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Association between reduced mid-expiratory flow and early airway impairment in smokers with preserved spirometry: a cross-sectional analysis*

Abdurrahman Koç[1]*, Abdullah Enes Ataş[2], Hasan Eryeşil[3]

[1]*Department of Pulmonary Medicine, Meram State Hospital, Konya, Turkiye*

[2]*Department of Radiology, Faculty of Medicine, Necmettin Erbakan University, Konya, Turkiye*

[3]*Department of Radiology, Tatvan State Hospital, Bitlis, Turkiye*

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ABSTRACT

Aims: To determine whether active smokers with preserved post-bronchodilator spirometry ($FEV_1/FVC \geq$ lower limit of normal [LLN]) and normal thoracic computed tomography (CT) show lower $FEF_{25–75}$ values and a higher prevalence of isolated small airway dysfunction than never-smokers, and to assess PEF-FEV_1 agreement for Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity staging.

Methods: We analysed spirometry data from 286 consecutive adults (≥40 years) at a single pulmonary function laboratory. Two chest radiologists independently reviewed all thoracic CT scans (ICC=0.95). Logistic regression included FVC z-score as a pre-specified covariate to account for the volume-dependence of FEF_{25-75}; model stability was confirmed by penalised regression and bootstrap validation.

Results: Among 244 participants with preserved FEV_1/FVC (136 smokers, 108 never-smokers), $FEF_{25–75}$ was lower in smokers (76.2±26.1% vs 93.5±21.9%; p<0.001; rank-biserial r=0.40). Isolated Spirometric small airway dysfunction (sSAD) prevalence was 28.7% versus 4.6% (OR 8.28; p<0.001). After FVC z-score adjustment, smoking remained the strongest predictor (aOR 13.15; 95% CI 4.07-42.42; optimism-corrected AUC=0.848). Female smokers showed greater impairment than males despite equivalent pack-year exposure (66.3% vs 80.9%; p<0.001), and combined biomass-plus-smoking exposure carried the highest sSAD prevalence (58.1%). PEF showed poor agreement with FEV_1 for GOLD staging (unweighted κ=0.095; mean bias -20.0%).

Conclusion: Active smoking is independently associated with spirometric small airway dysfunction before FEV_1/FVC falls below the LLN, with women and biomass co-exposed individuals at greatest risk. PEF cannot replace FEV_1 for GOLD severity classification in this population.

Keywords: $FEF_{25–75}$, small airway disease, pre-COPD, peak expiratory flow, spirometry

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is among the leading causes of death worldwide. By current knowledge, the 2025 Global Initiative for Chronic Obstructive Lung Disease (GOLD) report states: the majority of individuals destined to develop COPD will have already sustained important and frequently irreversible airway damage by the time post-bronchodilator spirometry will show an abnormality[1] A high proportion of smokers with preserved FEV_1/FVC have radiological and functional lung abnormalities, not detectable with conventional imaging or spirometry, but detectable with high-resolution Computed tomography (CT) scans or more sensitive spirometric indices.[2] The term "pre-COPD" was used to refer to smokers with respiratory symptoms or structural and functional lung abnormalities (eg, CT emphysema, reduced diffusing capacity, and small airway dysfunction), but no spirometric airflow obstruction.[3,4] A closely related but distinct phenotype is preserved ratio impaired spirometry (PRISm) defined as $FEV_1/FVC \geq LLN$ and FEV_1<80% predicted. PRISm phenotype is associated with increased all-cause mortality, increased cardiovascular events, and a progression to spirometric COPD in ~20% of cases.[5]

$FEF_{25–75}$ reflects expiratory flow rates towards the end of an FVC maneuver, and is more sensitive than ratio measurements of peripheral airway obstruction such as FEV_1/FVC, yet $FEF_{25–75}$ may be reduced before the decrease in the FEV_1/FVC ratio falls below the LLN. Isolated spirometric Spirometric small airway dysfunction (sSAD) (defined by a $FEF_{25–75}$ z-score less than -1.645 and an FEV_1/FVC above the LLN) has been linked to the future development of COPD, with hazard

***Corresponding Author:** Abdurrahman Koç, koc.abdurrahman@gmail.com

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ratios ranging from 1.57 to 3.01.[6] sSAD may also be associated with chronic bronchitis, and an increased prevalence of smokers with chronic bronchitis was detected in the presence of sSAD.[7] Micro-CT studies show that the process has already started in spirometrically normal lungs.[8,9]

In SPIROMICS, FEF_{25-75} was associated with emphysema, gas trapping, and functional small airways disease, as assessed by PRM.[10,11] In a study of Tasmanian adults, pre-bronchodilator FEV_1/FVC at the 10th percentile predicted a 36-fold higher risk of incident COPD over 8 years. The GOLD strategy of 2025 now recommends the use of pre-bronchodilator spirometry for case finding in pre-COPD.[1,12]

In resource-limited settings, PEF is used instead of FEV_1 in staging GOLD severity. However, it is unknown whether this practice is valid in a population with preserved normal lung function, where pre-COPD screening is of greatest interest. We performed a cross-sectional comparison of FEF_{25-75} and isolated sSAD prevalence between active smokers and never smokers with preserved FEV_1/FVC and normal thoracic CT, in order to evaluate the PEF-FEV_1 agreement for staging GOLD severity in this target group. Regression analysis was adjusted for FVC z-score, which was kept in the model a priori to account for the volume-dependent and flow-dependent component of the FEF_{25-75} signal.

METHODS

Ethics

This study was conducted with the approval of the Karatay University Ethics Committee for Non-pharmaceutical and Non-medical Device Researches (Date: 27.11.2025, Decision No: 2025/014). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This cross-sectional retrospective study was performed between 15 May 2024 and 1 November 2025 using data obtained from the pulmonary function testing laboratory of a secondary care state hospital in a metropolitan city in Turkiye.

We included subjects aged ≥40 years who had technically acceptable and reproducible spirometry (meeting 2019 ATS/ERS criteria) performed within 12 months preceding thoracic CT and showed no evidence of emphysema, airway wall thickening or chronic bronchitis on CT.[15] We excluded subjects with obstructive airway disease, interstitial lung disease, restrictive ventilatory defect (FVC<LLN with preserved FEV_1/FVC), acute respiratory symptoms within the previous four weeks, and incomplete smoking status. Former smokers were excluded from all primary analyses due to variable cessation periods.

The qualifying CT examinations had been requested for a range of clinical reasons, including pulmonary nodule and emphysema screening, evaluation of cough, dyspnoea, chest pain or lower respiratory tract infection, and other indications. Referrals came from the emergency department, the pulmonology outpatient clinic and other outpatient services. Because indications were not coded uniformly in the source records, we could not retrieve an exact count for each category, and referring indication was not used as a selection criterion.

Spirometry was performed with a BTL spirometer (BTL Industries, Prague, Czech Republic) calibrated daily with a 3-L syringe. Manoeuvres were performed before and 15 minutes after inhalation of 400 µg salbutamol; post-bronchodilator values constituted the primary analysis. FVC, FEV_1, FEV_1/FVC and FEF_{25-75} were reported as percent predicted and z-scores using GLI-2012 multi-ethnic prediction equations.[16] PEF predicted values and LLN were calculated using NHANES III reference equations, as GLI-2012 does not provide PEF reference values.[17] Pre-bronchodilator measurements are detailed in **Supplementary Table S1**.

Supplementary Table S1. Pre-bronchodilator vs post-bronchodilator FEF_{25-75} analysis (active smokers vs never-smokers, n=244)

Parameter	Active smokers (n=136)	Never-smokers (n=108)	p-value
Pre-BD FEF_{25-75} (% pred), mean±SD	86.1±31.9	102.6±25.4	<0.001*
Pre-BD FEF_{25-75} (% pred), median [IQR]	92.0 (61.8-105.0)	101.5 (87.8-117.0)	—
Pre-BD isolated SAD, n (%)	19 (14.0%)	1 (0.9%)	<0.001†
Pre→Post BD FEF_{25-75} change, mean±SD	-9.9±8.8%	-9.1±7.5%	<0.001‡

*Mann-Whitney U; Cohen's d=-0.574. †Fisher's exact; OR=17.38 (95% CI 2.28-132.5). ‡Wilcoxon signed-rank (within-group). The parallel pre-to-post decrement in both groups reflects bronchodilator-induced FVC expansion shifting the 25-75% sampling window, not differential pharmacological responsiveness. BD: Bronchodilator; IQR: Interquartile range, Pred: Predicted, SAD: Small airway dysfunction, SD: Standard deviation

Two chest radiologists (each ≥8 years of thoracic imaging experience) reviewed CT scans independently, blinded to spirometric data (ICC=0.95, 95% CI 0.907-0.969). Scans were visually assessed for emphysema, airway wall thickening or chronic bronchitis using qualitative criteria; quantitative CT analysis was not performed. Paired expiratory images for gas trapping assessment were not routinely available; participants are therefore characterised as having macroscopic structural disease excluded rather than subclinical abnormality ruled out. Biomass exposure was defined as using wood, crop residues, or animal dung as primary household fuel for ≥10 years, following the PLATINO study definition.[18]

Analysis of PEF and FEV_1 Agreement

FEV_1 and PEF percent predicted values were classified into Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stages (Stage 1, ≥80%; Stage 2, 50-79%; Stage 3, 30-49%; Stage 4, <30%). All values were derived from the same post-bronchodilator manoeuvre. Agreement was assessed using Pearson's correlation, unweighted, linear weighted and quadratic weighted Cohen's κ, and the Bland-Altman method.[14] A sensitivity analysis was performed in 13 active smokers with obstructive FEV_1/FVC.

Statistical Analysis

Normality was tested using the Shapiro-Wilk test. As FEF_{25-75} values were non-normally distributed, group differences were tested with Mann-Whitney U tests with rank-biserial correlation as effect size. Logistic regression was performed to identify independent predictors of isolated reduced mid-

expiratory flow, with FVC z-score included a priori to account for volume-dependence of FEF_{25-75}. Model performance was assessed by calibration (Hosmer-Lemeshow test), multicollinearity testing, and discrimination (bootstrap-corrected AUC); penalised logistic regression confirmed robustness given the borderline events per variable. Sensitivity analyses included standing height and mMRC dyspnoea score. Sex-stratified estimates and a smoking-by-sex interaction term were specified as secondary analyses. Pack-years were analysed only among smokers (undefined in never-smokers). All analyses were conducted in Python 3.10 (SciPy 1.11, statsmodels 0.14). Post-hoc power analysis confirmed sufficient power for the primary comparison.

RESULTS

Study Population

Among 286 subjects with qualifying CT, 244 had well-preserved FEV_1/FVC, 136 were current smokers, and 108 were never-smokers (**Figure 1**). Fourteen former smokers and 28 with obstructive FEV_1/FVC were excluded, leaving 244 well-preserved FEV_1/FVC subjects for the analysis. The 13 active smokers with obstructive FEV_1/FVC defined the obstructive sensitivity group for the PEF-FEV_1 pair. Mean age was similar in both groups (55.4±11.4 vs 55.8±11.9 years; p=0.81). The median FVC percent predicted was also similar between groups (93.0% vs 94.5%, p=0.77). However, the majority of smokers were men, comprising 67.6% of smokers, as opposed to 32.4% of never-smokers (p<0.001; **Table 1**).

Primary outcome: FEF_{25-75} Comparison

Post-bronchodilator FEF_{25-75} was lower in smokers than in never-smokers (76.2±26.1% vs. 93.5±21.9%; median 81.5 [IQR 50.8-90.5] vs. 94.0% [IQR 80.8-106.2]; p<0.001). Compared to never-smokers, the frequency of sSAD in smokers with a

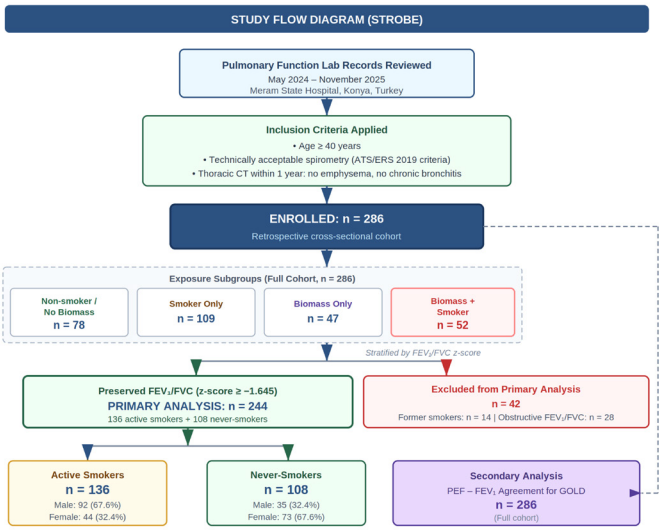


Figure 1. STROBE flow diagram. Of 286 participants with qualifying thoracic CT (reviewed by two independent chest radiologists; ICC=0.95, 95% CI 0.907-0.969), 42 were excluded: 14 former smokers and 28 with obstructive FEV_1/FVC. The primary analysis cohort comprised 244 participants: 136 active smokers and 108 never-smokers with preserved FEV_1/FVC

CT: Computed tomography, ICC: Intra-class correlation coefficients, CI: Confidence interval, FEV_1: Forced expiratory volume 1 s, FVC: Forced vital capacity

FEF_{25-75} z-score <-1.645 and normal FEV_1/FVC was greater (28.7% [39/136] vs. 8.8% [11/125]) (OR=4.04, 95%CI 1.97-8.29, p<0.001; d=-0.72; rrb=-0.398). Prevalence of isolated sSAD was 4.6% [5/108]; OR 8.28, 95% CI 3.14-21.88; p<0.001 (**Figure 2A**). Among smokers, isolated sSAD was seen in 13/93 (14.0%) non-biomass exposed and 25/43 (58.1%) biomass exposed, giving an overall prevalence of 28.7% (**Table 2**, **Figure 2A**).

Pre-Bronchodilator Spirometric Comparison

The group difference was present prior to bronchodilator: Pre-BD FEF25-75% was lower in smokers than in never-smokers (86.1±31.9% vs 102.6±25.4%; p<0.001, Cohen's d=-

Table 1. Baseline characteristics of the primary analysis cohort (n=244)

Characteristic	Active smokers (n=136)	Never-Smokers (n=108)	p-value
Demographics			
Age (years)	55.4±11.4 | 52 (47-63)	55.8±11.9 | 55 (45.5-66)	0.811
BMI (kg/m²)	28.5±4.1 | 28.5 (26.3-31.3)	30.4±6.7 | 29.5 (25.5-35.7)	0.052
Male sex, n (%)	92 (67.6)	35 (32.4)	<0.001*
Height (cm)	170 (164.8-175.2)	160 (155.0-166.0)	<0.001*
Exposure history			
Pack-years	29.3±13.9 | 30 (20-40)	—	—
Biomass exposure, n (%)	43 (31.6)	46 (42.6)	0.073
Post-bronchodilator spirometry			
FVC (% predicted)	94.5±14.9 | 93.0 (83-104)	95.1±13.9 | 94.5 (84.8-106)	0.773
FEV_1 (% predicted)	95.1±18.1 | 96.0 (83-109)	103.9±14.4 | 103.0 (95.8-114)	<0.001*
★FEF_{25-75} (% predicted)	76.2±26.1 | 81.5 (50.8-90.5)	93.5±21.9 | 94.0 (80.8-106.2)	<0.001*
PEF (% predicted)	76.1±24.0 | 71.0 (60-91)	83.7±20.4 | 84.5 (65.8-102)	0.004*
Clinical features			
Chronic cough/sputum, n (%)	96 (70.6)	56 (51.9)	0.003*
Dyspnoea, n (%)	77 (56.6)	34 (31.5)	<0.001*
mMRC score, median (IQR)	1 (0-2)	0 (0-1)	<0.001*

Mean±SD (median [IQR]) for continuous; n (%) for categorical. *p<0.05. Mann-Whitney U for continuous; χ^2 for categorical. ★ Primary outcome (r_rb=−0.398, large effect). BMI: Body-mass index, FEF_{25-75}: Forced expiratory flow 25-75%;-, FEV_1: Forced expiratory volume 1 s, FVC: Forced vital capacity, PEF: Peak expiratory flow, IQR: Interquartile range; mMRC: Modified Medical Research Council, IQR: Interquartile range

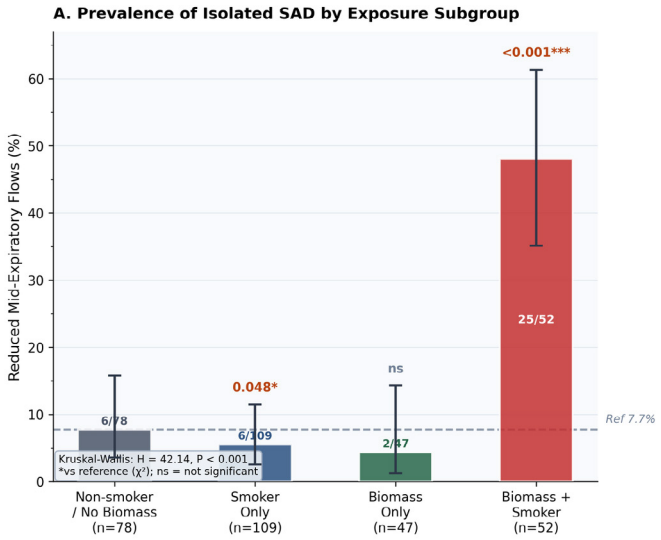


Figure 2A. Prevalence of isolated small airway dysfunction (FEF_{25-75} z-score<-1.645 with preserved FEV_1/FVC) by exposure subgroup, using primary-cohort denominators (n=244): Non-smoker/No Biomass 3/62 (4.8%), Smoker Only 14/93 (15.1%), Biomass Only 2/46 (4.3%), Biomass+Smoker 25/43 (58.1%). Error bars show 95% confidence intervals.

SAD: Small airway dysfunction, FEF_{25-75}: Forced expiratory flow 25-75%, FEV_1: Forced expiratory volume 1 s, FVC: Forced vital capacity

Table 2. FEF_{25-75} by exposure subgroup (full cohort, n=286) and isolated sSAD prevalence (primary cohort, n=244)

Subgroup	n	FEF_{25-75} mean±SD	Isolated sSAD n (%)	p vs ref
Non-smoker/no biomass	62	94.5±22.3	3 (4.8%)	Reference
Smoker only	93	80.9±26.1	14 (15.1%)	0.043*
Biomass only	46	88.0±18.8	2 (4.3%)	0.156
★ Biomass+smoker	43	66.0±39.2	25 (58.1%)	<0.001*

All n values and isolated sSAD prevalences restricted to the primary analysis cohort (n=244; preserved FEV_1/FVC). Former smokers (n=14) and participants with obstructive FEV_1/FVC (n=28) excluded. Kruskal-Wallis, H=42.14, p<0.001 (FEF_{25-75} across groups). ★ Highest-risk phenotype. sSAD: Spirometric small airway dysfunction. p vs Reference (isolated sSAD): Smoker Only p=0.043; Biomass Only p=0.897; Biomass+Smoker p<0.001 (Fisher exact), FEF_{25-75}: Forced expiratory flow 25-75%

0.574). Pre-BD isolated sSAD was present in 14.0% (19/136) of smokers and in 0.9% (1/108) of never-smokers (OR 17.38; p<0.001; Fisher's exact). See **Supplementary Table S1**. Post-bronchodilator FEF_{25-75} was lower than pre-bronchodilator in both smokers (mean difference -9.9±8.8%, Wilcoxon p<0.001) and never-smokers (-9.1±7.5%, p<0.001). This is an expected volume artifact: salbutamol increases FVC, which moves the 25-75% sampling window to a lower flow region, such that the FEF_{25-75} is lower in the absence of any change in small airway resistance. Since this decrement was the same in both groups pre-bronchodilator, the between-group difference is thought to represent fixed airway damage rather than reversible bronchoconstriction.

Logistic Regression: FVC Z-Score Adjusted Model

Active smoking was the strongest independent predictor of isolated sSAD (aOR 13.15; 95% CI 4.07 to 42.42; p<0.001) (**Table 3**). The smoking odds ratio increased from 8.28 to 13.15 on adjustment for FVC z-score, supporting that the difference in FEF_{25-75} could not be explained merely by a reduction in lung volume. After controlling for potential confounding, both biomass exposure and FVC z-score were independently associated with sSAD (aOR 6.67, 95% CI 2.02-22.04; p=0.002 and aOR 0.45, 95% CI 0.27-0.73; p=0.001, respectively). The

Table 3. Logistic regression: predictors of isolated reduced mid-expiratory flows (n=244)

Variable	Univariable OR (95% CI)	p	aOR† (95% CI)	p
★Active smoking	8.28(3.14-21.88)	<0.001*	13.15 (4.07-42.42)	<0.001*
Age (per year)	1.06(1.03-1.09)	<0.001*	1.01 (0.96-1.06)	0.780
BMI (per kg/m^2)	0.98(0.92-1.04)	0.570	0.95 (0.87-1.05)	0.313
Female sex	0.99(0.51-1.90)	0.974	1.32 (0.55-3.18)	0.540
Biomass exposure	5.12(2.53-10.35)	<0.001*	6.67 (2.02-22.04)	0.002*
‡ FVC z-score		—	0.45 (0.27-0.73)	0.001*

★ Primary predictor. ‡ Pre-specified volume-dependence covariate. † Adjusted for all listed variables. Discrimination: bootstrap optimism-corrected AUC 0.848. Sensitivity analysis adjusting for mMRC: Smoking aOR 2.52 (95% CI 0.58-10.90, p=0.21), mMRC is positioned as a mediator from smoking to sSAD in the pre-specified DAG (Supplementary Figure S1), so the model without mMRC is the primary analysis, OR: Odds ratio, Aor: Adjusted odds ratio, CI: Confidence interval, BMI: Body-mass index, FVC: Forced vital capacity

negative association of FVC z-score with sSAD was expected given its inverse relationship with the probability of being below the FEF_{25-75} LLN (volume-dependence). Age, BMI, and sex were nonsignificant predictors. There was no collinearity detected (VIF<3.0 after mean-centering). The AUC was high (apparent 0.870; bootstrap optimism-corrected AUC 0.848, optimism 0.021) and L2-penalized regression had nearly identical discrimination (AUC=0.867). The model is stable given the borderline events-per-variable ratio (44/7=6.3), and a sensitivity analysis that included standing height (OR 0.98; p=0.43) showed that height was not associated with sSAD and did not confound the effect of smoking (aOR 12.82, p<0.001), suggesting that FVC z-score adequately captured anthropometric confounding. In a pre-specified sensitivity analysis adjusting for mMRC, the smoking aOR fell to 2.52 (95% CI 0.58 to 10.90; p=0.21), as discussed below.

Dose-Response Relationship Between Pack-Year Exposure and FEF_{25-75}

Among the 134 active smokers with pack-year data available, tobacco dose showed no association with postbronchodilator FEF_{25-75} (Pearson r=-0.087, p=0.316; Spearman r_s=-0.080, p=0.359; linear regression β=-0.165%/pack-year, R^2=0.008). There were no important differences between the tertiles of pack years in postbronchodilator FEF_{25-75} (Kruskal-Wallis H=0.41; p=0.815; **Supplementary Table S2**). This finding within the preserved-spirometry cohort suggests that peripheral airway disease may not scale with cumulative tobacco exposure for reasons discussed.

Supplementary Table S2. FEF_{25-75} by pack-year tertile in active smokers- dose-response analysis (n=134)

Pack-year tertile	n	FEF_{25-75} mean±SD (%)	FEF_{25-75} median (IQR) (%)
Low (<25 pack-years)	44	77.1±18.5	80.0 (66.0-90.0)
Mid (25–30 pack-years)	13	71.7±23.0	81.0 (43.0-90.0)
High (>30 pack-years)	77	76.1±30.3	83.0 (45.0-95.0)

Kruskal-Wallis H=0.41; p=0.815 (across tertiles). Pearson r=-0.087, p=0.316; Spearman r_s=-0.080, p=0.359. Linear regression: β=-0.165%/pack-year (R^2=0.008; p=0.316). Two participants with missing pack-year data excluded (n=134 analysed). FEF_{25-75}: Forced expiratory flow 25-75%, SD: Standard deviation, IQR: interquartile range.

Sex-Stratified Analysis

FEF_{25-75} was lower in female than in male smokers (66.3±19.1%; median 69 [48-83]% vs. 80.9±27.7%; median

86 [56-97]%; p=0.0006; |rrb|=0.366), but although pack-year exposure (p=0.386) and age were similar. Among never-smokers, FEF_{25-75} did not differ by sex (93.9±15.6% vs. 93.4±24.5%; p=0.956; **Figure 2B**). The pattern suggests that the sex difference in smokers is related to smoking rather than to baseline physiology, but the small female stratum limits how far this can be taken. A higher proportion of female than male smokers showed isolated sSAD (36.4% vs. 25.0%; χ^2=1.37; p=0.243), but this difference was not statistically significant and the analysis was underpowered (**Table 4**).

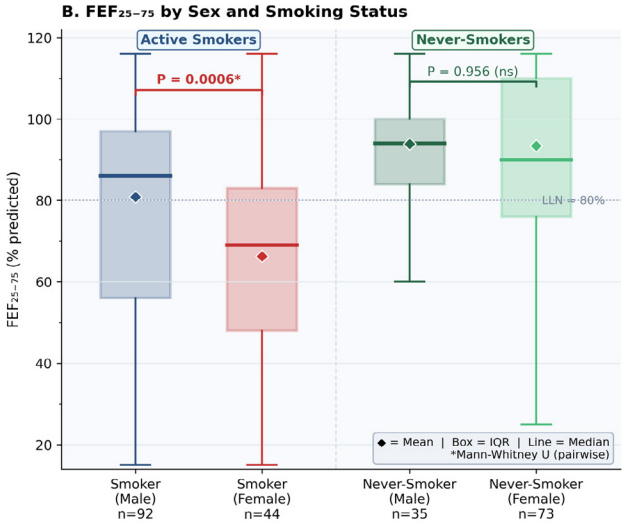


Figure 2B. Post-bronchodilator FEF_{25-75} distribution by sex and smoking status. Boxes represent the interquartile range; horizontal line, median; diamond, mean; whiskers, 1.5×IQR. Mann-Whitney U: female vs male smokers p=0.0006 (|rrb|=0.366); male vs female never-smokers p=0.956

FEF_{25-75}: Forced expiratory flow 25-75%, LLN: Lower limit of normal

In the female subgroup, active smoking was associated with isolated sSAD after adjustment (aOR 11.89, 95% CI 2.69-52.51; p=0.001; AUC 0.841; **Table 4**). In the male subgroup, complete separation prevented a stable adjusted estimate; Fisher's exact test gave a directional association (p=0.0005) but no usable point estimate. The smoking-by-sex interaction term was not statistically significant (p=0.999), and with only 44 female smokers the analysis had limited power to detect interaction (about 70% for an OR of 2.5). The apparent sex difference should therefore be read as suggestive rather than definitive.

PEF-to-FEV_1 Ratio as a GOLD Staging Tool

At the level of the population, PEF correlated only moderately with FEV_1 (Pearson r=0.578; r^2=0.334, p<0.001). At the level of individual patients, agreement between GOLD stages was poor: unweighted kappa =0.095 (slight); linear weighted kappa =0.183 (slight); quadratic weighted kappa =0.300 (fair). Of the 286 patients classified by both methods, 146 (51.0%) were concordant. In 139 of 140 clashing patients (99.3%) PEF classified disease severity higher than CAT class. Of 252 GOLD stage 1 patients, 120 (47.6%) were misclassified as more severe by PEF. The Bland-Altman plot showed a systematic bias of -20.0% (95% CI: -22.2% to -17.7%) with limits of agreement of 76 percentage points (-58.1% to+18.2%) (**Figure 3**). The obstructive

Figure 3A. PEF-FEV_1 agreement analysis, full cohort (n=286). Bland-Altman plot of differences (PEF-FEV_1, % predicted) against their means. Solid line: mean bias (-20.0%, 95% CI -22.2 to -17.7%); dashed lines: 95% limits of agreement (-58.1% to+18.2%). Points are colour-coded by FEV_1-based GOLD stage: green, Stage 1 (n=252); amber, Stage 2 (n=32); red, Stage 3 (n=2)

PEF: Peak expiratory flow, GOLD: Global Initiative for Chronic Obstructive Lung Disease

Table 4. Sex-stratified analysis of FEF_{25-75}, isolated sSAD prevalence, and logistic regression

	Active smokers		Never-smokers	
Parameter	**Male (n=92)**	**Female (n=44)**	**Male (n=35)**	**Female (n=73)**
Age (years), mean±SD	54.5±10.6	57.3±12.7	55.8±11.9	55.8±11.9
Pack-years, mean±SD	30.1±14.4	27.6±12.8	—	—
FEF_{25-75} (% pred), mean±SD †	80.9±27.7	66.3±19.1	93.9±15.6	93.4±24.5
FEF_{25-75} (% pred), median (IQR)	86 (56-97)	69 (48-83)	94 (84-100)	90 (76-110)
Isolated sSAD, n (%)	23 (25.0)	16 (36.4)	0 (0.0)	5 (6.8)
Female vs male smokers: p=0.0006, |rrb|=0.366; sSAD χ^2=1.365, p=0.243				
Logistic regression: Active smoking as predictor of isolated sSAD				
	Male subgroup (n=127; events=23)		**Female subgroup (n=117; events=21)**	
	Estimate	**p**	**Estimate**	**p**
Active smoking (aOR [95% CI])	Complete separation ‡	—	11.89 (2.69-52.51)	0.001
Fisher's exact test	p=0.0005		—	
Model AUC	N/A		0.841	

† Primary outcome variable. ‡ Complete separation in males precludes standard logistic regression; Fisher exact result is directional. Models adjusted for age, BMI, height, FVC z-score, and biomass exposure in each stratum. Smoking×sex interaction: p=0.999 (underpowered; female stratum n=44). sSAD: Spirometric small airway dysfunction, aOR: Adjusted odds ratio, IQR: Interquartile range, N-S: Never-smokers, CI: Confidence interval, AUC: Area under the curve

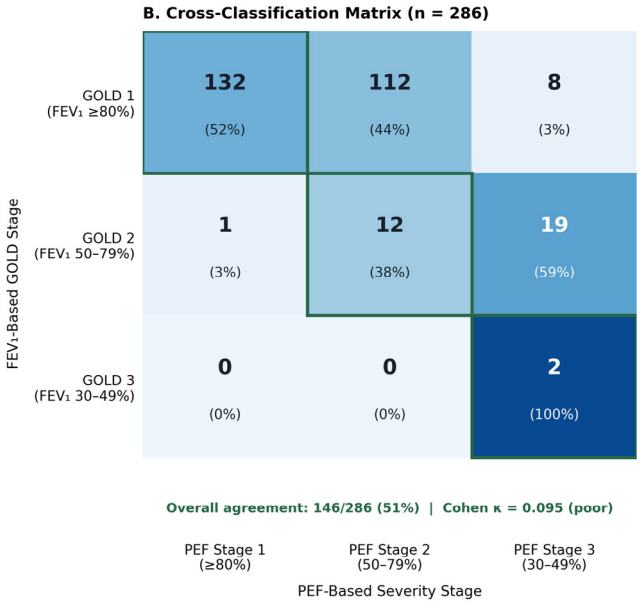
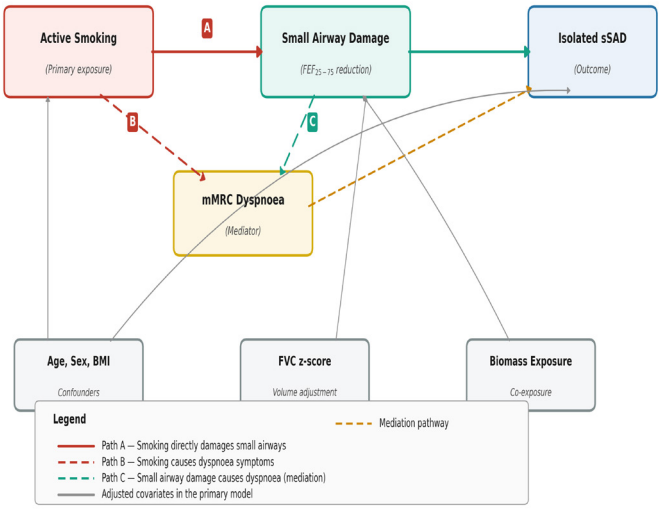


Figure 3B. PEF-FEV_1 agreement analysis, full cohort (n=286) Cross-classification matrix; bold diagonal cells denote concordant classifications (overall agreement 146/286, 51.0%; unweighted κ=0.095; linear weighted κ=0.183; quadratic weighted κ=0.300)

PEF: Peak expiratory flow, FEV_1: Forced expiratory volume 1 s



Supplementary Figure S. Directed Acyclic Graph (DAG): Proposed Causal Framework. mMRC adjustment attenuated smoking OR from 13.15 to 2.52 (p=.21), consistent with partial mediation. The primary model excludes mMRC, in accordance with best practice for mediator variables in cross-sectional designs. Alternative interpretations (confounding by tobacco burden, collider bias) are discussed in the main text.

EF_{25-75}: Forced expiratory flow 25-75%, . sSAD: Spirometric small airway dysfunction, mMRC: modified Medical Research Council dyspnea scale, FVC: forced vital capacity, BMI: Body-mass index

sensitivity subgroup (n=13) also had poor agreement (κ=0.103; concordance=5/13, 38.5% (**Table 5**).

Table 5. Cross-classification of GOLD severity stages: FEV_1 vs PEF (n=286)

FEV_1 GOLD stage	PEF stage 1 (≥80%)	PEF stage 2 (50-79%)	PEF Stage 3 (30-49%)	Row total
GOLD 1 (≥80%)	132 ★	112	8	252 (88.1%)
GOLD 2 (50-79%)	1	12 ★	19	32 (11.2%)
GOLD 3 (30-49%)	0	0	2 ★	2 (0.7%)
PEF total	133 (46.5%)	124 (43.4%)	29 (10.1%)	286

★ Concordant cells (diagonal). Overall concordance: 146/286 (51.0%); unweighted κ=0.095 (slight), linear weighted κ=0.183 (slight), quadratic weighted κ=0.300 (fair); Bland-Altman bias: -20.0% (95% LoA: -58.1% to +18.2%); Obstructive subgroup (n=13): κ=0.103, PEF: Peak expiratory flow, GOLD: Global Initiative for Chronic Obstructive Lung Disease

DISCUSSION

Active smokers with preserved post-bronchodilator FEV_1/FVC and radiologically normal CT had lower FEF_{25-75} and roughly eight times the prevalence of isolated sSAD compared with never-smokers. After adjusting adjustment for FVC z-score, the odds ratio for smoking actually increased, confirming that the spirometric difference is not a volume artefact. The inverse association of FVC z-score with sSAD was biologically expected: smaller lung volumes lower the FEF_{25-75} threshold by definition, reinforcing why z-score-based LLN is methodologically preferable to a fixed percent-predicted cutoff in studies of this kind.[19] Because the design is cross-sectional, our findings are best read as associations rather than evidence of a causal pathway, and whether reduced FEF_{25-75} predicts progression to spirometric COPD remains a question for longitudinal cohorts.

When mMRC was added to the model as a sensitivity analysis, the smoking odds ratio fell substantially and became non-significant. This attenuation is best understood through the pre-specified directed acyclic graph (**Supplementary Figure S**). In our proposed causal framework, active smoking directly damages small airways (path A), while also causing respiratory symptoms (path B); small airway dysfunction itself contributes to dyspnoea (path C). Under this framework, mMRC functions primarily as a mediator on the causal pathway from smoking to sSAD; adjusting for a true mediator will always attenuate the exposure-outcome estimate, consistent with epidemiological best practice. Alternative explanations include confounding (heavier smokers may have higher mMRC scores and greater sSAD simultaneously) and collider bias: we selected participants on the basis of normal CT findings, and among symptomatic smokers who satisfied this criterion, conditioning on CT normality may create a spurious backdoor path between mMRC and FEF_{25-75} that would not exist in an unselected sample. For these reasons, the mMRC-adjusted model should be regarded as complementary rather than definitive, and the pre-specified primary model remains the reference estimate. Cross-sectional data cannot fully settle whether mMRC is a mediator or a partial confounder; an alternative reading in which it carries some confounding signal for example, through shared upstream factors that we did not measure remains plausible. A formal mediation analysis would require longitudinal data that our design does not provide, so we report both estimates and leave readers to weigh them.

These findings are clinically relevant to the pre-COPD framework. The GOLD report defines pre-COPD as respiratory symptoms or structural and functional lung abnormalities in the absence of spirometric obstruction, recognising that measurable airway damage, including micro-CT-visible terminal bronchiole loss, and functional impairment detectable by spirometry, can be years ahead of any change in FEV_1/FVC.[3,4,6,9,20] Our smoker cohort showed a 28.7% prevalence of isolated sSAD, placing more than one in four participants in this pre-COPD continuum at the time of study, undetected by conventional spirometric criteria.

The phenotype we describe differs from PRISm. PRISm is defined by $FEV_1/FVC \geq LLN$ with FEV_1 below 80% predicted and carries an increased risk of mortality and cardiovascular events.[5] In our cohort, FEV_1/FVC was preserved and FEV_1 was within normal limits for all participants; only FEF_{25-75} fell below the LLN. This profile-preserved FEV_1 with isolated FEF_{25-75} reduction-may represent an early pre-COPD phenotype with peripheral airway-selective impairment. The China Pulmonary Health Study has documented that these early spirometric categories carry distinct symptom profiles and are largely undertreated, which highlights the gap in early-detection tools for routine practice.[21]

Our findings also map onto the evolving GOLD framework. The 2024-2025 GOLD report refined COPD staging with the ABE classification, which weights symptom burden and exacerbation history above spirometric grade in treatment decisions.[1] The 2026 GOLD report goes further, introducing a formal algorithm for COPD case-finding and advocating systematic spirometric evaluation of high-risk individuals, including smokers and those with unexplained dyspnoea.[22] Our study aligns with this case-finding rationale: FEF_{25-75} z-score, obtainable at no additional cost during routine spirometry, identified a substantial subgroup of smokers with peripheral airway impairment who would have been missed by FEV_1/FVC alone. The poor PEF-FEV_1 agreement we document is particularly relevant to these case-finding algorithms in resource-limited settings where PEF meters may be the only spirometric device available.

The lack of a significant linear dose-response relationship between pack-years and FEF_{25-75} in our smoker subgroup deserves comment. At least three explanations are plausible, and they are not mutually exclusive. A threshold model would suggest that peripheral airway damage occurs after a relatively modest smoking exposure and then plateaus. Survivor bias is a second possibility: smokers with the heaviest cumulative exposure were more likely to have developed overt airflow obstruction and were therefore excluded by our design. Third, the markedly greater FEF_{25-75} impairment in female smokers despite equivalent pack-year exposure points to host susceptibility as a dominant determinant of sSAD, one that would dilute any dose signal in a sex-mixed sample. The clinical implication is that cumulative tobacco dose alone is a poor guide to who among preserved-spirometry smokers will develop sSAD.

The 28.7% sSAD prevalence we observed is consistent with published data. Isolated small airway obstruction with preserved FEV_1/FVC was associated with a nearly threefold increased risk of future chronic airflow obstruction in the multinational study by Knox-Brown et al.,[7] and FEF_{25-75} abnormalities in symptomatic smokers predicted COPD progression in roughly 21% over 10 years.[6,20] In a Chinese prospective cohort, concurrent sSAD and chronic bronchitis carried the highest COPD risk among all pre-COPD markers examined.

Biomass fuel exposure was a strong independent predictor of sSAD, and the combined biomass-plus-smoking subgroup showed a prevalence of 58.1%, suggesting that tobacco smoke and biomass combustion products act synergistically on the distal airways, possibly through converging inflammatory and oxidative pathways.[18] In regions where both exposures co-occur, this combined-risk phenotype should prompt targeted screening.

The sex differential in our cohort is consistent with a growing literature on tobacco susceptibility. Female smokers had significantly lower FEF_{25-75} than male smokers at equivalent pack-year exposure, yet no sex difference was seen among never-smokers. A population-based cohort of more than 105.000 individuals showed that the per-unit increase in risk of airway obstruction and respiratory mortality from tobacco exposure was greater in women, attributed to their smaller airway calibre relative to total lung volume.[23-25] Our findings are compatible with this picture, but the female smoker stratum was small (n=44) and the smoking-by-sex interaction was not significant; we therefore read the apparent sex difference as preliminary and treat confirmation in larger prospective cohorts as necessary before drawing population-level conclusions.

The poor PEF-FEV_1 agreement for GOLD staging was worse than in the confirmed-COPD sample reported by Pothirat et al.,[13] with considerably wider limits of agreement. PEF reflects upper airway calibre, respiratory muscle strength, and expiratory effort in addition to airway resistance, factors that widen the gap between PEF and FEV_1 in the absence of fixed lower-airway obstruction. A methodological caveat deserves more weight than we initially gave it. PEF percent predicted was derived from NHANES III because GLI-2012 does not provide PEF reference values, whereas FEV_1 percent predicted was based on GLI-2012.[16,17] The two equation sets differ in calibration sample, age structure and lower limit of normal, and a shift between the two reference scales could in itself produce part of the -20% bias and the wide limits of agreement we observed, even if PEF and FEV_1 tracked each other well on the raw measurement scale. We could not quantify this artefact directly because population-specific GLI PEF equations are not available. We therefore treat the reference-equation mismatch as a major limitation rather than a minor one, and the agreement statistics should be read with this caveat in mind. Even so, the practical message of our analysis is not changed: clinicians who use PEF in resource-limited settings face the same reference-equation problem, so PEF cannot reliably substitute for FEV_1 in GOLD severity classification in a preserved-spirometry case-finding context.

FEF_{25-75} carries its own limitations. The GLI-2012 dataset reports a between-subject coefficient of variation of 20-62%, and the parameter is inherently volume-dependent, which is why we built FVC z-score into the regression model from the outset. However, as Quanjer et al.[19] noted, this high variability does not preclude the use of these indices in aetiological studies where group-level differences may provide valuable clues. The observed effect sizes exceed the measurement noise by a wide margin. More sophisticated tools, including parametric response mapping, impulse oscillometry, and nitrogen washout testing, offer complementary characterisation of small airway disease but require specialised equipment not routinely available in resource-limited settings. Future multimodal studies correlating FEF_{25-75} with IOS-derived R5-

R20 and PRM-derived functional small airway disease would help establish the predictive value of spirometric small airway dysfunction for structural changes.[26] The treatable traits approach, now extended to pre-COPD, identifies smoking cessation, biomass reduction, and pulmonary rehabilitation as intervention targets even before COPD is established.[27] Within that framework, the FEF_{25-75} z-score could help identify preserved-spirometry smokers who might benefit from closer follow-up, although its clinical role still needs to be tested in longitudinal studies.

Limitations

Several limitations should be acknowledged. The cross-sectional design precludes determination of whether reduced FEF_{25-75} progresses to overt obstruction. The study sample was drawn from a single pulmonary function laboratory in urban Turkiye, and generalisability to demographically different populations cannot be assumed. Although CT scans were reviewed by two independent radiologists with excellent inter-rater agreement, quantitative CT analysis was not performed and expiratory CT for gas trapping was not routinely available; participants are therefore characterised as having macroscopic structural disease excluded rather than subclinical abnormality ruled out. The between-subject variability of FEF_{25-75} and its dependence on FVC limit its diagnostic utility at the individual level, although the pre-specified FVC z-score covariate and the large group-level effect size mitigate this concern. Symptom phenotyping was limited to mMRC, as the COPD Assessment Test was not collected; the role of mMRC in the multivariable model remains ambiguous without formal mediation analysis. Several exposures relevant to small airway disease were not captured in our dataset. Biomass exposure was recorded as a yes/no variable without data on duration, fuel type or stove ventilation. Occupational exposure to dusts, fumes, vapours and gases was not documented in a way that allowed retrospective coding. Residential ambient air pollution ($PM_{2.5}$ and NO_2) was not estimated, and second-hand smoke exposure among self-reported never-smokers was not recorded, so some "never-smokers" may carry meaningful cumulative exposure to environmental tobacco smoke. Markers of socioeconomic position, which often correlate with both exposure burden and lung function, were also unavailable. Residual confounding from these unmeasured factors cannot be excluded. Participants came from individuals who had undergone thoracic CT for clinical reasons rather than from a community screening cohort, and the retrospective design did not allow us to reconstruct the indication distribution across the sample. If symptomatic referrals are over-represented compared with the source community, the absolute prevalence of isolated sSAD reported here may be higher than what would be seen in an unselected population. The comparison between smokers and never-smokers is less vulnerable to this issue because both subgroups came from the same sampling frame, and the between-group effect size therefore carries more interpretative weight than the absolute prevalence figures. For the PEF agreement analysis, spirometric GOLD grading was used as the reference standard; however, our analysis should not be generalised to treatment decisions in established COPD. Finally, the female smoker stratum was small; the non-significant smoking-by-sex interaction reflects inadequate power rather than evidence of no interaction.

CONCLUSION

In smokers with preserved post-bronchodilator FEV_1/FVC and a normal thoracic CT, reduced FEF_{25-75} was associated with a higher prevalence of isolated sSAD. The lower FEF_{25-75} seen in female smokers at comparable pack-year exposure should be read with caution given the small female stratum. PEF showed poor agreement with FEV_1 for GOLD staging. The FEF_{25-75} z-score may have a role as a screening or research marker for peripheral airway impairment, but its clinical value remains to be tested in longitudinal cohorts.

ETHICAL DECLARATIONS

Ethics Committee Approval

This study was conducted with the approval of the Karatay University Ethics Committee for Non-pharmaceutical and Non-medical Device Researches (Date: 27.11.2025, Decision No: 2025/014).

Informed Consent

As this was a retrospective study, formal written informed consent was not required and was therefore not obtained. This retrospective study used pre-existing anonymized patient data. No additional intervention was performed, and there was no direct patient contact. The study was approved by the Ethics Committee, and the requirement for written informed consent was waived by the ethics committee.

Peer Review Process

This manuscript was subject to external peer review.

Conflict of Interest

The authors declare no conflicts of interest related to this study.

Financial Disclosure

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Author Contributions

Concept: AK; Design: AK, AEA; Control: AEA, HE; Data Collection and/or Processing: AK, AEA, HE; Analysis and/or Interpretation: AK, AEA, HE; Literature Review: AK, AEA, HE; Article Writing: AK; Critical Review: All Authors.

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