

# Diffusing Capacity of Carbon Monoxide in Assessment of COPD



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**BACKGROUND:** Diffusing capacity of the lung for carbon monoxide (DLCO) is inconsistently obtained in patients with COPD, and the added benefit of DLCO testing beyond that of more common tools is unknown.

**OBJECTIVE:** The goal of this study was to determine whether lower DLCO is associated with increased COPD morbidity independent of emphysema assessed via spirometry and CT imaging.

**METHODS:** Data for 1,806 participants with COPD from the Genetic Epidemiology of COPD (COPDGene) study 5-year visit were analyzed, including pulmonary function testing, quality of life, symptoms, exercise performance, and exacerbation rates. DLCO percent predicted was primarily analyzed as a continuous variable and additionally categorized into four groups: (1) DLCO and FEV<sub>1</sub> > 50% (reference); (2) only DLCO ≤ 50%; (3) only FEV<sub>1</sub> ≤ 50%; and (4) both ≤ 50% predicted. Outcomes were modeled by using multivariable linear and negative binomial regression, including emphysema and FEV<sub>1</sub> percent predicted among other confounders.

**RESULTS:** In multivariable analyses, every 10% predicted decrease in DLCO was associated with symptoms and quality of life (COPD Assessment Test, 0.53 [ $P < .001$ ]; St. George's Respiratory Questionnaire, 1.67 [ $P < .001$ ]; Medical Outcomes Study Short Form 36 Physical Function, -0.89 [ $P < .001$ ]), exercise performance (6-min walk distance, -45.35 feet;  $P < .001$ ), and severe exacerbation rate (rate ratio, 1.14;  $P < .001$ ). When categorized, severe impairment in DLCO alone, FEV<sub>1</sub> alone, or both DLCO and FEV<sub>1</sub> were associated with significantly worse morbidity compared with the reference group ( $P < .05$  for all outcomes).

**ABBREVIATIONS:** 6MWD = 6-min walk distance; ATS = American Thoracic Society; CAT = COPD Assessment Test; DLCO = diffusing capacity of the lung for carbon monoxide; HRCT = high-resolution CT; KCO = efficiency of gas transfer; %LAA<sub>.950</sub> = percent low attenuation areas at or below -950 Hounsfield units consistent with emphysema; SF-36 = Medical Outcomes Study Short Form 36; SGRQ = St. George's Respiratory Questionnaire

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**CONCLUSIONS:** Impairment in DLCO was associated with increased COPD symptoms, reduced exercise performance, and severe exacerbation risk even after accounting for spirometry and CT evidence of emphysema. These findings suggest that DLCO should be considered for inclusion in future multidimensional tools assessing COPD. CHEST 2019; 156(6):1111-1119

**KEY WORDS:** COPD; pulmonary diffusing capacity; pulmonary gas exchange

COPD affects > 15.7 million adults<sup>1</sup> and is the fourth leading cause of death in the United States.<sup>2</sup> Spirometry has been the cornerstone of diagnosis, with the presence of airflow obstruction a key diagnostic criterion. More recently, to achieve a multidimensional evaluation, the approach to COPD assessment has broadened from primarily spirometry to include assessment of symptoms, impact on health status, quantitative assessment of emphysema by CT imaging, and risk of exacerbations.<sup>3-6</sup> One diagnostic tool that is noninvasive and widely available, but not currently integrated in commonly used COPD assessment models,<sup>5</sup> is measurement of diffusing capacity of the lung for carbon monoxide (DLCO).

DLCO is a measure of gas transfer that reflects the complex interactions at the alveolar capillary interface. It has been strongly associated with decline in lung function and is one of the best correlates of emphysema in COPD.<sup>7,8</sup> Studies evaluating DLCO as a predictor of

mortality are conflicting, with results dependent on the degree of airflow limitation and emphysema.<sup>9-13</sup> A few small studies suggest an association between gas transfer defects and frequent exacerbations,<sup>14,15</sup> but they did not examine these associations independent of emphysema. Although DLCO provides insight regarding respiratory physiology beyond that provided with spirometry, including indirect measurement of pulmonary vascular abnormalities, little information is available on the clinical utility of DLCO in predicting outcomes independent of spirometry or emphysema.

As a large, well-characterized cohort, the Genetic Epidemiology of COPD (COPDGene) study provides an ideal opportunity to analyze the relation between DLCO and COPD morbidity. We hypothesized that DLCO, independent of FEV<sub>1</sub> and quantitative CT measures of emphysema, is associated with worse COPD morbidity, including symptoms, quality of life, exercise performance, and exacerbations.

## Patients and Methods

### Study Population

COPDGene was approved by institutional review boards at all participating centers. Each participant provided written informed consent. COPDGene study methods have been previously reported.<sup>16</sup> Smokers with a history of  $\geq 10$  pack-years and age 45 to 80 years from 21 clinical centers were enrolled in the years 2007 to 2012. Participants with postbronchodilator FEV<sub>1</sub>/FVC < 70% were defined as having COPD, and they were further categorized according to severity based on postbronchodilator percent predicted FEV<sub>1</sub> using Global Obstructive Lung Disease spirometry stage I to IV criteria.<sup>5</sup> Participants with COPD who completed the COPDGene visit conducted 5 years following the original enrollment (2013-2017) and who had DLCO measurements and complete data for all relevant covariates were included. Of these 1,806 participants, 1,564 had CT data available (Fig 1).

### Physiologic Testing

Spirometry and DLCO measurements were conducted by using the EasyOne Pro (ndd Medical Technologies) in accordance with American Thoracic Society (ATS)/European Respiratory Society guidelines, with standardization of protocols and quality control procedures across clinical sites.<sup>17</sup> Only subjects with tests judged acceptable and reproducible were included. FEV<sub>1</sub> and DLCO percent predicted values were calculated by using Global Lung Initiative reference equations,<sup>18,19</sup> with DLCO values adjusted for hemoglobin

and altitude.<sup>18</sup> Six-minute walk distance (6MWD) tests were conducted according to ATS guidelines.<sup>20</sup>

### CT Scans

CT scans were acquired by using individual site CT scanners, with previously published protocols for each scanner type.<sup>21</sup> Total percent emphysema, defined as the percentage of voxels with attenuation at or below -950 Hounsfield units (%LAA<sub>-950</sub>), was calculated by using parametric response mapping software.

### Patient-reported Outcomes

COPD Assessment Test (CAT), St. George's Respiratory Questionnaire (SGRQ), and Medical Outcomes Study Short Form 36 (SF-36) were administered and scored to assess quality of life and impact of symptoms.

### Exacerbations

Exacerbation rate was determined from self-reported episodes of increased COPD symptoms requiring antibiotics or steroids in the 12 months preceding this study. Severe exacerbations were defined as the subset of exacerbations requiring an ED visit or hospitalization, whereas moderate exacerbations were those that did not.

### Statistical Analysis

All analyses were performed by using SAS version 9.4 (SAS Institute, Inc.), and *P* values < .05 were considered significant.

Participant baseline characteristics were described by using medians with interquartile ranges. Multivariable linear regressions were constructed wherein DLCO and FEV<sub>1</sub> were modeled as continuous variables with results presented for every 10% predicted value decrease. Models included age, sex, ethnicity, BMI categories ( $\leq 21$ , 21-30, and  $> 30$  kg/m<sup>2</sup>), education, smoking exposure in pack-years, smoking status (current, former, or current-to-former smoker), anemia, diabetes, congestive heart failure, sleep apnea, %LAA<sub>.950</sub>, percent predicted DLCO, and percent predicted FEV<sub>1</sub>. Generalized estimating equations were used to account for correlation between participants at each center. Identical analyses were conducted evaluating percent predicted KCO, a measure of the efficiency of gas transfer accounting for alveolar volume.

Participants were also categorized into four groups based on the presence or absence of severe impairment in FEV<sub>1</sub> and DLCO, defined by a value  $\leq 50\%$  predicted. The groups are described as follows: (1) reference (FEV<sub>1</sub> and DLCO both  $> 50\%$  predicted); (2) DLCO impaired (FEV<sub>1</sub>  $> 50\%$  and DLCO  $\leq 50\%$ ); (3) FEV<sub>1</sub> impaired (FEV<sub>1</sub>  $\leq 50\%$  and DLCO  $> 50\%$ ); and (4) both impaired (FEV<sub>1</sub> and DLCO  $\leq 50\%$ ). Multivariable regression models were adjusted for confounders as noted earlier, comparing the latter three groups vs the reference group.

Exacerbation rate was modeled by using multivariable negative binomial regressions with the confounders described earlier. Given the low number of events in the study population, emphysema was categorized into those with missing high-resolution CT (HRCT) data,  $\leq 5\%$  LAA<sub>.950</sub>, and  $> 5\%$  LAA<sub>.950</sub>. Categorization in this manner allowed for inclusion of participants with missing HRCT data (e-Table 1).

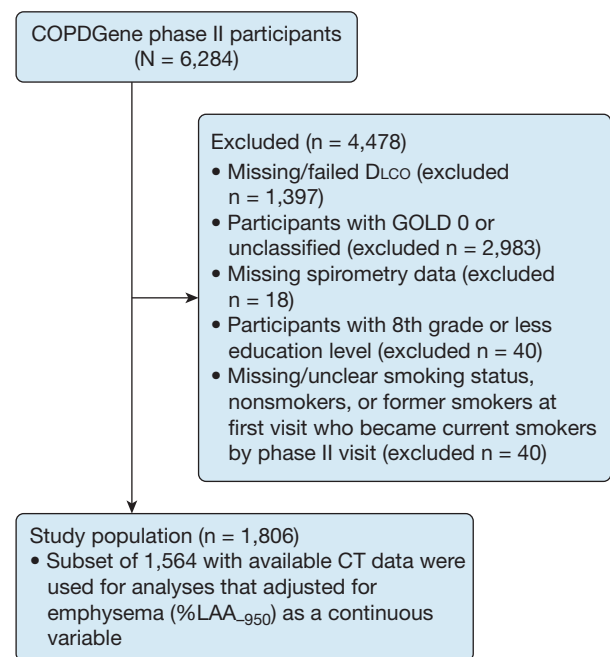


Figure 1 – Participant selection. Models with and without emphysema (%LAA<sub>.950</sub>) are presented for all outcomes in Tables 2, 3, and e-Table 2. COPDGene = Genetic Epidemiology of COPD; DLCO = diffusing capacity of the lung for carbon monoxide; GOLD = Global Obstructive Lung Disease; %LAA<sub>.950</sub> = percent low attenuation areas at or below -950 Hounsfield units consistent with emphysema.

## Results

### Participant Characteristics

A total of 1,806 participants with COPD Global Obstructive Lung Disease spirometry stages I to IV in whom DLCO measurements were available from the year 5 visit were identified; of these, 1,564 had available HRCT percent emphysema data and were used in most analyses (Fig 1). Baseline characteristics and respiratory outcomes for the 1,564 participants analyzed are presented in Table 1. The participants were 54% male, 82% white, had a median 45 pack-year smoking history, a postbronchodilator FEV<sub>1</sub> of 70% predicted, and a DLCO of 66% predicted.

Participants were moderately symptomatic, with a median CAT score of 13, SGRQ of 28, SF-36 Physical Function of 42, and 6MWD of 1,280 feet. There was a high prevalence of emphysema among the participants with available HRCT data, with 741 (47%) exhibiting  $> 5\%$  LAA<sub>.950</sub> according to CT scan. A moderate negative correlation was observed between DLCO and %LAA<sub>.950</sub>, with a Spearman correlation coefficient of  $-0.6$  ( $P < .001$ ) (e-Fig 1).

The baseline characteristics and outcomes for the total 1,806 participants and participants with missing CT data

are provided in e-Table 1. The group with missing CT data reported lower percent predicted FEV<sub>1</sub> and DLCO, increased morbidity according to symptom and quality of life scores (CAT, SGRQ, and SF-36 Physical Function), and decreased 6MWD than those with CT data.

### Association Between DLCO and Respiratory Outcomes, Independent of FEV<sub>1</sub> and Percent Emphysema

In multivariable models, lower percent predicted DLCO was associated with increased COPD morbidity, independent of FEV<sub>1</sub> and %LAA<sub>.950</sub> (Table 2). These findings were noted in multiple domains, including symptoms and quality of life (CAT, SGRQ, and SF-36 Physical Function), exercise performance (6MWD), and severe COPD exacerbations (Table 3). For example, a decrease of 10% predicted DLCO was associated with a decrease in 6MWD of 45.35 feet, demonstrating diminished exercise performance. The magnitude of association was similar to that of FEV<sub>1</sub>. The independent effect of DLCO tended to be lower than the effect of FEV<sub>1</sub> for all other outcomes but was still in clinically relevant ranges. For example, a decrease in DLCO of 10% predicted was associated with approximately a

14% higher rate of hospitalization for COPD exacerbation compared with the 27% higher hospitalization rate for a decrease in FEV<sub>1</sub> of 10% predicted. The results were not appreciably different when %LAA<sub>-950</sub> was not included as a covariate (e-Table 2). Similar results were observed when percent predicted KCO was examined (e-Tables 3, 4).

### Severe Impairment of FEV<sub>1</sub> and DLCO Worsens Outcomes, Independent of FEV<sub>1</sub> and Percent Emphysema

To further characterize the independent and combined effects of DLCO and FEV<sub>1</sub> abnormalities, we created four categories of participants based on the presence or absence of severe impairment in FEV<sub>1</sub> and DLCO, defined by a value ≤ 50% predicted. In adjusted analyses that included %LAA<sub>-950</sub> and other potential confounders, severe impairment in either FEV<sub>1</sub> alone, DLCO alone, or both FEV<sub>1</sub> and DLCO was associated with worse CAT, SGRQ, SF-36 Physical Function, and 6MWD compared with the reference (*P* < .05 for all comparisons) (Fig 2). In addition, outcomes reflective of physical functioning, most evidently 6MWD, show a pattern in which those with severe impairment in both FEV<sub>1</sub> and DLCO displayed significantly worse outcomes than impairment in FEV<sub>1</sub> or DLCO alone (*P* < .05 for 6MWD).

All groups with severe impairment in FEV<sub>1</sub>, DLCO, or both reported increased exacerbation rates compared with the reference group (e-Fig 2). Similar to the findings for 6MWD, combined severe reduction in FEV<sub>1</sub> and DLCO tended to exhibit a higher rate of severe exacerbations compared with isolated impairment in either individual measure (Fig 3).

## Discussion

In this large, well-characterized cohort of individuals with COPD, lower DLCO was associated with increased measures of COPD morbidity across multiple domains, including increased respiratory symptoms, worse health-related quality of life, reduced exertional capacity, and increased rate of exacerbations for COPD. These findings were independent of spirometry and of emphysema analysis conducted using quantitative CT imaging. Severe reduction in DLCO was associated with worsening of all outcomes, and the combination of a severely reduced FEV<sub>1</sub> and DLCO showed greater impairment than either FEV<sub>1</sub> or DLCO alone for physical

**TABLE 1 ] Characteristics of the Study Population**

Characteristic	Analysis (N = 1,564)
Age, y	68 (62-74)
Male	841 (54%)
Black	281 (18%)
Education	
High school, no diploma	117 (7%)
High school graduate or GED	379 (24%)
Some college or technical school, no degree	467 (30%)
College or technical school graduate (bachelor's or associate degree)	437 (28%)
Master's or doctoral degree	164 (10%)
BMI, kg/m <sup>2</sup>	28 (24-31)
Obese (BMI ≥ 30 kg/m <sup>2</sup> )	519 (33%)
Anemia	197 (13%)
Diabetes	249 (16%)
Congestive heart failure	60 (4%)
Sleep apnea	280 (18%)
Pack-years of smoking	45 (34-63)
Smoking status	
Former smoker	484 (31%)
Current-to-former smoker <sup>a</sup>	191 (12%)
Current smoker	889 (57%)
FEV <sub>1</sub> % predicted	70 (51-89)
≤ 50%	378 (24%)
DLCO % predicted	66 (50-82)
≤ 50%	388 (25%)
KCO % predicted	73 (58-87)
≤ 50%	246 (16%)
CAT	13 (7-20)
SGRQ	28 (13-45)
SF-36 Physical Function	42 (33-50)
SF-36 Mental	55 (46-60)
6MWD, feet	1,280 (1,000-1,512)
%LAA <sub>-950</sub>	4 (1-14)
LAA <sub>-950</sub> > 5%	741 (47%)
Resting SpO <sub>2</sub> , %	96 (94-97)

Data are expressed as median (interquartile range) or No. (%) as appropriate. 6MWD = 6-min walk distance; CAT = COPD Assessment Test; DLCO = diffusing capacity of the lung for carbon monoxide; GED = General Education Diploma; KCO = gas transfer efficiency coefficient; %LAA<sub>-950</sub> = percent low attenuation areas at or below -950 Hounsfield units consistent with emphysema; SF-36 = Medical Outcomes Study Short Form 36; SGRQ = St. George's Respiratory Questionnaire; SpO<sub>2</sub> = oxygen saturation.

<sup>a</sup>Participants who went from being current smokers at the phase I visit to former smokers by the phase II visit.

**TABLE 2 ]** Reductions in DLCO and FEV<sub>1</sub> Are Associated With Increased COPD Morbidity

Outcome	DLCO % Predicted		FEV <sub>1</sub> % Predicted	
	Regression Coefficient (95% CI)	P Value	Regression Coefficient (95% CI)	P Value
CAT score	0.53 (0.33 to 0.73)	< .001	1.16 (0.96 to 1.36)	< .001
SGRQ score	1.67 (1.23 to 2.1)	< .001	2.94 (2.58 to 3.31)	< .001
Activity	2.58 (1.74 to 3.41)	< .001	3.99 (3.48 to 4.51)	< .001
Impact	1.3 (0.86 to 1.74)	< .001	2.25 (1.86 to 2.64)	< .001
Symptom	1.23 (0.70 to 1.76)	< .001	3.33 (2.93 to 3.72)	< .001
SF-36 Physical Function	-0.89 (-1.18 to -0.6)	< .001	-1.29 (-1.58 to -1.00)	< .001
SF-36 Mental	0.03 (-0.37 to 0.42)	.900	-0.01 (-0.31 to 0.31)	.954
6MWD, feet	-45.35 (-58.21 to -32.48)	< .001	-43.26 (-48.36 to -38.15)	< .001
Resting SpO <sub>2</sub> , %	-0.22 (-0.38 to -0.05)	.012	-0.19 (-0.24 to -0.14)	< .001

Associations are per 10% decrease in percent predicted DLCO or percent predicted FEV<sub>1</sub>. Models (N = 1,564) include age, sex, BMI category, ethnicity, education, smoking pack-years, smoking status, anemia status, diabetes status, congestive heart failure status, sleep apnea status, %LAA<sub>950</sub> (emphysema), percent predicted FEV<sub>1</sub>, and percent predicted DLCO. See Table 1 legend for expansion of abbreviations.

function outcomes and severe exacerbations. In the context of efforts to further classify patients with COPD by using multidimensional tools, these findings suggest that DLCO offers additional clinically valuable information that extends beyond what is captured by using spirometry and CT assessments of emphysema.

Current evaluation of phenotypes in COPD has moved away from the use of spirometry alone, with increasing data suggesting that spirometry is insufficient in predicting symptoms, quality of life, or exacerbation frequency.<sup>3,4</sup> One method of phenotyping uses CT identification of emphysema and, hitherto, emphysema has been well documented as being associated with impairment in DLCO. Pathologic, radiographic, and physiologic studies have shown a correlation between increasing emphysema and a reduction in DLCO, such that DLCO measurement may have utility in identifying patients with emphysema.<sup>7,8,22-24</sup> Although we found moderate correlation of DLCO and emphysema, variability in DLCO was not fully explained by CT-confirmed emphysema; in models adjusting for

emphysema, impairment in DLCO exhibited independent associations with worse outcomes in COPD, suggesting that DLCO is independently informative and may help define a subgroup of patients at increased risk for adverse health outcomes.

The results highlight the potential for DLCO to provide insight into patients with COPD at risk for limitations in physical function. Previous studies that have evaluated DLCO in the context of cardiopulmonary exercise testing have found that DLCO was associated with dyspnea and exercise intolerance in smokers with mild obstruction, as well as those with moderate to severe lung function impairment.<sup>25-28</sup> The current study extends these findings in a large COPD cohort to include an association between DLCO and functional exercise performance (indicated by 6MWD) and self-reported physical functioning (SGRQ activity, SF-36 Physical Function). These indicators suggest an association between DLCO and functional limitations that contribute to the overall burden of morbidity in the daily life of patients with COPD.

**TABLE 3 ]** Reductions in DLCO and FEV<sub>1</sub> Are Associated With Increased COPD Exacerbations

Outcome	DLCO % Predicted		FEV <sub>1</sub> % Predicted	
	Rate Ratio (95% CI)	P Value	Rate Ratio (95% CI)	P Value
Any exacerbations	1.05 (0.97 to 1.12)	.231	1.22 (1.19 to 1.27)	< .001
Moderate exacerbations	1.01 (0.93 to 1.10)	.759	1.20 (1.16 to 1.27)	< .001
Severe exacerbations	1.14 (1.05 to 1.20)	< .001	1.27 (1.20 to 1.33)	< .001

Associations are per 10% decrease in percent predicted DLCO or percent predicted FEV<sub>1</sub>. Exacerbation models (N = 1,806) include age, sex, ethnicity, BMI categories, education, pack-years, smoking status, diabetes status, anemia status, congestive heart failure status, sleep apnea status, emphysema as a categorical variable (missing data, ≤ 5% LAA<sub>950</sub>, and > 5% LAA<sub>950</sub>), percent predicted DLCO, and percent predicted FEV<sub>1</sub>. Any exacerbation refers to all episodes requiring antibiotics or steroids, moderate refers to only those episodes not resulting in an ED visit or hospitalization, and severe refers to those requiring an ED visit or hospitalization. See Table 1 legend for expansion of abbreviations.



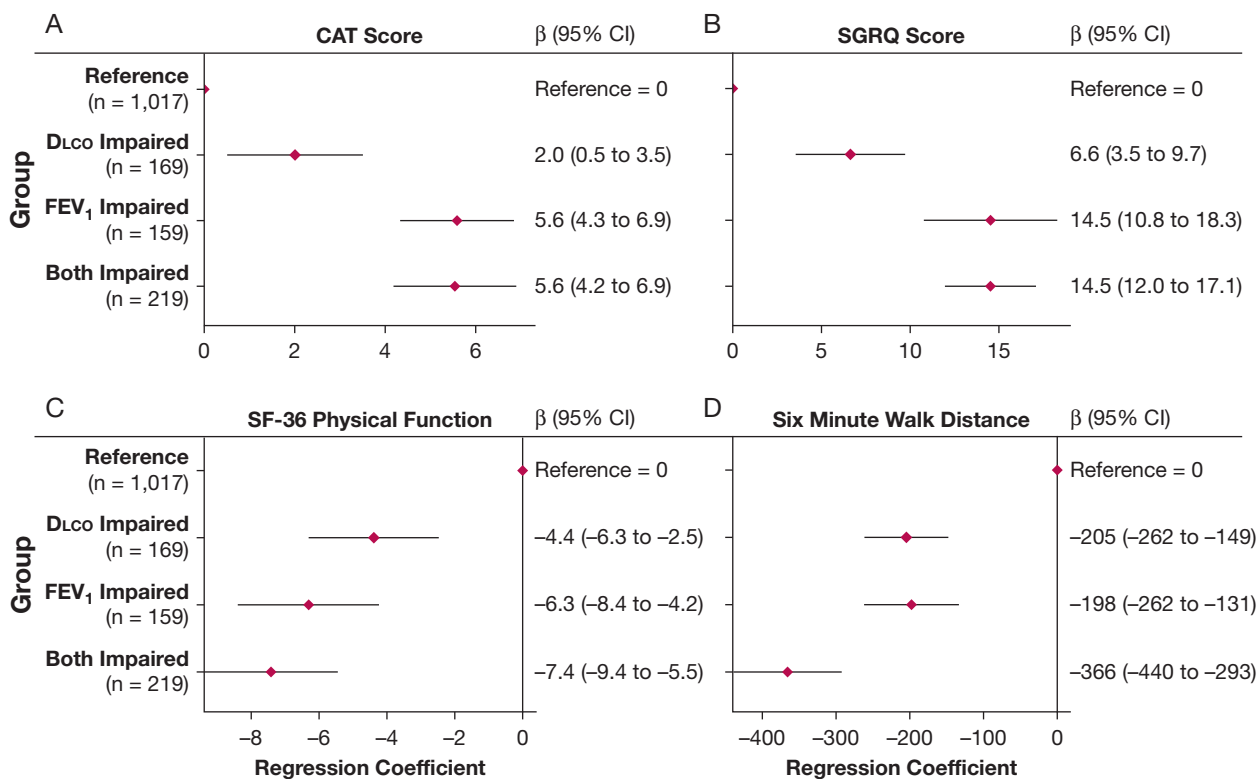
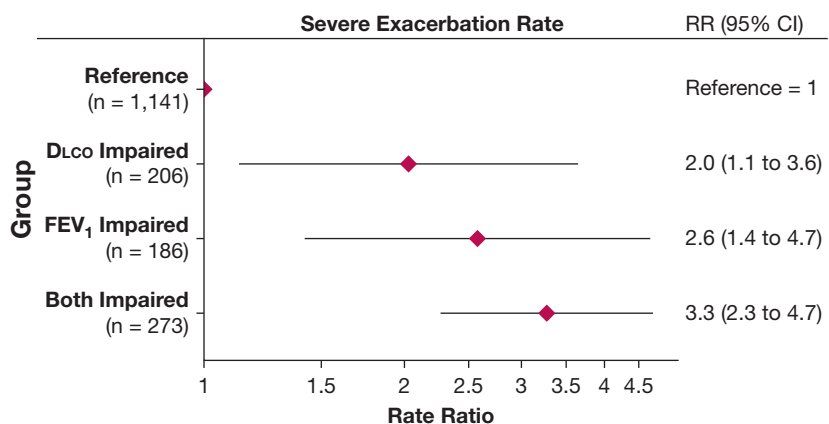


Figure 2 – Severe impairment in DLCO in isolation and in combination with severe impairment in FEV<sub>1</sub> is associated with increased COPD morbidity. Association between categories of percent predicted FEV<sub>1</sub> and DLCO with (A) COPD Assessment Test score, (B) St. George’s Respiratory Questionnaire score, (C) Medical Outcomes Study Short Form 36 Physical Function, and (D) 6-min walk distance in feet. Groups are defined as reference (FEV<sub>1</sub> and DLCO both > 50% predicted), DLCO impaired (FEV<sub>1</sub> > 50% and DLCO ≤ 50%), FEV<sub>1</sub> impaired (FEV<sub>1</sub> ≤ 50% and DLCO > 50%), and both impaired (FEV<sub>1</sub> and DLCO ≤ 50%). Models (N = 1,564) are adjusted for age, sex, BMI categories, ethnicity, education, smoking pack-years, smoking status, anemia status, diabetes status, congestive heart failure status, sleep apnea status, and %LAA-950 (emphysema). See Figure 1 legend for expansion of abbreviations.

Identification of patients at risk for frequent or severe exacerbations is a priority given the links between COPD exacerbations and mortality,<sup>29</sup> as well as the high degree of health-care utilization and associated costs.<sup>30</sup> To date, the most reliable predictor of future COPD exacerbations is a history of exacerbations in the

previous year.<sup>31-33</sup> It is notable that in a systematic review including 27 models to predict COPD exacerbations, DLCO was not considered as a predictor in any of the models.<sup>31</sup> Our results show that severe impairments in DLCO are independently associated with increased rates of COPD exacerbations, with a

Figure 3 – Severe impairment in DLCO in isolation and in combination with severe impairment in FEV<sub>1</sub> is associated with higher severe COPD exacerbation rates. Association between categories of FEV<sub>1</sub> and DLCO and self-reported rate of severe exacerbations. Groups are defined as reference (FEV<sub>1</sub> and DLCO both > 50% predicted), DLCO impaired (FEV<sub>1</sub> > 50% and DLCO ≤ 50%), FEV<sub>1</sub> impaired (FEV<sub>1</sub> ≤ 50% and DLCO > 50%), and both impaired (FEV<sub>1</sub> and DLCO ≤ 50%). Model is adjusted for age, sex, ethnicity, BMI categories, smoking pack-years, smoking status, anemia status, diabetes status, congestive heart failure status, sleep apnea status, and emphysema as a categorical variable (missing, ≤ 5% LAA-950, > 5% LAA-950), with N = 1,806. Severe refers only to those exacerbations requiring an ED visit or hospitalization. RR = rate ratio. See Figure 1 legend for expansion of other abbreviations.



particularly strong association between DLCO and severe exacerbations requiring an ED visit or hospitalization. These findings add to those of previous small studies that have shown diminished gas transfer and gas transfer efficiency among frequent exacerbators.<sup>14,15</sup> Of note, the associations reported here are of DLCO and COPD exacerbations in the previous year and are therefore cross-sectional in nature. The COPDGene data are not currently available to investigate the ability of DLCO to predict future exacerbations, but the findings reported here suggest that this is an important next step.

The independent association between DLCO and COPD morbidity may be indicative of underlying pathophysiologic injury that cannot be wholly accounted for by airflow obstruction or emphysema. In general, the physiologic mechanisms by which COPD can impair DLCO are through decreased diffusivity across the alveolar capillary membrane, or through decreased pulmonary vascular volume associated with gas-exchanging units. In previous studies partitioning DLCO into membrane diffusivity and pulmonary vascular volume in COPD, a demonstrable decrease in both measures was reported.<sup>23,34,35</sup> This outcome has been attributed to airspace destruction and associated capillary membrane destruction secondary to emphysema, with resultant decreased gas exchange surface area. Although this mechanism likely contributes to the association detected, we postulate that pulmonary vascular injury, including vascular thickening, distal vessel pruning, and capillary rarefaction reflected in the DLCO measurement, is playing a role. Pulmonary vascular volume impairment has been observed independent of and even prior to development of emphysema in COPD<sup>23,36-40</sup> and is associated with worse outcomes.<sup>41-44</sup> We postulate that one of the drivers of the independent association between DLCO and COPD morbidity is subclinical pulmonary vascular injury, an area that warrants further study in patients with COPD.

This study is limited in part by the cross-sectional nature and low frequency of the exacerbation events, curtailing discussion regarding prediction of future exacerbations. These results are a reflection, however, of a frequent exacerbator phenotype, and the associations with DLCO noted here help characterize this subgroup. In creating categorical subgroups, dichotomization of FEV<sub>1</sub> and DLCO above and below 50% predicted was conducted to represent severe impairment in neither, either, or both values. This analysis shows the independent and combined influences of each measure on outcomes and

was not designed to formally evaluate threshold effects. To describe independent associations of DLCO, we used quantitative CT assessment of emphysema; however, there is the possibility that DLCO is a marker for microscopic emphysema below the level of detection by current CT measures. This theory deserves further exploration to fully understand the pathophysiology of DLCO in COPD but does not detract from the notion that DLCO offers information beyond readily available and currently utilized clinical tools. Further characterization of individuals for the presence or absence of pulmonary hypertension was unavailable, but assessment of alternative causes for pulmonary vascular disease, including sleep apnea and congestive heart failure, were included in the analyses. In addition, body plethysmography, which would account for hyperinflation and its impact on COPD morbidity, was unavailable in this cohort. Finally, the results of this study represent those based on testing in a clinical research setting, and generalizability may be limited due to variability in adherence to quality control procedures of DLCO measurements in clinical testing.<sup>45</sup> However, the results presented offer evidence to support future investigations surrounding the clinical utility of DLCO under real-world conditions.

## Conclusions

The current study showed that DLCO measurement, a readily available, frequently obtained test, provides clinically relevant information beyond spirometry and CT evidence of emphysema. Although many multidimensional prognostic models assessing mortality and morbidity do not include DLCO, findings from this study suggest that inclusion of DLCO in such models should be considered. Specifically, DLCO measurement may provide information regarding functional status and identify subgroups of patients who display diminished exercise performance or frequent exacerbations that are incompletely captured by existing indices. Furthermore, it may provide a window into the interactions between vascular and pulmonary physiology, an area that should be further investigated. Future studies investigating the utility of DLCO in prognostic indices of morbidity and mortality, the relationship between DLCO and vascular disease in COPD, and the implications of longitudinal changes in DLCO are warranted. DLCO offers clinically important information beyond that obtained from spirometry and radiography and should be considered in characterizing and managing patients with COPD.

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