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Authors

Balasubramanian, Aparna
Putcha, Nirupama
MacIntyre, Neil
et al.

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Diffusing Capacity and Mortality in Chronic Obstructive Pulmonary Disease

Aparna Balasubramanian[1], Nirupama Putcha[1], Neil R. MacIntyre[2], Robert L. Jensen[3], Gregory Kinney[4], William W. Stringer[5], Craig P. Hersh[6], Russell P. Bowler[7], Richard Casaburi[5], MeiLan K. Han[8], Janos Porszasz[5], R. Graham Barr[9], Elizabeth Regan[4,10], Barry J. Make[4], Nadia N. Hansel[1], Robert A. Wise[1], and Meredith C. McCormack[1]

[1]Division of Pulmonary & Critical Care Medicine, Johns Hopkins University, Baltimore, Maryland; [2]Division of Pulmonary & Critical Care Medicine, Duke University, Durham, North Carolina; [3]Division of Pulmonary & Critical Care Medicine, University of Utah, Salt Lake City, Utah; [4]Department of Epidemiology, Colorado School of Public Health, University of Colorado, Denver, Colorado; [5]Lundquist Institute for Biomedical Innovation at Harbor–UCLA Medical Center, Torrance, California; [6]Channing Division of Network Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [7]Division of Pulmonary, Critical Care and Sleep Medicine and [10]Division of Rheumatology, National Jewish Health, National Jewish Health, Denver, Colorado; [8]Division of Pulmonary & Critical Care Medicine, University of Michigan, Ann Arbor, Michigan; and [9]Department of Epidemiology, Columbia University, New York, New York

ORCID IDs: 0000-0002-1342-4334 (C.P.H.); 0000-0002-8353-2349 (R.A.W.); 0000-0003-1702-3201 (M.C.M.).

Abstract

Rationale: Chronic obstructive pulmonary disease (COPD) mortality risk is often estimated using the BODE (body mass index, obstruction, dyspnea, exercise capacity) index, including body mass index, forced expiratory volume in 1 second, dyspnea score, and 6-minute walk distance. Diffusing capacity of the lung for carbon monoxide (D_{LCO}) is a potential predictor of mortality that reflects physiology distinct from that in the BODE index.

Objectives: This study evaluated D_{LCO} as a predictor of mortality using participants from the COPDGene study.

Methods: We performed time-to-event analyses of individuals with COPD (former or current smokers with forced expiratory volume in 1 second/forced vital capacity < 0.7) and D_{LCO} measurements from the COPDGene phase 2 visit. Cox proportional hazard methods were used to model survival, adjusting for age, sex, pack-years, smoking status, BODE index, computed tomography (CT) percent emphysema (low attenuation areas below −950 Hounsfield units), CT airway wall thickness, and history of cardiovascular or kidney diseases. C statistics for models with D_{LCO} and BODE scores were used to compare discriminative accuracy.

Results: Of 2,329 participants, 393 (16.8%) died during the follow-up period (median = 4.9 yr). In adjusted analyses, for every 10% decrease in D_{LCO} percent predicted, mortality increased by 28% (hazard ratio = 1.28; 95% confidence interval, 1.17–1.41, $P < 0.001$). When compared with other clinical predictors, D_{LCO} percent predicted performed similarly to BODE (C statistic $D_{LCO} = 0.68$; BODE = 0.70), and the addition of D_{LCO} to BODE improved its discriminative accuracy (C statistic = 0.71).

Conclusions: Diffusing capacity, a measure of gas transfer, strongly predicted all-cause mortality in individuals with COPD, independent of BODE index and CT evidence of emphysema and airway wall thickness. These findings support inclusion of D_{LCO} in prognostic models for COPD.

Keywords: COPD; pulmonary gas exchange; pulmonary diffusing capacity; mortality

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Correspondence and requests for reprints should be addressed to Meredith McCormack, M.D., M.H.S., Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, 1830 E. Monument Street, 5th Floor, Baltimore, MD 21205. E-mail: mmccor16@jhmi.edu.

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Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death in the United States, with approximately 46.3 deaths per 100,000 people per year attributable to COPD in 2020 (1–3). The BODE index, commonly used to predict mortality risk in COPD, incorporates measures of body mass index, airflow obstruction, dyspnea, and exercise performance by 6-minute walk distance (4).

One key clinical physiologic measure that is frequently obtained, but not yet incorporated into routine prognostic models, is diffusing or transfer capacity of the lung for carbon monoxide (D_{LCO}). D_{LCO} is a measure of gas transfer across the alveolar-capillary membrane and provides independent and complementary physiologic information to the more frequently used prognostic measures, such as forced expiratory volume in 1 second (FEV_1) and imaging evidence of emphysema. Prior studies both in healthy and in COPD-specific populations have offered suggestions that D_{LCO} is useful in predicting mortality (5–8), but with the advancement of deeper phenotyping in COPD, particularly imaging measures, the independent utility of D_{LCO} beyond reflecting emphysema is less well understood.

This study seeks to evaluate diffusing capacity as a predictor of mortality among individuals with COPD and to compare D_{LCO} with other common predictors of disease severity and prognosis. We hypothesize that diffusing capacity will be an independent predictor of mortality and will offer additional value to existing predictors of death among individuals with COPD. The COPDGene study offers a large, well-characterized cohort with a wide range of disease severity in which to assess D_{LCO} as a predictor of mortality in COPD.

Methods

Study Population and Design

COPDGene is a multicenter prospective observational cohort study of individuals ages 45–80 years with a smoking history of ⩾10 pack-years from 21 clinical centers (9). Institutional review boards at all centers approved COPDGene, and all participants provided written informed consent. Enrollment occurred from 2007 to 2012, with subsequent in-person visits every 5 years. D_{LCO} testing was initiated at the visit 5 years after initial enrollment. The current investigation is a time-to-event survival analysis of participants with COPD (defined as FEV_1/forced vital capacity < 0.7 and ⩾10 pack-year smoking history) who underwent D_{LCO} testing.

Physiologic Testing

Physiologic testing was conducted on all participants including spirometry, D_{LCO}, and 6-minute walk testing in accordance with American Thoracic Society/European Respiratory Society guidelines (10–12). Tests that were judged acceptable and reproducible were included in analyses; sensitivity analyses were conducted including individuals with failed D_{LCO} measurements. D_{LCO} and FEV_1 percent predicted values were calculated using Global Lung Initiative equations (13, 14), with D_{LCO} values adjusted for site altitude and hemoglobin (13).

Survival Data

Vital status was obtained from the Social Security Death Index and the COPDGene longitudinal follow-up program. Survival time was calculated from the date of D_{LCO} measurement to the date of death or censoring. Observations were administratively censored on December 18, 2016. For participants where vital status was searched using the Social Security Death Index, follow-up time was back-censored 3 months before the last Social Security Death Index search to account for lags in reporting, whereas for survival data obtained from longitudinal follow-up, censoring occurred at the time of most recent active participation. Cause of death was adjudicated by a committee using all available evidence of record, including death certificates. Towards a Revolution in COPD Health (TORCH) guidelines were used to classify cause of death into five categories: respiratory, cardiovascular, cancer, other, and unknown (15).

Computed Tomography (CT)

CT scans of the chest were performed as per previously published protocols on individual site CT scanners (16). Total percent emphysema ($\%LAA_{-950}$), defined as the percentage of voxels with attenuation equal to or below −950 Hounsfield units, and airway wall thickness (Pi10), defined as the square root wall area of an airway with a 10-mm internal perimeter, were calculated using Thirona software (Thirona, Nijmegen, the Netherlands; http://www.thirona.eu).

Statistical Analysis

Participant characteristics were described by vital status and by D_{LCO} percent predicted. With Kaplan-Meier methods and log-rank testing, unadjusted survival was compared between individuals with D_{LCO} above or below 50% predicted, a cutoff selected on the basis of previous work (17), and above or below the lower limit of normal (LLN). D_{LCO} percent predicted was also treated as a continuous variable in Cox proportional hazard models. To verify linearity in the association between D_{LCO} and log hazard of mortality, observed hazard ratios for bins of every 10% predicted D_{LCO} were plotted alongside an unadjusted Cox model.

Multivariable Cox models were built with additional clinical predictors, including age, gender, body mass index, smoking status, pack-years, FEV_1 percent predicted, $\%LAA_{-950}$, Pi10, and comorbidities. Comorbidities included self-reported diabetes, chronic kidney disease, and cardiovascular disease, a composite variable encompassing any report of coronary artery disease, hypertension, or congestive heart failure. All covariates were selected *a priori*, on the basis of plausible mechanism and clinical relevance. With a relatively low rate of mortality in the population, covariates were minimized for parsimony and tested for multicollinearity using variance inflation factors (18, 19).

Models were constructed using BODE index scores in addition to the individual components. The BODE score was dichotomized above or below 4 points, based approximately on an estimated 50% survival at 4 years (4). One hundred ninety-four participants were missing $\%LAA_{-950}$ and Pi10 data; sensitivity analyses were conducted that categorized participants with emphysema into those with ⩽5%, with >5%, and data missing, and Pi10 into 92.5 mm (median value), >2.5 mm, and data missing. Additional analyses evaluating carbon monoxide transfer coefficient and smokers without COPD were also performed.

We compared the discriminative performance of D_{LCO} percent predicted individually and in combination with other predictors using Harrell's C statistics (20–22), calculated by *somersd* and *estat concordance* (STATA; StataCorp LLC, College Station, TX). The former uses a jackknife approach with conservative assumptions regarding right-censored individuals (23–25). C-statistics calculated

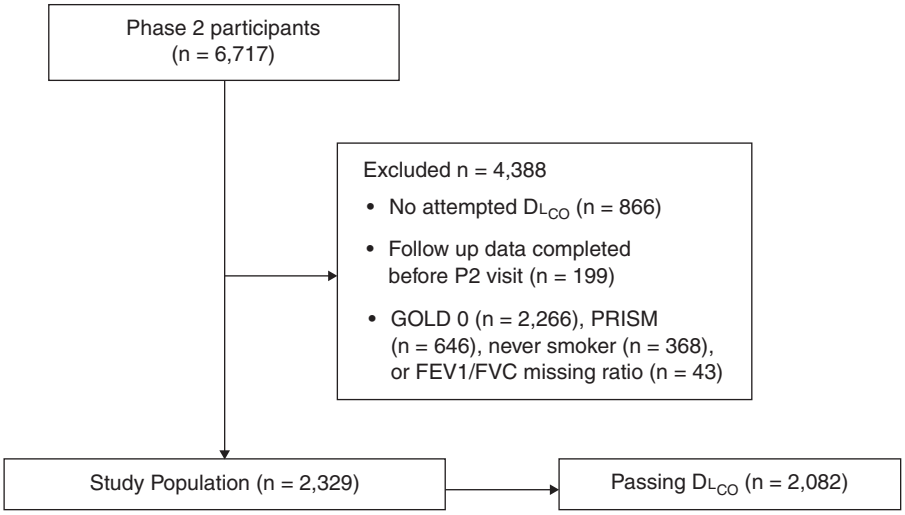

Figure 1. Study population. Selection of study population with description of excluded individuals. From the study population, 195 individuals were missing computed tomography emphysema or airway wall thickness measurements. D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GOLD 0 = global initiative for obstructive lung disease spirometry grade 0; P2 visit = phase 2 visit of the COPDGene study; PRISM = preserved ratio impaired spirometry.

using *estat concordance* are provided in the online supplement. To evaluate differences in cause of death, percentages within each TORCH category (15) were graphed among individuals with D_{LCO} above or below 50% predicted and those who failed D_{LCO} measurement.

Results

Participant Characteristics

The study population consisted of 2,329 COPD participants with an attempted D_{LCO} and available follow-up survival data, 2,082 of whom had acceptable and reproducible D_{LCO} measurements (Figure 1). There were 393 (16.8%) deaths during the observed follow-up time, with a median follow-up of 4.9 years (interquartile range, 3.6–5.8 yr). Baseline participant characteristics by vital status are noted in Table 1. Individuals who had died during follow-up were older, at a mean age of 71; had a lower average body mass index of 26.2 kg/m^2; and had a higher number of smoking pack-years than those who were alive during follow-up. Sixty-one percent of those who died were male, compared with 54% male among those still alive at the end of follow-up. There was severe airflow obstruction (FEV_1, 49 ± 21% predicted), moderate to severe gas transfer impairment (D_{LCO}, 53 ± 22% predicted), and increased CT evidence of emphysema (median, 10.9%) in deceased individuals, compared with milder impairments in airflow obstruction and diffusing capacity (FEV_1, 64 ± 22% predicted; D_{LCO}, 69 ± 22% predicted), and less CT emphysema (median, 4.9%) in those still alive at the end of follow-up. Furthermore, comorbidities including coronary artery disease, hypertension, diabetes, congestive heart failure, and chronic kidney disease were more commonly reported among those who died.

Additional participant characteristics by D_{LCO} noted increased airflow obstruction, CT percent emphysema, oxygen use, preponderance of congestive heart failure, and BODE score among those with either a failed D_{LCO} maneuver or a D_{LCO} below 50% predicted as compared with those above 50% predicted (Table E1).

Diffusing capacity is a predictor of survival, independent of airflow obstruction and emphysema. Unadjusted 1-, 3-, and 5-year survival in the study population was 98%, 91%, and 82%, respectively. Participants with $D_{LCO} \leq 50\%$ predicted had significantly worse mortality than those with $D_{LCO} > 50\%$ predicted, log-rank $\chi^2(1, N = 127)$, $P \leq 0.001$) (Figure 2A). Using the LLN as a threshold, individuals with a $D_{LCO} <$ LLN also had significantly worse mortality than those with $D_{LCO} \geq$ LLN, log-rank $\chi^2(1, N = 56)$, $P \leq 0.001$ (Figure 2B). Further, the 247 individuals who attempted a D_{LCO} but were unable to generate acceptable and reproducible maneuvers had similar but

Table 1. Clinical characteristics at phase 2 visit by vital status

Characteristic	Died (*n* = 393)	Alive (*n* = 1,936)
Age, yr	71 ± 8	67 ± 8
Female, *n* (%)	154 (39)	886 (46)
African American, *n* (%)	85 (22)	444 (23)
BMI, kg/m^2	26.7 ± 5.9	28.2 ± 6.2
Smoking status, *n* (%)		
Former smoker	258 (66)	1,252 (65)
Current smoker	133 (34)	668 (35)
Pack-years, median (IQR)	51 (40–70)	45 (33–61)
FEV_1, % predicted, mean ± SD	49 ± 21	64 ± 22
FVC, % predicted, mean ± SD	74 ± 19	85 ± 20
D_{LCO}, % predicted, mean ± SD	53 ± 22	69 ± 22
KCO, % predicted, mean ± SD	62 ± 24	75 ± 21
Emphysema, %, median (IQR)	10.9 (3.5–24.3)	4.9 (1.6–13.8)
Airway wall thickness, mm, mean ± SD	2.7 ± 0.6	2.5 ± 0.6
Resting oxygen saturation, %, mean ± SD	94 ± 4	95 ± 3
Coronary artery disease, *n* (%)	70 (18)	186 (10)
Diabetes, *n* (%)	75 (19)	308 (16)
Hypertension, *n* (%)	244 (62)	1,009 (52)
Congestive heart failure, *n* (%)	42 (11)	75 (4)
Sleep apnea, *n* (%)	73 (19)	331 (17)
Kidney disease, *n* (%)	24 (6)	54 (3)
BODE index score, median (IQR)	5 (2–7)	2 (0–4)

Definition of abbreviations: BMI = body mass index, BODE = body mass index, obstruction, dyspnea, and exercise capacity; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IQR = interquartile range; KCO = carbon monoxide transfer coefficient; SD = standard deviation.
Values are presented as mean ± SD, *n* (%), or median (IQR).

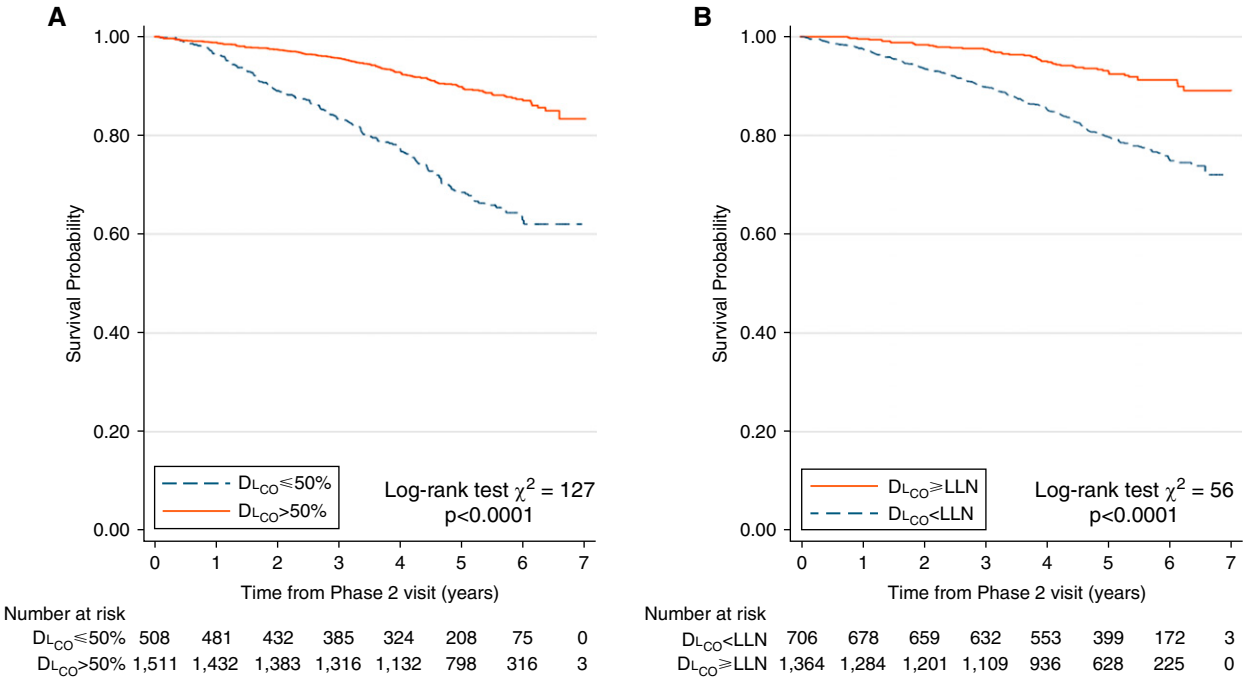

Figure 2. Severe diffusing capacity impairment is associated with mortality in COPD. Kaplan-Meier survival curves by categories of D_{LCO}. (*A*) Solid line represents D_{LCO} >50% predicted; dashed line refers to D_{LCO} ≤50% predicted. (*B*) Solid line represents D_{LCO} ≥ lower limit of normal (LLN); dashed line refers to D_{LCO} < LLN. Log-rank test and at-risk table are provided. COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide.

slightly worse mortality than those with D_{LCO} ≤50% predicted (Figure E1).

In unadjusted Cox models, D_{LCO} percent predicted was a significant predictor of mortality (hazard ratio, 1.37; 95% confidence interval [CI], 1.29–1.44; $P < 0.001$), along with age, sex, body mass index, pack-years smoked, FEV_1 percent predicted, $\%LAA_{-950}$, Pi10, cardiovascular comorbidities, and chronic kidney disease (Table 2). To verify that D_{LCO} percent predicted as a continuous variable maintained a linear association with log hazard of death, without any obvious threshold effect, observed hazard ratios for every 10% predicted D_{LCO} were plotted in conjunction with an unadjusted Cox model–predicted hazard ratio (Figure 3).

Table 2. Clinical predictors of mortality

	Unadjusted			Adjusted Model 1 (*n* = 1,854)			Adjusted Model 2 (*n* = 1,799)		
Characteristic	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**	**HR**	**95% CI**	***P* Value**
Age	**1.05**	**1.04–1.06**	**<0.001**	**1.06**	**1.04–1.08**	**<0.001**	**1.05**	**1.04–1.07**	**<0.001**
Sex (female vs. male)	**0.75**	**0.62–0.92**	**0.006**	**0.68**	**0.52–0.89**	**0.004**	**0.66**	**0.50–0.86**	**0.003**
BMI	**0.96**	**0.94–0.98**	**<0.001**	0.99	0.97–1.01	0.409	—	—	—
Pack-years	**1.01**	**1.01–1.01**	**<0.001**	1.00	1.00–1.01	0.336	1.00	1.00–1.01	0.181
Smoking status (current vs. former)	1.12	0.91–1.38	0.28	**1.62**	**1.17–2.23**	**0.003**	**1.64**	**1.20–2.24**	**0.002**
D_{LCO} (per 10% predicted reduction)	**1.37**	**1.29–1.44**	**<0.001**	**1.28**	**1.17–1.41**	**<0.001**	**1.26**	**1.15–1.38**	**<0.001**
FEV_1 (per 10% predicted reduction)	**1.31**	**1.25–1.38**	**<0.001**	**1.16**	**1.06–1.27**	**0.001**	—	—	—
$\%LAA_{-950}$	**1.03**	**1.02–1.04**	**<0.001**	0.99	0.97–1.00	0.145	0.99	0.98–1.01	0.276
Pi10	**1.68**	**1.42–1.98**	**<0.001**	**1.34**	**1.03–1.75**	**0.029**	**1.43**	**1.14–1.81**	**0.002**
Cardiovascular disease	**1.61**	**1.29–2.00**	**<0.001**	**1.36**	**1.04–1.79**	**0.026**	**1.35**	**1.02–1.78**	**0.034**
Kidney disease	**2.11**	**1.39–3.19**	**0.001**	**2.32**	**1.42–3.80**	**0.001**	**2.16**	**1.32–3.54**	**0.002**
Diabetes	1.24	0.97–1.60	0.088	1.13	0.81–1.57	0.465	1.05	0.75–1.47	0.778
BODE index (:4 vs. <4)	**3.98**	**3.25–4.89**	**<0.001**	—	—	—	**2.36**	**1.74–3.21**	**<0.001**

Definition of abbreviations: BMI = body mass index; BODE = body mass index, obstruction, dyspnea, and exercise capacity; CI = confidence interval; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; HR = hazard ratio; $\%LAA_{-950}$ = percent low attenuation areas below −950 Hounsfeld units; Pi10 = airway wall thickness of 10-mm internal perimeter airways. Unadjusted and adjusted hazard ratios for various clinical predictors of mortality. Adjusted model 1 includes age, sex, BMI, pack-years smoked, smoking status, D_{LCO} percent predicted (per 10% predicted reduction), FEV_1 percent predicted (per 10% reduction), computed tomography percent emphysema, airway wall thickness, cardiovascular disease, kidney disease, and diabetes as covariates. Adjusted model 2 includes the predictors of adjusted model 1, but in lieu of BMI and FEV_1 percent predicted, the BODE index is included as a covariate. Bolded values refer to statistically significant results.

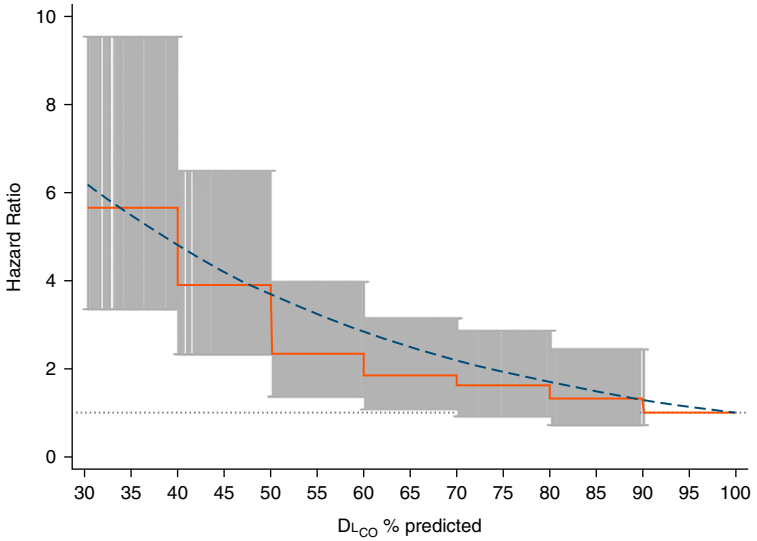

Figure 3. D_{LCO} is associated with mortality across the range of observed values. Dashed line represents predicted hazard ratios from a Cox proportional hazard model with D_{LCO} percent predicted as a continuous variable. Solid line and gray bars represent observed hazard ratios with 95% confidence intervals for categories every 10% predicted D_{LCO}. For both predicted and observed hazard ratios, the reference was set at a D_{LCO} 100% predicted. Dotted line represents a hazard ratio of 1. D_{LCO} = diffusing capacity of the lung for carbon monoxide.

The Cox model–predicted values closely approximated the observed hazard ratios. Notably, the observed data demonstrated a significant increase in hazard ratio below a D_{LCO} of approximately 70% predicted as compared with the reference of D_{LCO} 100% predicted.

In adjusted models, D_{LCO} percent predicted was an independent predictor of mortality, as were FEV_1 percent predicted, age, sex, smoking status, airway wall thickness, and chronic kidney disease (Table 2). Notably, $\%LAA_{-950}$ was no longer a significant predictor of mortality in multivariable analysis. In models including the BODE index, BODE scores were significantly associated with mortality (hazard ratio, 2.37; 95% CI, 1.74–3.22; $P < 0.001$) and D_{LCO} percent predicted remained a significant independent predictor. Sensitivity analyses including individuals with missing $\%LAA_{-950}$ and Pi10 data did not alter the association between D_{LCO} percent predicted and mortality, but they further demonstrated smoking status and cardiovascular disease as significant predictors (Table E2). Additional sensitivity analyses were conducted considering hemoglobin, 6-minute walk distance, and modified medical research council dyspnea scores, all covariates independently associated with mortality. These results continued to demonstrate the independent association between D_{LCO} percent predicted and mortality with some observed attenuation of the effect magnitude in models including a 6-minute walk distance (Table E3). Similar results were also identified when carbon monoxide transfer coefficient percent predicted was used as a predictor in lieu of D_{LCO} percent predicted (hazard ratio, 1.25; 95% CI, 1.15–1.35; $P < 0.001$) (Table E4).

Additional sensitivity analyses were conducted among smokers with normal spirometry (Global Initiative for Obstructive Lung Disease spirometry grade 0), and smokers without obstruction but with a reduced FEV_1 on spirometry, or preserved ratio impaired spirometry). Kaplan-Meier curves of unadjusted survival among those with a D_{LCO} above and below 50% predicted (Figure E2) and adjusted models of survival demonstrated a similar association between survival and D_{LCO} (Table E5).

Accuracy of D_{LCO} compared with other common predictors in predicting survival. D_{LCO} percent predicted was observed to have the highest C statistic of 0.68 (95% CI, 0.64–0.71) among individual predictors, including FEV_1 percent predicted, CT emphysema, and CT airway wall thickness (Figure 4). Additionally, there was no statistically significant difference in C statistics between D_{LCO} percent predicted and BODE score (difference, 0.019; 95% CI, −0.01 to 0.05; $P = 0.21$). The addition of D_{LCO} to BODE improved the Harrell's C statistic to 0.71 (95% CI, 0.67–0.74), with statistically significant differences compared

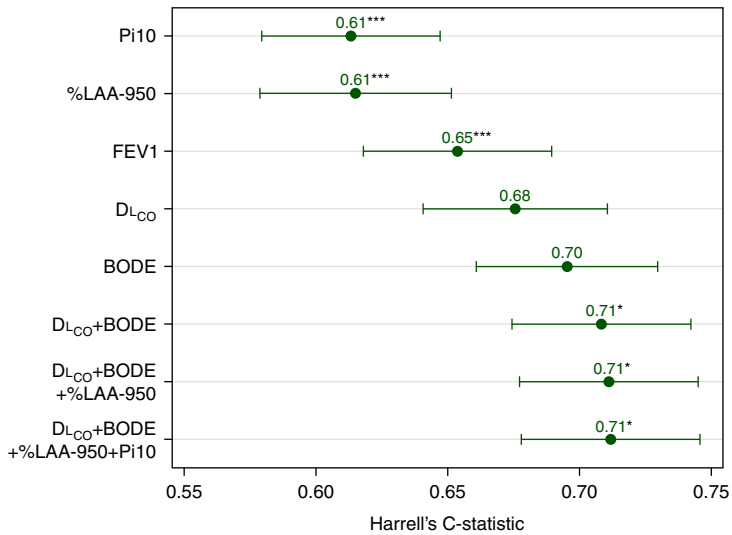

Figure 4. Diffusing capacity performance compared with commonly used predictors of mortality in COPD. Harrell's C-statistic estimates and 95% confidence intervals for various predictors of mortality, calculated using Somer's D statistic. Predictors included in each model are listed along the *y* axis. *P* value comparisons are against the model of BODE (body mass index, obstruction, dyspnea, exercise capacity) as the sole predictor. $^*P < 0.05$ and $^{***}P < 0.001$. COPD = chronic obstructive pulmonary disease; D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; Pi10 = airway wall thickness of 10-mm internal perimeter airways; %LAA-950 = percent low attenuation areas below −950 Hounsfeld units.

with D_{LCO} alone (difference, 0.03; 95% CI, 0.01–0.05; $P = 0.001$) or BODE alone (difference, 0.01; 95% CI, 0.002–0.02; $P = 0.04$). No significant improvement in discriminative performance was noted with the addition of CT measures of emphysema or airway wall thickness to D_{LCO} and BODE. Harrell's C statistics were also calculated using more liberal assumptions regarding right-censored data with similar results (Table E6).

Cause of Death

Adjudicated cause of death was available for 107 (28%) of the 378 individuals who died during follow-up. When separated into categories consisting of respiratory, cardiovascular, cancer, other, and unknown primary etiologies of death, approximately 45% ($n = 19$) of individuals with $D_{LCO} \leq 50\%$ predicted had a respiratory cause of death as compared with 27% ($n = 9$) among those who died with a $D_{LCO} > 50\%$ predicted (Figure 5). Notably, individuals with unacceptable D_{LCO} maneuvers had a similarly large proportion of deaths due to respiratory causes as compared with individuals with $D_{LCO} \leq 50\%$ predicted.

Discussion

Among participants in the COPDGene study, diffusing capacity is a strong predictor of all-cause mortality in COPD, independent of airflow obstruction and CT evidence of emphysema and airway wall thickness. We observed that this measurement of gas transfer offered equal discriminative accuracy in modeling survival as the BODE index, and addition of D_{LCO} to the BODE index offered even better performance in this population. As gas exchange is a primary function of the respiratory system, these findings emphasize the clinical relevance of this noninvasive, minimal-risk, and inexpensive tool and strongly support the inclusion of D_{LCO} in prognostic models.

Our findings extend prior work that have demonstrated discordant results regarding diffusing capacity as a predictor of mortality. A study of the National Health and Nutrition Examination Survey cohort noted a significantly increased hazard of death, with reductions in D_{LCO} beginning at a threshold of approximately 85% predicted (6). The National Health and Nutrition Examination Survey focused on the general population, specifically highlighting associations in those with an FEV_1 over 90% predicted and without clinical diagnosis of respiratory disease. As such, the population studied was younger, and diffusing capacity was overall preserved, with an average D_{LCO} of approximately 95% (6). Recently, a study examining 360 individuals with COPD who had an FEV_1/forced vital capacity < 0.7 and an $FEV_1 \geq 80\%$ predicted demonstrated that D_{LCO} less than 60% predicted was associated with increased mortality (26), similar to our own findings. Our study expands on the results from this study, with 22% of our study population including individuals with similar spirometric severity and the remaining individuals comprising participants with moderate-to-severe impairment in FEV_1. Numerous small studies conducted in COPD populations have demonstrated, on average, lower D_{LCO} percent predicted values among nonsurvivors as compared with survivors (5, 7, 27–29). By way of contrast, the National Emphysema Treatment Trial, which was a cohort with severe emphysema and severe diffusing capacity impairment, demonstrated in univariate analyses that D_{LCO} was associated with mortality, but that effect was no longer significant in multivariable analyses (8). Of note, median D_{LCO} in this study was 28% predicted with minimal variability, which may have limited these findings. Additionally, a single-center study conducted in London of 604 outpatient COPD participants demonstrated that D_{LCO} was a significant predictor of mortality, after adjusting for spirometry, but did not address further phenotyping such as CT evidence of emphysema (5). Our findings offer strong evidence in a large, well-phenotyped COPD cohort with a wide range of disease severity supporting diffusing capacity as a predictor of mortality.

Although FEV_1 has been well established as a predictor of mortality, our compelling results demonstrated that D_{LCO} has an even stronger association with survival. This is a novel finding in the COPD population, where airflow obstruction has traditionally been the mainstay of prognostication. This result suggests that the drivers of mortality in obstructive lung disease may ultimately be related to pathways by which there is impaired gas transfer. Stated another way, as the primary function of the lung is gas exchange, pathology that limits diffusing capacity is also a primary determinant of survival. Studies examining the physiologic mechanisms associated with reductions in D_{LCO} as it translates to increased dyspnea have noted reduced ventilatory efficiency, leading to higher inspiratory drive, reductions in inspiratory reserve, and lower peak oxygen uptake during exercise (30–32). Similar mechanisms may contribute to the associations with mortality, although further investigation is needed to elucidate these pathways.

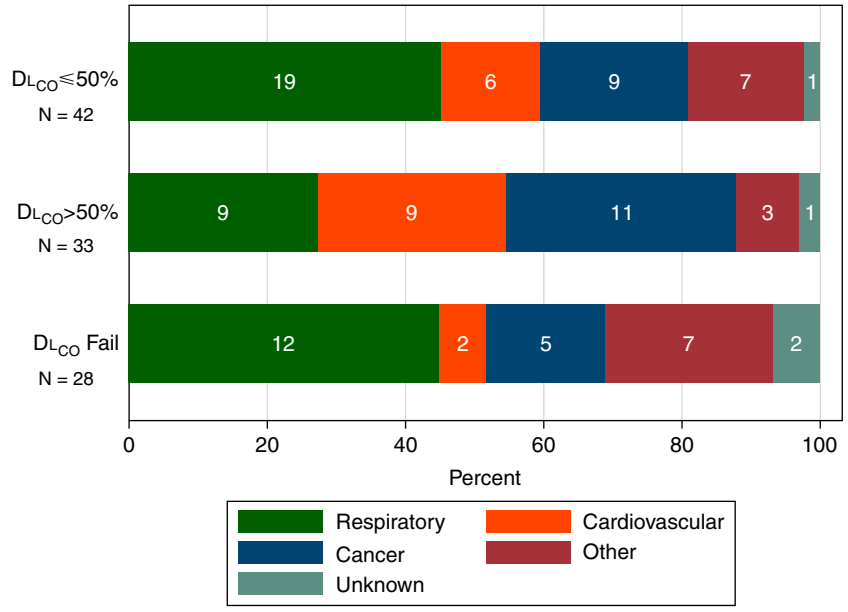

Figure 5. Cause of death by diffusing capacity impairment. Percentages of cause of death among TORCH categories (15), by D_{LCO} category. Higher percentages of respiratory-related death were observed among individuals with $D_{LCO} \leq 50\%$ predicted. D_{LCO} = diffusing capacity of the lung for carbon monoxide.

Ultimately, recent evidence has suggested that airflow obstruction may be insufficient in predicting morbidity outcomes in COPD (33, 34); our findings extend those results to mortality outcomes and offer diffusing capacity as an additional predictor that improves prognostication.

The present results do not offer a clear pathway by which impairment in diffusing capacity is associated with increased mortality. In light of the results being independent of airflow obstruction and emphysema, one possible explanation relates to additional comorbid conditions that may result in both a lower D_{LCO} and increased mortality. One such possibility is the presence of pulmonary vascular disease, with many prior studies suggesting that pulmonary vascular involvement in COPD may be underappreciated (17, 30, 35, 36). It is well known that pulmonary hypertension is associated with increased mortality in COPD as compared with individuals with COPD alone (37, 38). Furthermore, studies have demonstrated impairment in D_{LCO} associated with increased mortality among patients with COPD and pulmonary hypertension (39, 40). Similarly, gas transfer impairment is widely observed among individuals with heart failure, both with reduced and with preserved ejection fraction, and has been associated with mortality (41–43). Finally, the Lung Cancer Screening Score–COPD study identified diffusing capacity reduction as a predictor of lung cancer, raising another plausible pathway to explain the observed associations (44). Although we attempted to adjust for comorbidities within the models, there is likely some degree of residual confounding, especially with respect to cancer and pulmonary vascular disease. Further, although the evaluation of cause of death supported predominantly respiratory etiologies among those with severe D_{LCO} reductions, nearly three-quarters of the deaths reported did not have adjudicated cause-of-death information, limiting these findings.

Another key finding was that even mild diffusing capacity impairment was found to be consequential with respect to survival. Our study noted reductions in D_{LCO} roughly below 70% predicted to be significantly associated with mortality, similar to the National Health and Nutrition Examination Survey, which identified a threshold of 85% predicted in a general population (6), and the study of Global Initiative for Obstructive Lung Disease spirometry grade I individuals, which identified a threshold of 60% predicted (26). These results suggest that D_{LCO} is a sensitive marker of early changes in the integrity of the alveolar-capillary interface. Common clinical practice in COPD is to use D_{LCO} below 50% predicted as a marker of hypoxemia with exertion (45), knowing that severe hypoxemia is associated with increased mortality (46, 47). Our findings suggest that even mild impairment is relevant well before clinical evidence of hypoxemia. Furthermore, we observed that individuals who fail D_{LCO} maneuvers either by acceptability or reproducibility criteria have outcomes similar to those with severe gas transfer impairment. Although traditional use of D_{LCO} has focused on severe reductions, our findings highlight the value of more modest impairment and even an inability to obtain a D_{LCO} measurement to clinical prognostication.

The present results have a few key limitations. First, the mortality rate in this cohort is lower than those observed in the cohorts used to develop and validate the BODE index score (4). This raises the possibility that these findings only pertain to a healthier population of COPD patients. External validation of these findings in a distinct prospective cohort would address this limitation as well as offer more robust evidence supporting the performance of D_{LCO} as a predictor of mortality. There are only a few longitudinal studies that include D_{LCO} measurements (48, 49), of which COPDGene has the largest sample size and the necessary power to adequately evaluate mortality. A similar large-scale COPD research study that includes D_{LCO} measurements and mortality data is not yet available to serve as a validation cohort. Even a recent 10-year mortality risk score developed from the COPDGene cohort does not include D_{LCO}, as measurement was unavailable at the initial enrollment visit (50). One concern that has traditionally been considered and has likely limited inclusion of D_{LCO} in research studies is reproducibility. However, analysis of intrasubject variability in COPDGene has demonstrated a low coefficient of variation, at only 3.2% (51). The present findings strongly support the inclusion of D_{LCO} in future studies to validate these results and study inclusion of D_{LCO} in prognostic models of survival. The relatively infrequent deaths also limited the number of covariates included in multivariable models. As a result, there is likely residual confounding, especially as it pertains to comorbid conditions. Comorbidities were self-reported and noted to be less common than anticipated in a COPD population. Additionally, accurate measures of lung volumes to account for hyperinflation or air trapping were unavailable and may contribute to residual confounding, as a previous study noted associations between the ratio of inspiratory capacity to total lung capacity and mortality (52). Finally, the modest sample size for cause of death analysis limits the ability to draw conclusions regarding the underlying mechanism being described by D_{LCO} impairment. However, the findings clearly demonstrate that D_{LCO} offers distinct and relevant information beyond two prominent pathophysiologic characteristics of COPD: airflow obstruction and emphysema.

In conclusion, in this well-characterized cohort of COPD participants, we have identified diffusing capacity measurement to be a strong, independent predictor of mortality, similar in its predictive performance to the BODE index. D_{LCO} measurement is often obtained in the clinical setting, but its utility has hitherto been poorly understood and therefore has been excluded from multidimensional assessment and prognostic tools in COPD. These findings add to the literature identifying D_{LCO} as a marker of increased morbidity and mortality in COPD and further support consideration of D_{LCO} in prognostic models. Future studies examining the underlying mechanism reflected by the impairment of gas transfer as it relates to both morbidity and mortality, factors conferring susceptibility to reductions in D_{LCO}, and the impact of longitudinal trajectories of D_{LCO} on clinical outcomes are necessary. In the context of a growing interest in deep phenotyping and precision medicine in COPD, a simple minimal-risk measurement of gas transfer offers important prognostic information that should be considered in assessing and managing COPD patients. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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