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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

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Informed consent: written informed consent was obtained from all participants before enrollment. The study did not involve animal subjects or tissue.

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

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Abstract

Chronic obstructive pulmonary disease (COPD) is heterogeneous, yet severity is conventionally graded by spirometry [forced expiratory volume in 1 second (FEV₁)] on the assumption that airflow limitation reflects parenchymal damage. Biomass-related non-smoking COPD (NS-COPD) is common in low- and middle-income countries. In this hospital-based cross-sectional study, we compared the physiological phenotypes of smoking COPD (S-COPD) and biomass-related NS-COPD and tested the concordance between Global Initiative for Chronic Obstructive Lung Disease (GOLD) spirometric severity and diffusion-based gas-exchange impairment. A total of 91 stable COPD patients (S-COPD, n=54; NS-COPD, n=37) underwent post-bronchodilator spirometry, single-breath diffusing capacity of the lung for carbon monoxide (DLCO) with transfer coefficient (KCO), residual volume to total lung capacity ratio, and the 6-minute walk test; cohorts were stratified by exposure (>10 pack-years vs. >60 hour-years of biomass) and compared using the Student t-test and Fisher's exact test. Compared with smokers, non-smokers had higher DLCO (71.4±12.4 vs. 57.7±17.5% predicted; p<0.001) and KCO (0.95±0.19 vs. 0.71±0.22 mmol/min/kPa/L; p<0.001). All non-smokers with severe (GOLD 3) airflow limitation (8/8, 100%) retained normal or only mildly impaired diffusion [7/8 (87.5%) strictly normal], whereas 14/28 (50.0%) GOLD 3 smokers had impaired gas exchange [4/28 (14.3%) severe]. Non-smokers more often retained a normal DLCO [31/37 (83.8%) vs. 26/54 (48.1%); odds ratio 5.6, 95% confidence interval 2.0-15.5; p<0.001]. This difference persisted after multivariable adjustment for age, sex and body mass index (odds ratio 30.0, 95% confidence interval 2.5-358.5; p=0.007) and after further adjustment for FEV₁ percent predicted (odds ratio 21.1, 95% confidence interval 1.6-282.7; p=0.021), indicating that the dissociation was not explained by these covariates or by the degree of airflow limitation itself. GOLD staging tended to overestimate parenchymal severity in biomass-related NS-COPD, in which airflow obstruction was largely uncoupled from gas-exchange loss, whereas in smokers the two were more tightly coupled. These cross-sectional, single-center findings, limited by a sex imbalance and the absence of imaging confirmation, support routine DLCO/KCO measurement to phenotype these patients and, where imaging is scarce, as a low-cost structural surrogate.

Key words: biomass, diffusing capacity, non-smoking COPD, spirometry, transfer coefficient.

Introduction

Chronic obstructive pulmonary disease (COPD) is a heterogeneous respiratory condition defined by persistent airflow limitation arising from a variable combination of small-airway disease (obstructive bronchiolitis) and parenchymal destruction (emphysema) [1]. Although COPD has historically been framed as a disease of cigarette smoking, an estimated 90% of COPD-related deaths now occur in low- and middle-income countries, where non-tobacco exposures—chiefly the combustion of solid biomass fuels for cooking and water heating—drive a substantial proportion of cases [2,3].

The diffusing capacity of the lung for carbon monoxide (DLCO), together with its volume-corrected transfer coefficient (KCO), provides a complementary, physiology-based assessment of gas exchange and is a sensitive surrogate for emphysematous parenchymal and pulmonary vascular loss [4]. The diagnosis of COPD rests on a post-bronchodilator forced expiratory volume in 1 second (FEV1) to forced vital capacity (FVC) ratio below 0.70, and disease severity is conventionally graded by the FEV1 percent predicted according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) classification [1,5]. Implicit in this framework is the assumption that the degree of airflow limitation reflects the extent of structural lung damage; however, FEV1 measures mechanical airflow and is agnostic to the integrity of the alveolar–capillary membrane.

This understanding is now recognized to be unsound. FEV1 reflects the global sum of all coexisting COPD pathologies and cannot by itself discriminate the obstructive from the destructive component of the disease [6-8]. The FEV1/FVC ratio, being a ratio between two forced volumes rather than the true Tiffeneau ratio of FEV1 to slow vital capacity, conveys little information about the loss of elastic recoil. The choice of the functional parameter used to estimate lung impairment is therefore itself an important determinant of what is detected, and recent comparative work indicates that diffusive indices outperform spirometric ones for this purpose [9,10].

There is growing recognition that smoking-related COPD (S-COPD) and biomass-related non-smoking COPD (NS-COPD) may represent distinct endotypes [2,11,12]. Tobacco smoke produces a “coupled” pattern of synchronous airway and alveolar–vascular destruction, whereas biomass smoke is thought to favor an airway-predominant, “uncoupled” pattern characterized by chronic bronchitis, peribronchiolar fibrosis, and relative preservation of the alveolar architecture [11,12]. If this is correct, FEV1-based GOLD staging may systematically overstate the burden of parenchymal disease in NS-COPD, creating a clinically important

mismatch between spirometric severity and true gas-exchange impairment. Few studies have directly quantified this discordance in rural Indian populations—including the aging rural communities of India with sustained exposure to both bidi smoking and household biomass smoke [3]—where DLCO is rarely measured and computed tomography is seldom available. We therefore conducted a cross-sectional study in a rural agrarian region of southern India to compare the physiological phenotypes of S-COPD and biomass-related NS-COPD and, specifically, to test the concordance between GOLD spirometric severity and DLCO-defined gas-exchange impairment in the two cohorts.

Materials and Methods

Study design and setting

This hospital-based cross-sectional study was conducted in the Department of Respiratory Medicine of a rural tertiary-care teaching hospital in Karnataka, southern India, over an 18-month period (April 2024 to September 2025). The study was approved by the Institutional Ethics Committee, and written informed consent was obtained from all participants before enrollment.

Participants

Consecutive patients aged 40 years or older with stable COPD, confirmed by a post-bronchodilator FEV1/FVC below 0.70 in accordance with GOLD criteria, were eligible. Patients were excluded if they had active pulmonary tuberculosis, known lung malignancy, interstitial lung disease, bronchial asthma, an acute exacerbation at screening, or were physically unable to perform the six-minute walk test. The rigorous exclusion of post-tuberculous and other structural lung disease was intended to ensure that the non-smoking cohort represented true biomass-induced COPD.

Exposure stratification

Patients were stratified into two cohorts by exposure history. Significant tobacco exposure was defined as a cumulative history exceeding 10 pack-years, consistent with thresholds used in large screening cohorts [5]. Significant biomass exposure was quantified using a Biomass Exposure Index, calculated as the product of mean daily hours of cooking or water heating and the duration of exposure in years (hour-years); an index exceeding 60 hour-years defined the biomass phenotype, a threshold previously identified and validated in a rural South Indian

(Mysore district, Karnataka) cohort as the minimum level significantly associated with chronic respiratory disease [13]. This yielded a smoking cohort (S-COPD, n=54) and a biomass-related non-smoking cohort (NS-COPD, n=37).

Physiological measurements

All participants underwent post-bronchodilator spirometry using a calibrated spirometer. Single-breath DLCO was measured in accordance with the 2017 ERS/ATS technical standards, with values corrected for hemoglobin and altitude; KCO was derived as DLCO per unit alveolar volume and expressed in absolute units [4]. Static lung volumes were recorded and the residual volume to total lung capacity (RV/TLC) ratio computed as an index of air trapping. The six-minute walk test was performed in a 30-meter flat corridor according to the 2014 ERS/ATS field-walking-test standard [14]. Two-dimensional echocardiography was performed to estimate pulmonary artery systolic pressure (PASP) and to confirm preserved left ventricular function.

Severity grading and definition of discordance

Airflow limitation was graded by GOLD spirometric stage (1–4). Gas-exchange impairment was graded from DLCO percent predicted using established ATS/ERS interpretative criteria [15]. For the concordance analysis, DLCO was collapsed into three bands: preserved/normal ($\geq 60\%$ predicted), mild-to-moderate impairment (40–59%), and severe impairment ($< 40\%$). Percent-predicted thresholds were applied deliberately—rather than the z-score-based severity descriptors of the 2022 ERS/ATS interpretative standard [16]—to preserve clinical interpretability and comparability with prior literature in this resource-limited setting. Discordance was defined as severe airflow limitation (GOLD 3 or 4) accompanied by preserved gas exchange (“disproportionate airflow obstruction”) or, conversely, severe gas-exchange impairment occurring at a milder spirometric grade (“disproportionate diffusion impairment”).

Statistical analysis

Data were analyzed using IBM SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA). Continuous variables were expressed as mean $\pm$ standard deviation (SD) and compared using the independent-samples Student t-test. Equality of variances was assessed by Levene's test; the pooled-variance t-test (degrees of freedom = 89) was used for between-cohort

comparisons, and Welch's correction was applied where variances were unequal. Categorical variables were summarized as frequencies and percentages and compared using the Pearson chi-square test, with Fisher's exact test where any expected cell count was below five. The relationship between GOLD stage and DLCO band was examined using cross-tabulated contingency (discordance) matrices stratified by smoking status. For each comparison, the relevant test statistic (t, chi-square, or—for Fisher's exact comparisons—the odds ratio [OR]) is reported alongside the p-value. A two-sided p-value below 0.05 was considered statistically significant.

To address potential confounding, multivariable linear regression models were fitted with DLCO percent predicted, KCO, RV/TLC and six-minute walk distance as dependent variables and exposure cohort as the variable of interest, adjusted for age, sex and body mass index, and in a further model for FEV1 percent predicted. Logistic regression modelled the probability of a preserved DLCO ($\geq 60\%$ predicted) using the same covariate sets. Collinearity was assessed by the variance inflation factor, with a sensitivity analysis restricted to women. Dose–response was examined by correlating cumulative exposure with DLCO percent predicted.

Results

Study population and exposure characteristics

Ninety-one patients with stable COPD were enrolled, comprising 54 (59.3%) in the S-COPD cohort and 37 (40.7%) in the NS-COPD cohort. The mean age of the overall population was 60.2 ± 9.4 years, with no significant difference between cohorts (59.8 ± 9.7 versus 60.7 ± 9.0 years; $t(89)=0.45$, $p=0.657$). The smoking cohort had a heavy cumulative tobacco burden (mean 32.9 ± 12.1 pack-years) with negligible biomass exposure, whereas the non-smoking cohort had substantial biomass exposure (mean 73.0 ± 18.3 hour-years) and no tobacco history, confirming a clean separation of etiologies. Consistent with the gendered division of domestic cooking labor in this region, the smoking cohort was predominantly male (49/54, 90.7%) and the biomass cohort predominantly female (32/37, 86.5%; Fisher's exact $p<0.001$). Demographic and exposure characteristics are summarized in Table 1.

Comparative physiological phenotype

The two cohorts differed markedly across all key physiological domains (Table 2). Compared with smokers, non-smokers had a significantly higher body mass index (BMI; 28.0 ± 3.4 versus 21.5 ± 2.9 kg/m²; mean difference 6.5 kg/m², 95% CI 5.2 to 7.8; $t(89)=9.79$, $p<0.001$) and

higher FEV1 percent predicted (57.8 ± 9.1 versus 43.7 ± 11.5 ; mean difference 14.1, 95% CI 9.6 to 18.6; $t(89)=6.24$, $p<0.001$). Crucially, gas exchange was substantially better preserved in non-smokers: mean DLCO was $71.4 \pm 12.4\%$ predicted versus $57.7 \pm 17.5\%$ in smokers (mean difference 13.7 percentage points, 95% CI 7.1 to 20.3; $t(89)=4.10$, $p<0.001$), and KCO was 0.95 ± 0.19 versus 0.71 ± 0.22 mmol/min/kPa/L (mean difference 0.24, 95% CI 0.151 to 0.329; $t(89)=5.33$, $p<0.001$). Non-smokers also showed less air trapping (RV/TLC 0.52 ± 0.06 versus 0.67 ± 0.09 ; mean difference -0.15 , 95% CI -0.185 to -0.115 ; $t(89)=8.50$, $p<0.001$) and a modestly greater six-minute walk distance (356.7 ± 41.1 versus 333.8 ± 55.6 m; mean difference 22.9 m, 95% CI 1.6 to 44.2; $t(89)=2.14$, $p=0.035$). Although statistically significant, this 22.9-m difference in six-minute walk distance lies at or just below the minimal clinically important difference (approximately 25–30 m) commonly cited for COPD, indicating that its clinical relevance is modest. The preserved KCO in the non-smoking cohort indicates that, at an equivalent GOLD spirometric stage, the integrity of the alveolar–capillary membrane was largely maintained even where airflow obstruction was severe.

Concordance between spirometric severity and gas exchange

Cross-tabulation of GOLD stage against DLCO band revealed a striking divergence between cohorts (Tables 3 and 4). In the non-smoking cohort, all eight patients with severe airflow limitation (GOLD 3) retained normal or only mildly impaired diffusion (8/8, 100%), and seven of these eight (87.5%) had strictly normal DLCO ($\geq 60\%$ predicted). No non-smoker exhibited severe DLCO impairment at any spirometric grade. In sharp contrast, among smokers with GOLD 3 obstruction, 14 of 28 (50.0%) showed impaired gas exchange, including four (4/28, 14.3%) with severe DLCO impairment. The smoking cohort also displayed the opposite pattern of disproportionate diffusion impairment, with 2 of 19 (10.5%) GOLD 2 (moderate) smokers already demonstrating severe DLCO impairment—evidence of significant emphysematous destruction preceding severe airflow limitation. Thus, in non-smokers the severity implied by spirometry consistently overstated the degree of gas-exchange loss, whereas in smokers airflow limitation and diffusion loss tracked more closely and could even understate early emphysema. Non-smokers were significantly more likely than smokers to retain a normal DLCO ($\geq 60\%$ predicted; 31/37 [83.8%] versus 26/54 [48.1%]; Fisher's exact $p<0.001$; OR 5.6, 95% CI 2.0 to 15.5), and severe diffusion impairment occurred in eight smokers (8/54, 14.8%) but in no non-smoker (0/37; Fisher's exact $p=0.019$). Within the GOLD 3 subgroup, impaired gas exchange was more frequent in smokers (14/28, 50.0%) than in non-smokers (1/8, 12.5%;

Fisher's exact $p=0.10$); this subgroup comparison was descriptive and underpowered owing to the small number of non-smokers with severe airflow limitation.

Multivariable analysis and potential confounders

The between-cohort difference in gas exchange was not explained by demographic or anthropometric differences (Table 5). After adjustment for age, sex and body mass index, biomass exposure remained associated with a 15.1 percentage-point higher DLCO percent predicted (95% CI 2.8 to 27.5; $p=0.017$). Body mass index was not independently associated with DLCO (β -0.26 per kg/m^2 ; $p=0.629$), nor within either cohort separately (r -0.088 and 0.019 ; interaction $p=0.572$). Reduced air trapping persisted after adjustment (RV/TLC β -0.189 , 95% CI -0.255 to -0.123 ; $p<0.001$), whereas the difference in six-minute walk distance did not (β 5.1 m; $p=0.801$).

The divergence persisted when the cohorts were compared at an equivalent degree of airflow limitation. The odds of a preserved DLCO ($\geq 60\%$ predicted) in biomass-exposed patients relative to smokers were 5.6 (95% CI 2.0 to 15.5) unadjusted, 30.0 (95% CI 2.5 to 358.5; $p=0.007$) after adjustment for age, sex and body mass index, and 21.1 (95% CI 1.6 to 282.7; $p=0.021$) after further adjustment for FEV1 percent predicted; the continuous model was attenuated to borderline significance ($p=0.072$). Because sex and exposure type were strongly associated ($\phi=0.77$; VIF 3.52), these intervals are wide. Restricted to women, DLCO remained higher in the biomass cohort (71.9 ± 12.8 versus $51.0 \pm 13.6\%$ predicted; $p=0.009$).

Cumulative exposure intensity did not account for the findings: biomass hour-years were unrelated to DLCO in non-smokers ($r=-0.174$, $p=0.304$; adjusted $p=0.643$), as were pack-years in smokers ($r=-0.168$, $p=0.225$).

Pulmonary hemodynamics

Resting PASP did not differ significantly between patients with moderate (GOLD 2) and severe or very severe (GOLD 3/4) airflow limitation (41.2 ± 5.48 versus 39.3 ± 3.99 mmHg; $t(85.52)=1.822$, $p=0.072$), and preserved left ventricular function was confirmed across the cohort (mean left ventricular ejection fraction $51.7 \pm 5.2\%$). This argues against differential resting pulmonary hypertension between spirometric strata as a confounder of the observed phenotypic differences.

Discussion

In this rural South Indian cohort, smoking and biomass-related non-smoking COPD emerged as physiologically distinct entities, and the relationship between spirometric severity and gas-exchange impairment differed fundamentally between them. The central finding is that GOLD spirometric staging systematically overestimated the degree of parenchymal disease in NS-COPD: every non-smoker with severe (GOLD 3) airflow limitation retained normal or only mildly impaired diffusing capacity, with seven of eight showing strictly normal diffusion. In smokers, by contrast, airflow limitation and diffusion loss were more tightly coupled, and severe gas-exchange impairment could appear even at moderate spirometric grades. This dissociation has direct implications for how clinicians interpret a GOLD stage in a never-smoking, biomass-exposed patient.

Coupled versus uncoupled disease

The divergence is best explained by the differing nature of the inhalational insult. Cigarette and bidi smoke generate intense distal oxidative injury that destroys both the alveolar walls and the pulmonary capillary bed, producing emphysema in which airflow obstruction and diffusion loss arise together—a coupled process reflected in the smokers' low KCO and high RV/TLC. Biomass smoke, with its larger particulate load, tends to deposit more proximally and to drive chronic bronchitis, mucus hypersecretion, and peribronchiolar fibrosis while relatively sparing the alveoli [11,12]. The preserved KCO in our non-smokers is the physiological signature of this airway-predominant, uncoupled pattern: obstruction arises from airway narrowing and remodeling rather than tissue destruction, so the alveolar–capillary membrane—and hence DLCO—remains intact.

Comparison with existing literature

Our results align with and extend prior work describing biomass COPD as a distinct, more airway-centered and less emphysematous phenotype than tobacco COPD, frequently occurring in women with higher body mass and better-preserved diffusion [2,11,12]. In a large retrospective series of 499 patients, Golpe et al. similarly found that biomass-exposed patients had significantly higher body mass index and FEV1 percent predicted and a lower prevalence of the emphysema phenotype than tobacco-exposed patients (31.9% versus 45.9%) [17]—a pattern that closely parallels the higher BMI, higher FEV1, and preserved diffusion observed in our non-smokers. Olloquequi et al., comparing tobacco-, biomass-, and dual-exposed COPD,

likewise reported milder airflow obstruction and significantly higher DLCO in biomass COPD than in tobacco COPD, directly mirroring our central diffusion finding [18]. Together with the autopsy and computed-tomography literature describing predominant bronchiolar and bronchitic injury in wood-smoke exposure, these data support the interpretation that biomass-related obstruction is driven more by airway remodeling than by parenchymal destruction. Our observation of lower RV/TLC (i.e., less air trapping) in non-smokers, however, contrasts with the greater air trapping reported in biomass COPD by Camp et al. using quantitative computed tomography [11]. This divergence may reflect differences in the type and intensity of exposure (open-fire wood smoke in Latin American cohorts versus mixed household cooking-fuel use in our setting), differences in case mix and disease stage, or the inferential nature of a static lung-volume measure compared with direct imaging. It underscores that air-trapping behavior in biomass COPD remains unsettled and warrants direct, imaging-anchored comparison in future studies.

The choice of the functional parameter

A caveat in the present design deserves emphasis. The discordance is referenced to FEV1 and to the GOLD stage derived from it, yet FEV1 is itself an imperfect instrument for this purpose, for the reasons set out above. The uncoupling should therefore be understood as operating at two levels: one biological, reflecting a genuinely airway-predominant injury in biomass exposure, and one methodological, reflecting the limited capacity of a forced expiratory index to register parenchymal loss. Both converge on the same conclusion, that spirometric staging alone cannot indicate the structural state of the lung.

This is reinforced by recent evidence that the parameter chosen determines what is detected. Dal Negro et al., comparing functional indices against computed-tomography-quantified emphysema burden in stable COPD, found that the simultaneous single-breath sDLNO/sDLCO measurement and pulmonary capillary blood volume (Vc) identified the destructive component with greater sensitivity and specificity than standard spirometry [9]. Zavorsky et al. reported that DLCO alone may miss alveolar–capillary impairment and that the combined nitric oxide–carbon monoxide approach, expressed as summed z-scores, classified impairment more accurately [10]. These findings indicate that DLCO and KCO, the only diffusive indices available to us, represent a floor rather than a ceiling of diagnostic sensitivity, and that sDLNO/sDLCO and Vc merit application in biomass-exposed populations.

Treatable traits and developmental factors

Incorporating DLCO and KCO allows treatable traits to be separated: vascular and emphysematous loss predominant in smokers versus airway-predominant disease with preserved gas exchange predominant in biomass COPD [19,20]. A developmental contribution, such as dysanapsis or lower attained lung function, may further explain how non-smokers reach a severe GOLD grade without commensurate parenchymal loss [21]. The clean exposure separation in our cohort—heavy pack-year smokers with negligible biomass exposure versus high-index biomass users with no tobacco history—strengthens the attribution of these physiological differences to the type of inhalational injury rather than to confounding mixed exposures [22-25].

Clinical implications

These findings expose a diagnostic blind spot in the spirometry-only management of non-smoking COPD. Labeling a biomass-exposed patient as having severe disease purely on FEV1 risks both prognostic miscommunication and inappropriate escalation toward therapies aimed at emphysema and hyperinflation, when the dominant treatable trait is airway disease. Conversely, a near-normal FEV1 in a smoker does not exclude advanced emphysema, as a notable minority of moderate-grade smokers in this study already had severe diffusion loss. In resource-limited rural settings where high-resolution computed tomography (HRCT) is rarely feasible, DLCO—though underused in rural India—is markedly less costly and more deployable than HRCT and could be scaled to district hospitals.

Limitations

Several limitations should be acknowledged. First, the cross-sectional design captures a single time point and cannot establish the temporal trajectory implied by the uncoupled hypothesis; longitudinal study is required. Second, hospital-based recruitment may have skewed the sample toward more advanced disease (selection bias). Third, the cohorts were demographically bifurcated by sex (49/54 [90.7%] male in S-COPD versus 32/37 [86.5%] female in NS-COPD; Fisher's exact $p < 0.001$), reflecting regional reality but introducing potential sex-related confounding of lung function that cannot be fully disentangled from exposure type; multivariable models adjusting for age, sex and body mass index have now been fitted (Table 5) and the principal findings were unchanged, although the close association between sex and exposure type ($\phi = 0.77$) means their contributions cannot be fully separated.

Fourth, anatomical confirmation by HRCT was not performed, so emphysema was inferred physiologically rather than imaged. Fifth, severity was classified using percent-predicted DLCO bands rather than the z-score-based descriptors recommended in the 2022 ERS/ATS interpretative standard [16]; although percent-predicted thresholds remain widely used and clinically intuitive, they may misclassify severity at the extremes of age and height. Sixth, no formal sample-size or power calculation was performed; the study enrolled consecutive eligible patients over a fixed period, and the small number of non-smokers with severe airflow limitation limited the power of within-stage subgroup comparisons. Seventh, the true Tiffeneau ratio (FEV1 to slow vital capacity), which is more informative about elastic recoil than FEV1/FVC, was not measured. Eighth, gas exchange was assessed by DLCO and KCO alone, whereas sDLNO/sDLCO and pulmonary capillary blood volume detect the destructive component of COPD more sensitively [9,10]; mild parenchymal involvement may therefore have been under-detected in the biomass cohort, and the degree of uncoupling reported here should be regarded as an upper estimate. Ninth, residual confounding by unmeasured factors cannot be excluded. Finally, the single-center design and region-specific biomass practices may limit generalizability to other populations.

Conclusions

In this rural South Indian cohort, biomass-related non-smoking COPD and smoking COPD were physiologically distinct, and spirometric severity tracked gas-exchange impairment very differently in the two groups. GOLD staging consistently overstated parenchymal disease in non-smokers, in whom severe airflow limitation coexisted with preserved diffusing capacity, whereas in smokers obstruction and diffusion loss were more closely coupled. Reliance on FEV1 alone therefore creates a diagnostic blind spot that can misclassify biomass-related COPD. Routine incorporation of DLCO and KCO is needed to phenotype these patients accurately and, in resource-limited settings, provides a practical low-cost alternative to structural imaging. These conclusions should be read with the limitations of the reference parameter in mind: because FEV1 discriminates poorly between obstructive and destructive damage, part of the discordance reflects the insensitivity of spirometry itself, which strengthens rather than weakens the case against spirometry-only staging. The divergence persisted after adjustment for age, sex, body mass index and FEV1 percent predicted, and more sensitive indices such as sDLNO/sDLCO and Vc merit evaluation in biomass-exposed populations [9,10].

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Table 1. Demographic and exposure characteristics of the two cohorts

Characteristic	S-COPD (n=54)	NS-COPD (n=37)	Test statistic	p-value
Age, years	59.8 ± 9.7	60.7 ± 9.0	t(89) = 0.45	0.657
Male sex, n (%)	49 (90.7)	5 (13.5)	Fisher's exact (OR 62.7)	<0.001
Female sex, n (%)	5 (9.3)	32 (86.5)	—	—
Tobacco exposure, pack-years	32.9 ± 12.1	0	—	—
Biomass exposure, hour-years	1.8 ± 1.0	73.0 ± 18.3	—	—

Values are mean ± standard deviation (SD) unless otherwise stated. Sex distribution compared by Fisher's exact test. S-COPD, smoking COPD; NS-COPD, biomass-related non-smoking COPD; OR, odds ratio (for male sex, S-COPD versus NS-COPD); COPD, chronic obstructive pulmonary disease.

Table 2. Comparison of physiological parameters between smokers and non-smokers

Parameter	S-COPD (n=54)	NS-COPD (n=37)	t (df = 89)	p-value
Body mass index (kg/m ²)	21.5 ± 2.9	28.0 ± 3.4	9.79	<0.001
FEV1 (% predicted)	43.7 ± 11.5	57.8 ± 9.1	6.24	<0.001
DLCO (% predicted)	57.7 ± 17.5	71.4 ± 12.4	4.10	<0.001
KCO (mmol/min/kPa/L)	0.71 ± 0.22	0.95 ± 0.19	5.33	<0.001
RV/TLC ratio	0.67 ± 0.09	0.52 ± 0.06	8.50	<0.001
6-minute walk distance (m)	333.8 ± 55.6	356.7 ± 41.1	2.14	0.035

Values are mean ± standard deviation (SD); between-group comparisons by independent-samples Student t-test (pooled variance, df = 89). FEV1, forced expiratory volume in 1 second; DLCO, diffusing capacity of the lung for carbon monoxide; KCO, transfer coefficient (DLCO per unit alveolar volume); RV/TLC, residual volume to total lung capacity ratio.

Table 3. Spirometry–diffusion discordance in smokers (n=54): GOLD stage versus DLCO band

GOLD stage	Normal DLCO (≥60%)	Mild–moderate (40–59%)	Severe (<40%)
GOLD 1 (mild)	0	0	0
GOLD 2 (moderate)	11	6	2
GOLD 3 (severe)	14	10	4
GOLD 4 (very severe)	1	4	2

Values are numbers of patients. DLCO bands are expressed as percent predicted. GOLD, Global Initiative for Chronic Obstructive Lung Disease; DLCO, diffusing capacity of the lung for carbon monoxide. Between-cohort comparison of normal (≥60%) versus impaired (<60%) DLCO: Fisher's exact p<0.001 (see Table 4).

Table 4. Spirometry–diffusion discordance in non-smokers (n=37): GOLD stage versus DLCO band

GOLD stage	Normal DLCO (≥60%)	Mild–moderate (40–59%)	Severe (<40%)
GOLD 1 (mild)	0	0	0
GOLD 2 (moderate)	24	5	0
GOLD 3 (severe)	7	1	0
GOLD 4 (very severe)	0	0	0

Values are numbers of patients. DLCO bands are expressed as percent predicted. GOLD, Global Initiative for Chronic Obstructive Lung Disease; DLCO, diffusing capacity of the lung for carbon monoxide. Compared with smokers, non-smokers more frequently retained a normal DLCO (31/37 [83.8%] versus 26/54 [48.1%]; Fisher's exact p<0.001; OR 5.6, 95% CI 2.0–15.5).

Table 5. Multivariable models of gas exchange and lung mechanics, biomass-related versus tobacco-related COPD (n=91)

Model	Effect estimate (95% CI)	p-value
Linear regression: β for biomass versus tobacco exposure		
DLCO (% predicted), unadjusted	13.70 (7.07 to 20.33)	<0.001
DLCO (% predicted), adjusted for age, sex, BMI	15.12 (2.77 to 27.47)	0.017
DLCO (% predicted), adjusted for age, sex, BMI, FEV1 (% predicted)	12.44 (−1.13 to 26.00)	0.072
KCO (mmol/min/kPa/L), adjusted for age, sex, BMI	0.122 (−0.046 to 0.291)	0.153
RV/TLC, adjusted for age, sex, BMI	−0.189 (−0.255 to −0.123)	<0.001
6-minute walk distance (m), adjusted for age, sex, BMI	5.07 (−34.71 to 44.85)	0.801
Logistic regression: odds ratio for preserved DLCO ($\geq 60\%$ predicted), biomass versus tobacco exposure		
Unadjusted	5.56 (2.00 to 15.50)	0.001
Adjusted for age, BMI	12.03 (2.38 to 60.93)	0.003
Adjusted for age, sex, BMI	30.04 (2.52 to 358.53)	0.007
Adjusted for age, sex, BMI, FEV1 (% predicted)	21.08 (1.57 to 282.69)	0.021
Covariate coefficients within the DLCO (% predicted) model (n=91; $R^2 = 0.200$)		
Biomass exposure (versus tobacco)	15.12 (2.77 to 27.47)	0.017
Age, per year	0.36 (0.005 to 0.709)	0.047
Female sex	−0.11 (−10.62 to 10.41)	0.984
Body mass index, per kg/m ²	−0.26 (−1.30 to 0.79)	0.629

β , unstandardized regression coefficient; CI, confidence interval; BMI, body mass index; DLCO, diffusing capacity of the lung for carbon monoxide; KCO, transfer coefficient; RV/TLC, residual volume to total lung capacity ratio; FEV1, forced expiratory volume in 1 second. The reference category is smoking COPD, so a positive coefficient or an odds ratio above 1 denotes a higher value in the biomass-related non-smoking cohort. Sex and exposure type were strongly associated in this cohort ($\phi=0.77$; variance inflation factor for exposure 3.52), so the coefficient for sex is not independently interpretable and the confidence intervals of the adjusted odds ratios are wide.