

RESEARCH PAPER

Determinants Of Six-Minute Walk Distance In Chronic Obstructive Pulmonary Disease Differ By Exposure Type: a Cross-Sectional Study Of Smoking And Biomass-Related Disease In Rural South India

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Abstract

Background: The six-minute walk distance (6MWD) is a standard measure of functional capacity in chronic obstructive pulmonary disease (COPD). It is not clear whether walking distance depends more on airflow limitation, measured by the forced expiratory volume in one second (FEV1), or on gas exchange, measured by the diffusing capacity of the lung for carbon monoxide (DLCO). Nor is it clear whether the answer is the same in disease caused by tobacco and disease caused by biomass smoke.

Objective: To compare FEV1 and DLCO as predictors of 6MWD, and to test whether the dominant predictor differs between smoking COPD (S-COPD) and biomass-related non-smoking COPD (NS-COPD).

Methods: Ninety-one adults with stable COPD attending a rural teaching hospital in Karnataka, southern India, had post-bronchodilator spirometry, single-breath DLCO and a corridor six-minute walk test at a single visit. Fifty-four had smoked more than 10 pack-years (S-COPD); 37 had never smoked and had a biomass exposure index above 60 hour-years (NS-COPD). Pearson and Spearman coefficients described how lung-function measures related to walking distance, multiple linear regression identified independent predictors, and receiver operating characteristic (ROC) analysis tested how well each measure identified poor exercise capacity, defined in advance as a walk below 350 m.

Results: Across the cohort, FEV1 percent predicted tracked 6MWD more closely ($r=0.430$, $p<0.001$) than DLCO percent predicted ($r=0.287$, $p<0.01$), and FEV1 was the only independent predictor in regression (1.62 m per 1% predicted; $p<0.001$; model $R^2=0.217$). FEV1 also separated poor walkers better than DLCO (area under the curve 0.73 versus 0.62). Stratifying by exposure reversed this. Among smokers, diffusion severity was associated with walking distance ($\rho=-0.361$, $p=0.007$) and GOLD stage was not ($\rho=-0.204$, $p=0.139$). Among non-smokers, GOLD stage was associated with walking distance ($\rho=-0.421$, $p=0.009$) and diffusion severity was not ($\rho=0.092$, $p=0.588$).

Conclusions: FEV1 predicted walking distance better overall, but what limited walking differed with the causative exposure: gas exchange in smokers, airflow mechanics in biomass-exposed non-smokers. One severity number does not serve both groups. Reading spirometry alongside DLCO shows which mechanism is limiting a given patient.

Keywords: six-minute walk distance; exercise capacity; diffusing capacity; spirometry; biomass fuel; non-smoking COPD

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Introduction

Chronic obstructive pulmonary disease (COPD) is a leading cause of illness and death worldwide, and its effects reach well beyond the airflow limitation that spirometry measures¹. Functional exercise capacity, usually recorded as the six-minute walk distance (6MWD), predicts hospitalization and survival, and it depends on the respiratory, cardiovascular and musculoskeletal systems working together^{2,3}.

Severity is conventionally graded from the forced expiratory volume in one second (FEV1) under the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification¹. FEV1 measures mechanical airflow only, and it correlates imperfectly with how far a patient can walk. The diffusing capacity of the lung for carbon monoxide (DLCO) measures the alveolar-capillary membrane instead, and in some smoking cohorts it has predicted exercise capacity and exercise-induced desaturation more closely than FEV1^{3,4}. Which of the two measures better predicts function is still argued.

The heterogeneity of COPD complicates that argument. In low- and middle-income countries a large share of the disease follows household biomass smoke rather than tobacco. Physiological and imaging studies suggest that this biomass-related non-smoking COPD (NS-COPD) is weighted towards airway disease, with the alveolar-capillary surface comparatively spared, while smoking COPD (S-COPD) carries the emphysematous, gas-exchange-impaired pattern familiar from tobacco cohorts^{5,6,7}. If the structural substrate is not the same, the step that limits exercise, and therefore the measurement that best predicts walking distance, need not be the same either. That has seldom been tested in a single cohort containing both etiologies.

We examined the relationship between FEV1, DLCO and 6MWD in stable COPD patients drawn from a rural South Indian population, and asked whether the dominant predictor of functional capacity differs between smoking and biomass-related non-smoking disease.

Materials and Methods

Study design, setting and participants

Patients were drawn from the respiratory medicine services of a tertiary-care teaching hospital serving a mainly agrarian catchment in Mandya district, Karnataka. Recruitment ran continuously for eighteen months, from April 2024 to September 2025. The Institutional Ethics Committee cleared the study before the first enrollment, and every participant gave written consent after the procedures had been explained.

Adults of at least 40 years with COPD, confirmed by a post-bronchodilator FEV1 to forced vital capacity ratio below 0.70 and clinically stable at assessment, were eligible. We did not enroll patients with active pulmonary tuberculosis, a known lung malignancy, an interstitial process, physician-diagnosed bronchial asthma, an exacerbation in progress at screening, or any physical limitation that prevented a corridor walk test. Everyone meeting these conditions during the recruitment window was approached, so the series is consecutive rather than selected.

We did not perform an a priori sample-size or power calculation. The 91 patients analyzed are the whole of the consecutive series accrued over the fixed recruitment period. What this means for the precision of the subgroup estimates is taken up under Limitations.

Exposure classification

Exposure history decided cohort allocation. A cumulative tobacco burden above 10 pack-years, with negligible biomass exposure, defined the smoking cohort (S-COPD, n=54). In lifelong non-smokers, cumulative biomass exposure was expressed as a Biomass Exposure Index: the product of average daily hours spent cooking or heating water and the number of years of that activity. A value above 60 hour-years defined the biomass cohort (NS-COPD, n=37). This threshold was established in a rural Karnataka population as the lowest level associated with chronic respiratory disease.

Measurements

Every participant completed post-bronchodilator spirometry, a single-breath DLCO maneuver performed to the 2017 ERS/ATS technical standard with correction for hemoglobin and altitude, and a six-minute walk test in a 30-meter level corridor following the 2014 ERS/ATS field-walking-test standard^{4,8}. Oxygen saturation, heart rate and Borg dyspnea score were recorded before and after the walk. Predicted walking distance was taken from published South Indian reference equations. Airflow limitation was graded by GOLD stage, and gas-exchange impairment from DLCO percent predicted using ATS/ERS interpretative criteria. Two-dimensional echocardiography documented left ventricular function and gave an estimate of pulmonary artery systolic pressure (PASP).

Statistical analysis

All computation was carried out in IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables are given as mean $\pm$ standard deviation. The Pearson correlation coefficient quantified the association of continuous

percent-predicted FEV1 and DLCO with walking distance, and the Spearman rank correlation the association of the ordinal GOLD and DLCO severity grades. Both were computed for the cohort as a whole and again within each exposure stratum. Independent predictors were sought in a multiple linear regression model taking 6MWD as the dependent variable and FEV1, DLCO and PASP as covariates. How well FEV1 and DLCO separated patients with poor exercise capacity, defined in advance as a walking distance below 350 m, was summarized by the area under the receiver operating characteristic curve (AUC). Significance was set at a two-sided p-value below 0.05.

Results

Population and functional capacity

Ninety-one patients (S-COPD, n=54; NS-COPD, n=37) with a mean age of 60.2 ± 9.4 years were studied, and age did not differ between cohorts ($p=0.657$). Mean 6MWD for the whole cohort was 343.1 ± 51.2 m, with a range of 191 to 440 m. Smokers walked less far than non-smokers (333.8 ± 55.6 versus 356.7 ± 41.1 m; $p=0.035$). Left ventricular function

was preserved (mean ejection fraction $51.7 \pm 5.2\%$), and resting PASP did not differ between moderate and severe or very severe airflow limitation (41.2 versus 39.3 mmHg; $p=0.072$). Neither cardiac dysfunction nor resting pulmonary hypertension is therefore likely to have been a major determinant of walk distance in this cohort.

Overall predictors of walking distance

Across the whole cohort, FEV1 percent predicted showed a moderate positive correlation with 6MWD ($r=0.430$, $p<0.001$), stronger than that of DLCO percent predicted ($r=0.287$, $p<0.01$) (Table 1). Using ordinal grades, GOLD stage correlated with 6MWD slightly more strongly than DLCO severity grade ($\rho=-0.360$ versus -0.280). The RV/TLC ratio, a marker of hyperinflation, did not correlate with 6MWD ($r=-0.048$, $p=0.65$). In multiple linear regression including FEV1, DLCO and PASP, the model was significant ($p=0.0003$) and explained 21.7% of the variance in 6MWD ($R^2=0.217$). FEV1 was the only independent predictor (coefficient 1.62 m per 1% predicted, $p<0.001$); DLCO was borderline ($p=0.076$) and PASP was not significant.

Table 1: Correlation of lung-function measures with six-minute walk distance

Measure (and method)	Whole cohort	Smokers (n=54)	Non-smokers (n=37)
FEV1 % predicted (Pearson r)	0.430**	N/A	N/A
DLCO % predicted (Pearson r)	0.287*	N/A	N/A
GOLD stage (Spearman rho)	-0.360	-0.204 ($p=0.139$)	-0.421 ($p=0.009$)
DLCO severity (Spearman rho)	-0.280	-0.361 ($p=0.007$)	0.092 ($p=0.588$)

* $p < 0.01$; ** $p < 0.001$. Whole-cohort values use Pearson r for continuous percent-predicted values and Spearman rho for ordinal grades. FEV1: forced expiratory volume in one second; DLCO: diffusing capacity of the lung for carbon monoxide; GOLD: Global Initiative for Chronic Obstructive Lung Disease.

Reversal of the dominant predictor between exposures

Stratifying by exposure showed a clear reversal of the dominant predictor (Table 1). In smokers, the severity of diffusion impairment was associated with shorter walking distance ($\rho=-0.361$, $p=0.007$), while GOLD spirometric stage was not ($\rho=-0.204$, $p=0.139$). In non-smokers the pattern went the other way: GOLD stage predicted 6MWD ($\rho=-0.421$, $p=0.009$), and DLCO severity showed no association ($\rho=0.092$, $p=0.588$). Gas-exchange impairment governed exercise capacity in smokers, and airflow

limitation governed it in biomass-related non-smokers.

Discriminating poor exercise capacity

For identifying poor exercise capacity (6MWD below 350 m) in the whole cohort, FEV1 gave acceptable discrimination (AUC 0.73) and DLCO less (AUC 0.62) (Table 2). This fits the regression result. In an unstratified population where the milder grades were dominated by the biomass phenotype, FEV1 captures the average signal best, even though it is not the operative limiter inside the smoking subgroup.

Table 2: Discrimination of poor exercise capacity (6MWD below 350 m)

Predictor	AUC	Interpretation
FEV1 % predicted	0.73	Acceptable discrimination
DLCO % predicted	0.62	Poor discrimination

AUC: area under the receiver operating characteristic curve. Poor exercise capacity defined a priori as a six-minute walk distance below 350 m.

Discussion

FEV1 was the strongest overall predictor of functional exercise capacity in this cohort, outperforming DLCO in correlation, in multivariable regression and in discrimination of poor walkers. The more useful finding was that the dominant predictor of 6MWD reversed with the causative exposure: diffusion impairment drove walking distance in smokers, and airflow limitation drove it in biomass-related non-smokers. A single severity number therefore hides the mechanism that limits any particular patient.

Why the predictor changes with exposure

The reversal follows from the different structural basis of the two phenotypes. Smoking COPD is characterized by emphysematous destruction of the alveolar-capillary bed. During exercise the increased cardiac output drives erythrocytes through a depleted capillary bed too rapidly for full oxygen equilibration, which produces exercise-induced desaturation and early cessation of effort. DLCO indexes that capillary loss, so it predicts walking distance in smokers more faithfully than FEV1^{3,4}. Earlier work in tobacco-related disease found the same thing, with diffusing capacity a stronger independent determinant of 6MWD than spirometry³. In biomass-related non-smoking COPD the alveolar-capillary membrane is relatively preserved, so diffusion limitation contributes little. Here the constraint is mechanical, arising from airway narrowing and air trapping, and the spirometric grade captures it better^{5,6,7}. The limitation in this phenotype is closer to a ventilatory-mechanical pump constraint than to the gas-exchange failure of emphysema.

The functional split reported here fits what we observed on the structural side in the same patients, where severe airflow limitation in biomass-exposed non-smokers went with a largely intact diffusing capacity (unpublished observation, companion manuscript under review). A patient whose alveolar-capillary surface is preserved has little room for diffusion to become the limiting step during a corridor walk, so these correlations are close to what that observation would predict. The two analyses answer different questions: one asks whether the severity labels agree with each other, this one asks which measurement predicts what the patient can actually do.

Clinical implications

These results argue against relying on one number to gauge functional severity in COPD. Reading spirometry together with DLCO lets clinicians identify the operative limiter for each patient. In a smoker whose breathlessness is out of proportion to FEV1, a low DLCO points to gas-exchange failure

and supports attention to exercise-induced desaturation and assessment for ambulatory oxygen. In a biomass-exposed non-smoker the spirometric grade and airway-directed management remain the more relevant guide. The six-minute walk test integrates the whole oxygen-transport pathway, so it stays a useful adjunct that neither measurement fully replaces.

Limitations

Several limitations qualify these findings. A cross-sectional design cannot establish causal or temporal relationships. Recruitment from a tertiary center may have favored more advanced disease. No power calculation preceded the study, so the modest cohort size, and particularly the size of each exposure stratum, limits the precision of the subgroup correlations; those should be read as hypothesis-generating. The cohorts were split by sex, with mostly male smokers and mostly female biomass users. That split reflects how these exposures are distributed in the region, but it leaves sex-related confounding that this analysis cannot separate from exposure type. Exercise oxygen saturation was recorded but was not modeled as a mediator, and computed tomography was not available, so the mechanistic account given above is inferred from physiology rather than imaged. The participants are also the same individuals reported in the companion concordance analysis. The two studies are independent in question and method but not in sample, and their findings should not be read as mutual replication. The single-center design and region-specific biomass practices may limit how far these results generalize.

Conclusion

FEV1 was the strongest overall predictor of functional exercise capacity in this COPD cohort, but the dominant determinant of walking distance depended on the causative exposure: diffusion impairment in smokers, airflow limitation in biomass-related non-smokers. No single severity measure captures functional limitation across COPD phenotypes. Combining spirometry with DLCO, read in the light of exposure history, identifies the relevant limiting mechanism and should inform functional assessment, particularly where biomass-related COPD is common.

Declarations

Ethics approval and consent to participate: The study was approved by the Institutional Ethics Committee of Adichunchanagiri Institute of Medical Sciences (approval number AIMS/IEC/040/2024; Ethics Committee registration number EC/NEW/INST/2023/KA/0382) on 2 April 2024, and was conducted in accordance with the Declaration of

Helsinki (2013 revision). Written informed consent was obtained from every participant before enrollment. No animal subjects or tissue were involved.

Consent for publication: Not applicable. The manuscript reports aggregate data only and contains no individually identifiable data, images or details.

Overlapping data and related manuscripts: The data analyzed here come from the same consecutive cohort of 91 patients as a companion cross-sectional analysis by the same authors, titled "The diagnostic blind spot of spirometric staging in biomass-related non-smoking chronic obstructive pulmonary disease: a cross-sectional study of spirometry-diffusion discordance in a rural South Indian population", which has been submitted elsewhere and is under review. It is not cited in the reference list because it has not been accepted. The two manuscripts pose different research questions, analyze different dependent variables, use different statistical methods, and share no primary result; only descriptive characteristics of the cohort are common to both. The editors of both journals have been informed, and a copy of the companion manuscript can be supplied on request. The present work is original, is not under consideration by any other journal, and has not been published in whole or in part elsewhere.

Derivation from a postgraduate dissertation: This manuscript is derived from the approved postgraduate dissertation titled "Correlation between diffusing capacity of lung for carbon monoxide, 6 minute walking distance and FEV1 in smoking COPD and non smoking COPD".

Availability of data and material: De-identified participant data supporting the findings of this study are available from the corresponding author on reasonable request.

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Conflicts of interest: All authors declare that they have no competing interests. In compliance with the ICMJE uniform disclosure requirements, all authors confirm that they received no payment or services from any third party for the submitted work, have no financial relationships within the previous 36 months with any organization that might have an interest in

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