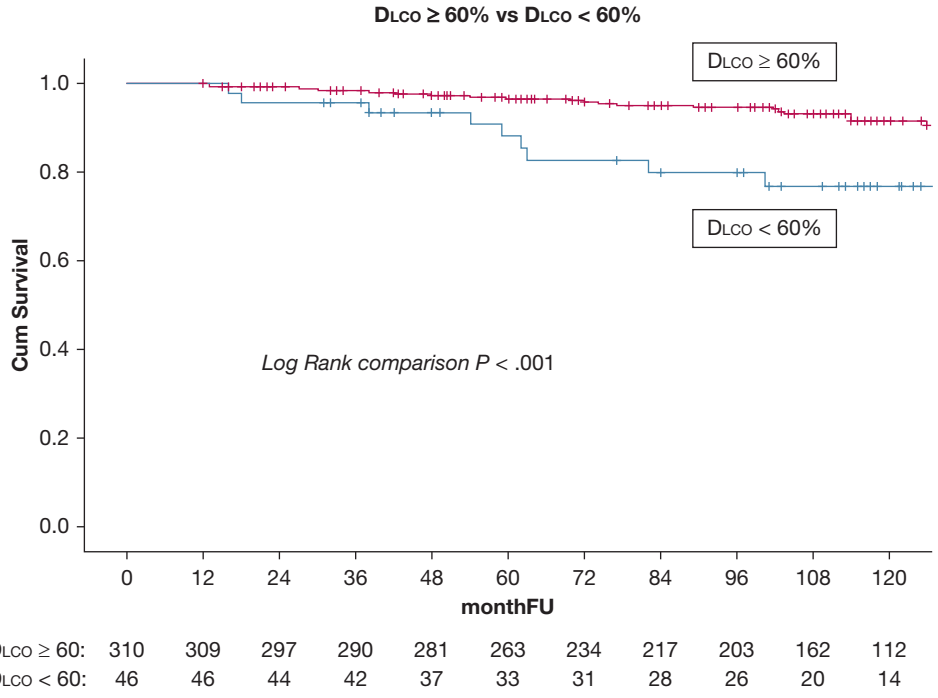

Figure 2 – *Kaplan-Meier survival curves of patients with DLCO ≥ 60% and <60% of predicted values.*

reliable information regarding all-cause mortality but not specific cause of death; therefore, any elaboration on potential causes of this important finding origin would be mere speculation. Further studies should help address this important question.

TABLE 2] Baseline Clinical and Physiological Characteristics of COPD Patients Classified According to DLCO % of Predicted Category

Variable	DLCO ≥ 60% (n = 313) 87%	DLCO < 60% (n = 47) 13%	*P*
Age, y	62 ± 8	65 ± 9	.07
Female, %	28	46	.01[a]
Follow-up, mo	111 ± 50	95 ± 47	.04[a]
BMI	27 ± 4	25 ± 5	.01[a]
Pack-years	43 ± 25	54 ± 28	.02[a]
Active smoking, %	42	44	.85
FEV_1, % predicted	92 ± 10	90 ± 10	.38
FVC%, predicted	113 ± 14	115 ± 19	.63
FEV_1/FVC	63 ± 6	61 ± 8	.26
IC/TLC	0.40 ± 0.08	0.37 ± 0.08	.02[a]
DLCO, % predicted	86 ± 16	47 ± 10	.001[a]
Charlson score	1.2 ± 1.5	0.9 ± 1.1	.46
MRC	0.7 ± 0.7	1.1 ± 0.9	.03[a]
6MWD, m	485 ± 113	443 ± 101	.03[a]
BODE index	0.2 ± 0.6	0.5 ± 0.5	.04[a]
Exacerbations per year	0.5 ± 1.2	0.3 ± 0.7	.20
Exacerbation in previous year, %	28	20	.47
Mortality, %	9	23	.01[a]

6MWD = 6-min walk distance; BODE = BMI, Obstruction, Dyspnea, and Exercise capacity; DLCO = diffusion capacity for carbon monoxide; IC = inspiratory capacity; MRC = medical research council; TLC = total lung capacity
[a]Statistically significant.

TABLE 3] Cox Proportional Analysis of the Baseline Variables Associated With All-Cause Mortality

Variable	Hazard Ratio (95% CI)	*P*
Age	1.05 (1.00-1.10)	.04
Sex	1.16 (0.41-3.32)	.77
BMI	0.97 (0.88-1.07)	.55
Pack-years	1.00 (0.99-1.01)	.23
Smoking status	1.55 (0.99-3.60)	.36
DLCO < 60%	3.37 (1.35-8.39)	.009

DLCO = diffusion capacity for carbon monoxide.

DLCO and Clinical Expression of COPD

The other novel finding from the current study was that those patients with a DLCO < 60% at baseline at similar FEV_1 (90% and 92% predicted, respectively) had a different clinical profile. A higher proportion of low DLCO patients were women (46% vs 28%), had a higher pack-year history (54 vs 43), lower BMI (25 vs 27), and lower IC/TLC ratio (0.37 vs 0.40). This probably suggests that these patients may represent the multi-organ loss of tissue phenotype previously described, which is associated with worse clinical course and prognosis.[20] Finally, although they have a similar baseline exacerbation rate/year (0.3 vs 0.5 exacerbation/year), they expressed more dyspnea (MRC score: 1.1 vs 0.7), walked less (443 vs 485 m), and had a higher BODE multidimensional index (0.5 vs 0.2). These findings could help explain why these patients have a higher mortality, because all these parameters have been previously described to be associated with worse survival in COPD patients.[8,21,22]

Our study has several limitations. First, it included COPD patients seen at pulmonary clinics, so the findings cannot be extrapolated to other COPD patients seen on other settings. Second, the information regarding the specific cause of death was not recorded, thereby limiting our ability to define potential organs to target therapeutically. However, this does not decrease the importance of our findings on all-cause mortality and other hard clinical outcomes determined in these patients. Third, unfortunately, detailed information on the presence of associated comorbidities in patients is missing, limiting the possibility of drawing other conclusions. We know that the Charlson score was low, suggesting a limited role of any of them on the outcomes here evaluated.

Interpretation

This long-term observational study of GOLD I COPD patients demonstrated that those with a baseline DLCO < 60% of predicted value have a worse clinical expression of the disease and are at increased risk of death. Comprehensive studies of this subgroup of patients can help clarify the mechanism(s) responsible for the low DLCO and perhaps help plan interventions directed at ameliorating the causes of the abnormality.

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References

1. Vogelmeier CF, Criner GJ, Martínez FJ, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive lung disease 2017 report: GOLD executive summary. *Arch Bronconeumol*. 2017;53:128-149.
2. Elbehairy AF, O'Donnell CD, Abd Elhameed A, el al. Low resting diffusion capacity, dyspnea, and exercise intolerance in chronic obstructive pulmonary disease. *J Appl Physiol*. 2019;127(4):1107-1116.
3. Balasubramanian A, MacIntyre NR, Henderson RJ, et al. Diffusing capacity of carbon monoxide in assessment of COPD. *Chest*. 2019;156(6):1111-1119.
4. Mannino DM, Buist AS, Petty TL, et al. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. *Thorax*. 2003;58(5):388-393.
5. Mannino DM, Doherty DE, Sonia Buist A. Global initiative on obstructive lung disease (GOLD) classification of lung disease and mortality: findings from the Atherosclerosis Risk in Communities (ARIC) study. *Respir Med*. 2006;100(1):115-122.
6. Perez-Padilla R, Wehrmeister FC, de Oca MM, et al. Outcomes for symptomatic non-obstructed individuals and individuals with mild (GOLD stage 1) COPD in a population based cohort. *Int J Chron Obstruct Pulmon Dis*. 2018;13:3549-3561.
7. Maltais F, Dennis N, Chan CK. Rationale for earlier treatment in COPD: a systematic review of published literature in mild-to-moderate COPD. *COPD*. 2013;10(1):79-103.
8. Celli BR, Cote C, Marin JM, et al. The body mass index, airflow obstruction, dyspnea, exercise performance (BODE) index in chronic obstructive pulmonary disease. *N Engl J Med*. 2004;350(10):1005-1012.
9. López-Campos JL, Peces-Barba G, Soler-Cataluña JJ. Chronic obstructive pulmonary disease history assessment in Spain: a multidimensional chronic obstructive pulmonary disease evaluation. Study methods and organization. *Arch Bronconeumol*. 2012;48(12):453-459.
10. Laszlo G. Standardisation of lung function testing: helpful guidance from the ATS/ERS Task Force. *Thorax*. 2006;61(9):744-746.
11. American Thoracic Society Statement. Lung function testing: selection of reference values and interpretative strategies. *Am Rev Respir Dis*. 1991;144(5):1202-1218.

12. Macintyre N, Crapo RO, Viegi G, et al. Standardization of the single-breath determination of carbon monoxide uptake in the lung. *Eur Respir J*. 2005;26(4):720-735.

13. Quanjer PH, Stanojevic S, Cole TJ, et al. Multi-ethnic reference values for spirometry for the 3-95-yr age range: the global lung function 2012 equations. *Eur Respir J*. 2012;40(6):1324-1343.

14. Stanojevic S, Graham BL, Cooper BG, et al. Official ERS technical standards: Global Lung Function Initiative reference values for the carbon monoxide transfer factor for Caucasians. *Eur Respir J*. 2017;50(3):1700010.

15. Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.

16. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

17. Buist AS, McBurnie MA, Vollmer WM, et al. International variation in the prevalence of COPD (the BOLD Study): a population-based prevalence study. *Lancet*. 2007;370(9589):741-750.

18. Menezes AM, Perez-Padilla R, Jardim JR, et al. Chronic obstructive pulmonary disease in five Latin American cities (the PLATINO study): a prevalence study. *Lancet*. 2005;366(9500):1875-1881.

19. Boutou AK, Shrikrishna D, Tanner RJ, et al. Lung function indices for predicting mortality in COPD. *Eur Respir J*. 2013;42(3):616-625.

20. Celli BR, Locantore N, Tal-Singer R, et al. Emphysema and extrapulmonary tissue loss in COPD: a multi-organ loss of tissue phenotype. *Eur Respir J*. 2018;51(2):1-10.

21. Nishimura K, Izumi T, Tsukino M, et al. Dyspnea is a better predictor of 5-year survival than airway obstruction in patients with COPD. *Chest*. 2002;121(5):1434-1440.

22. Cote CG, Pinto-Plata V, Kasprzyk K, et al. The 6-min walk distance, peak oxygen uptake, and mortality in COPD. *Chest*. 2007;132(6):1778-1785.