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ABSTRACT

Background Chronic obstructive pulmonary disease (COPD) is diagnosed and its severity graded by traditional spirometric parameters (forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) and FEV_1, respectively) but these parameters are considered insensitive for identifying early pathology. Measures of small airway function, including forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}), may be more valuable in the earliest phases of COPD. This study aimed to determine the prevalence of low FEF_{25-75} in ever-smokers with and without airflow limitation (AL) and to determine whether FEF_{25-75} relates to AL severity.

Method A retrospective analysis of lung function data of 1458 ever-smokers suspected clinically of having COPD. Low FEF_{25-75} was defined by z-score<−0.8345 and AL was defined by FEV_1/FVC z-scores<−1.645. The severity of AL was evaluated using FEV_1 z-scores. Participants were placed into three groups: normal FEF_{25-75}/ no AL (normal FEF_{25-75}/AL−); low FEF_{25-75}/ no AL (low FEF_{25-75}/AL−) and low FEF_{25-75}/ AL (low FEF_{25-75}/AL+).

Results Low FEF_{25-75} was present in 99.9% of patients with AL, and 50% of those without AL. Patients in the low FEF_{25-75}/AL− group had lower spirometric measures (including FEV_1 FEF_{25-75}/FVC and FEV_3/FVC) than those in the normal FEF_{25-75}/AL− group. FEF_{25-75} decreased with AL severity. A logistic regression model demonstrated that in the absence of AL, the presence of low FEF_{25-75} was associated with lower FEV_1 and FEV_1/FVC even when smoking history was accounted for.

Conclusions Low FEF_{25-75} is a physiological trait in patients with conventional spirometric AL and likely reflects early evidence of impairment in the small airways when spirometry is within the 'normal range'. FEF_{25-75} likely identifies a group of patients with early evidence of pathological lung damage who warrant careful monitoring and reinforced early intervention to abrogate further lung injury.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Studies have demonstrated that small airway dysfunction is prevalent in chronic obstructive pulmonary disease (COPD) and can be seen in some susceptible individuals without airflow limitation (AL), but studies using forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) as measure of small airways function have generally included only a small number of patients with or at risk of developing COPD.

WHAT THIS STUDY ADDS

⇒ Low FEF_{25-75} is present in essentially in all of patients with AL and detected in 50% of those without AL, which was associated with lower lung function indices than those with normal spirometry. This highlights that low FEF_{25-75} is a physiological feature in patients with AL and likely signifies earlier lung injury in the small airways before classical AL of COPD is present.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Low FEF_{25-75} without AL might detect a group of patients at risk of developing COPD, where evidence-based preventative strategies could be emphasised and implemented, thereby avoiding progressive lung damage.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is an inflammatory disease most commonly caused by significant exposure to noxious particles and, pathophysiologically, includes small airway disease and parenchymal destruction.[1–4] COPD is diagnosed based on subjective (respiratory symptoms, history of exposure to risk factors) and objective (physiologically by spirometry) assessments.[5] The Global Initiative for Obstructive Lung Disease (GOLD), defines airflow limitation (AL) using a fixed forced expiratory volume in 1 s (FEV_1)/forced vital capacity (FVC) ratio and severity defined by

FEV_1 % predicted.[5] Other bodies recommend using the lower limit of normal (LLN) based on z-scores for the ratio to define AL and stratify the severity of the disease as this is thought to be less biased at the extremes of age.[6 7]

COPD is a slowly progressive disease in most individuals[8] and FEV_1/FVC and FEV_1 lack the diagnostic sensitivity to identify early lung pathology.[9 10] As only a proportion of smokers develop COPD,[11] identifying individuals with early lung damage who are most at risk of developing overt COPD would enable a focused effort to prevent pathological progression.

The role of small airways in COPD has been explored in several studies.[3 12–14] Small airways loss precedes the development of emphysema and AL in pathological studies investigated by microcomputed tomographic radiology.[2 3 12] Further, in a longitudinal study of alpha-1 antitrypsin deficiency (AATD) patients using forced expiratory flow between 25% and 75% of vital capacity (FEF_{25-75}) as a measure of small airway,[15] a reduced FEF_{25-75} without AL was associated with worse health status and a faster subsequent decline in FEV_1 and appeared to precede AL defined by spirometry.[15] This, and other studies, suggest that measures of small airways function (SAF; especially FEF_{25-75}) may be more sensitive to early damage than traditional spirometric measures.[16–20]

We hypothesised that low FEF_{25-75}, would be ubiquitous in patients with AL, as this has been demonstrated to precede the development of AL.[21 22] Furthermore, we hypothesised that patients with low FEF_{25-75} but without AL would have physiological indicators of the risk of developing AL, even after the correction for potential confounders such as smoking history.

The study had five main aims:

1. To investigate the prevalence of low FEF_{25-75} in cigarette smokers with and without AL.
2. To assess whether low FEF_{25-75} without AL was associated with lower lung function measurements within the normal range, which might reflect an increased risk for developing AL.
3. To assess the relationships between FEF_{25-75} and other spirometric measures.
4. To assess the relationships between FEF_{25-75} and AL severity in established COPD.
5. To determine whether the presence of low FEF_{25-75} without AL was associated with lower lung function measurements, even after correction for potential confounders.

METHODS

Study design and setting

This was a retrospective, cross-sectional study of anonymised data from patients known to have or suspected of having COPD who underwent routine pulmonary function test at University Hospitals Birmingham National Health Service Foundation Trust, UK. The study included data obtained between 1 January 2016 and 30 April 2021 and all patients who had lung function during this period were screened for inclusion.

Eligibility criteria

All participants attending for lung function within the study period with the following included:

1. Symptoms suggestive of COPD (breathlessness and/or a persistent cough).
2. Age 30 years or older.
3. ≥10 pack-years history of cigarette smoking.
4. Either a confirmed diagnosis or suspected of having COPD by a senior physician.
5. All traditional spirometric measures including FEF_{25-75} were reported.

Participants were excluded if they had COPD related to AATD, a history/diagnosis of other chronic lung diseases or significant structural changes in the lung (such as bronchiectasis) defined radiologically. Patients with emphysema identified radiologically; however, were not excluded.

Study measures

Patients' demographic data were collected. Smoking history included smoking status at the time of testing (ex-smoker or current smoker), pack-years history and years since quitting smoking. The smoking exposure was categorised into light (<20 pack-year), moderate (20–40 pack-years) and heavy (>40 pack-year).[23] Regular medication use was documented.

FEV_1, FVC, FEV_1/FVC, FEF_{25-75}, FEV in the first 3 s (FEV_3), and FEV_3/FVC were assessed. Corrected FEF_{25-75} for lung volume (FEF_{25-75}/FVC) was also assessed.[17] Lung function assessments used the Ultima PF Pulmonary Lung Function System (Medical Graphics UK, Tewkesbury, UK) and were performed in accordance with national guidelines.[24] In this study, predicted values for routine spirometric measures were derived from the European Community for Steel and Coal.[25] The z-score for the routine spirometric measures were calculated using the Global Lung Function Initiative 2012 formula.[7]

The z-scores for FEF_{25-75} and FEV_1/FVC were used to define abnormality. A cut-off z-score for normality for FEF_{25-75} was chosen of −0.8435 as this has shown to predict COPD development.[21] The LLN (ie, z-score −1.645) was used for FEV_1/FVC to define AL, as recommended in the American Thoracic Society/European Respiratory Society guidelines.[6 7] Using these thresholds, participants were grouped into three groups: normal FEF_{25-75}/ no AL (normal FEF_{25-75}/AL−); low FEF_{25-75}/ no AL (low FEF_{25-75}/AL−); and low FEF_{25-75}/ AL (FEF_{25-75}/AL+). AL severity was defined using FEV_1 z-score,[26] to classify five severity groups.

FEF_{25-75} z-score was compared with z-scores of other physiological measures where available.

Statistical analysis

Statistical analysis was performed using IBM SPSS software (V.26). Data were not normally distributed, hence

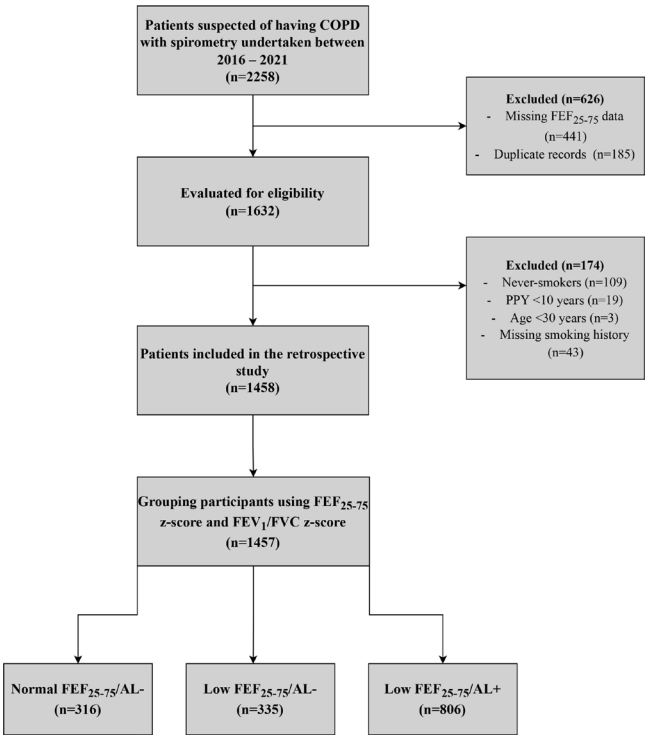

Figure 1 Flow chart of the retrospective study. This figure shows the selection of patients according to eligibility criteria. One participant did not meet any of the group definition and was therefore not included in the grouping analysis. AL, airflow limitation; COPD, chronic obstructive pulmonary disease; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; PPY, pack per year.

Kruskal-Wallis H tests were used throughout with the median and IQR reported. Where Kruskal-Wallis H tests were significant, a Mann-Whitney U test was conducted. For variables used in group definitions (FEF_{25-75} and FEV_1/FVC), no statistical analysis was conducted, except where the definition did not cause the variable to differ. Here, Mann-Whitney U tests was performed to determine the differences. Categorical variables were assessed using χ^2 or Fisher's exact test, with the count and percentage reported. The relationship of FEF_{25-75} z-score with z-score of other physiological measures and whether smoking behaviours have impact on the relationships were assessed using weight least-square regression. Coefficient of determination (r^2) was reported throughout. Curvilinear regression was used to determine the relationship between FEF_{25-75} % predicted or FEF_{25-75}/FVC with % predicted or ratio of other physiological measures, with r^2 reported throughout.

Logistic regression was performed to identify factors associated with the presence of low FEF_{25-75}. χ^2 and Mann-Whitney U test were used to identify relevant univariable risk factors and significant variables were included in the univariate logistic regression and ORs with 95% CIs reported. Significant variables in univariate analyses were included in the subsequent multivariate analysis. Variables, which were associated with multicollinearity (defined by variable inflation factor (VIF) >10) with other variables, were not included in the multivariate logistic regression. A p<0.05 was considered statistically significant throughout. For group comparisons, p values were adjusted using the Benjamini-Hochberg method[27] with adjusted p value significance level set at p<0.05. No power calculations were conducted for this pragmatic study.

Patient and public involvement

Patients and/or the public did not take part in the development, conduct, reporting or dissemination of this study.

RESULTS

Participant's selection

On initial screening, the dataset included 2258 records. After assessing for eligibility, 1458 ever-smokers were included (see figure 1 for a flow chart including reasons for exclusion). These participants were placed into the three groups based on the predefined criteria: normal FEF_{25-75}/AL− (n=316); low FEF_{25-75}/AL− (n=335) and low FEF_{25-75}/AL+ (n=806). One participant did not meet any of the grouping criteria and was therefore excluded from the final analysis.

Prevalence of low FEF_{25-75}

All but one participant with AL had low FEF_{25-75} (806/807; 99.9%). Of those without AL, 51.4% (335/650) had low FEF_{25-75}.

Demographics and clinical characteristics

Baseline demographics for the eligible participants and groups are shown in table 1. The average age was higher in low FEF_{25-75}/AL+ group (median 65 years; IQR 58–73) vs both normal FEF_{25-75}/AL− group (median 63 years (IQR 54.75–72); p=0.012) and low FEF_{25-75}/AL− group (median 63 years (IQR 54.75–72); p=0.025). There were no differences in sex across groups. Body mass index (BMI) was lower (p<0.001) in low FEF_{25-75}/AL+ group than both normal FEF_{25-75}/AL− group (median BMI 25.67; IQR 21.88–29.82 vs 30.20; IQR 25.34–34.71) and low FEF_{25-75}/AL− group (median BMI 28.94; IQR 25.33–34.071).

Participants in normal FEF_{25-75}/AL− group had generally smoked less (less heavy smokers and a lower pack-year history) compared with low FEF_{25-75}/AL− group and low FEF_{25-75}/AL+ group, with no differences between the latter 2.

Expectedly, patients in low FEF_{25-75}/AL+ group used more COPD-associated medications than those in normal FEF_{25-75}/AL− group or low FEF_{25-75}/AL− group, including short-acting beta-2 agonists (SABA), inhaled corticosteroids (ICS)/long-acting beta-2 agonists (LABA) and long-acting muscarinic antagonists (LAMA) (p<0.001 for all). Interestingly, participants in low FEF_{25-75}/AL− group used more COPD medications (including SABA and

Table 1 Baseline demographics of the included participants

Variable	Total n=1458	Normal FEF_{25-75}/AL− n=316	Low FEF_{25-75}/AL− n=335	Low FEF_{25-75}/AL+ n=806
Age (years)	64 (56.75–72)	63 (54.75–72)	63 (54.75–72)	65 (58–73)*†
Sex (male: female) n	744: 714	168: 148	150: 184	425: 382
Race (n, %)				
Caucasian	1382 (94.8)	286 (90.5)†‡	321 (96.1)	774 (94.8)
Black	22 (1.5)	9 (2.8)†	1 (0.3)	12 (1.5)
Asian	49 (3.4)	19 (6.0)‡	11 (3.3)	19 (2.3)
Others	5 (0.3)	2 (0.6)	1 (0.3)	2 (0.2)
Smoking status (n, %)				
Current smokers	842 (57.8)	163 (51.6)‡	197 (59)	482 (59.7)
Ex-smokers	616 (42.2)	153 (48.4)‡	137 (41)	325 (40.3)
Smoking exposure (n, %)				
Light	216 (14.8)	73 (23.1)†‡	43 (12.8)	100 (12.4)
Moderate	568 (39)	138 (43.7)	133 (39.7)	297 (36.8)
Heavy	673 (46.2)	105 (33.2)†‡	159 (47.5)	409 (50.7)
Pack-year	40 (25–55)	31 (20–45)†‡	40 (26–55)	41 (28–59)
Years quit§	10 (3–20)	11 (4–24.50)‡	10 (4–20)	8 (3–15)
BMI (kg/m^2)	27.32 (23.09–31.95)	30.20 (25.34–34.71)	28.94 (25.33–34.07)	25.67 (21.88–29.82)*†

Data are presented as median and IQR, unless otherwise stated.
In the group comparisons, the significance level for adjusted p value was set at 0.05.
*Significantly different from low FEF_{25-75}/AL−.
†Significantly different from low FEF_{25-75}/AL+.
‡Significantly different from normal FEF_{25-75}/AL−.
§Only assessed in ex-smokers.
AL, airflow limitation; BMI, body mass index; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity.

ICS/LABA) than normal FEF_{25-75}/AL− group (p<0.001 for all). Details of the medications used across groups are provided in online supplemental table E1.

Physiological assessment of lung function

Table 2 shows the baseline spirometric measures for the three groups. All spirometric measures were lower in low FEF_{25-75}/AL− group than normal FEF_{25-75}/AL− group (p<0.001).

Participants in low FEF_{25-75}/AL+ group had lower lung function (p<0.001 for all comparisons) than both low FEF_{25-75}/AL− group and normal FEF_{25-75}/AL− group. FVC z-score and FVC % predicted did not differ between low FEF_{25-75}/AL+ group and low FEF_{25-75}/AL− group. The distribution of FEF_{25-75} z-score, FEV_1 z-score, FEV_1/FVC z-score and FVC z-score across groups are shown graphically in figure 2. The distribution of FEF_{25-75}% predicted, FEF_{25-75}/FVC, FEV_1 % predicted, FVC % predicted, FEV_1/FVC ratio and FEV_3/FVC ratio across groups are shown in online supplemental figure E1.

The relationship of FEF_{25-75} with AL severity

Participants with AL were grouped according to AL severity. Table 3 summarises baseline demographics and measures of small airways of these participants. In this cohort, patients with very severe disease were younger than those with lesser severity (p<0.001 for all comparisons). There were no differences between subgroups for sex or ethnicity, although BMI was lower in patients with very severe disease compared with moderately severe patients (median BMI 23.43 (IQR 19.62–28.73) vs 26.99 (IQR 22.85–30.36), p=0.01). Of note, smoking status and pack-year history did not differ across severity groups but those with the most severe disease had stopped smoking later than the other groups.

FEF_{25-75} z-score worsened in a stepwise manner as the severity of AL increased (p<0.001; see figure 3). Of note, even in mild AL, FEF_{25-75} % predicted was substantially impaired (median 40.50% (IQR 33.74–48.48) and 41.93% (IQR 30.95–48.58) for FEF_{25-75} /FVC; see online supplemental figure E2).

The relationship of FEF_{25-75} with other lung function parameters

Including all participants (n=1458), FEF_{25-75} z-score demonstrated a strong relationship to FEV_1 (r^2=0.90, p<0.001; see figure 4) and FEV_1/FVC z-score (r^2=0.86, p<0.001; see figure 5), but a weaker relationship to FVC

Table 2 Baseline spirometric measures of the included participants

Variable	Total n=1458	Normal FEF_{25-75}/AL− n=316	Low FEF_{25-75}/AL− n=335	Low FEF_{25-75}/AL+ n=806
FEV_1				
z-score	−2.09 (−3.16 to −1.11)	−0.44 (−1.00 to 0.20)	−1.67 (−2.26 to −1.18)*	−2.97 (−3.70 to −2.12)*†
% predicted	67.05 (47.65 to 84.12)	93.68 (85.60 to 103.92)	74.05 (64.50 to 82.43)*	50.91 (37.25 to 66.36)*†
FVC				
z-score	−0.50 (−1.15 to 0.20)	−0.50 (−1.15 to 0.20)†‡	−1.34 (−2.02 to −0.63)	−1.19 (−2.02 to −0.35)
% Predicted	84.43 (71.96 to 96.75)	93.16 (83.37 to 103.37)†‡	80.44 (70.60 to 91.37)	82.05 (69.22 to 95.38)
FEV_1/FVC ratio§				
z-score	−1.93 (−3.34 to −0.63)	0.09 (−0.30 to 0.46)	−1.00 (−1.33 to −0.60)*	−3.18 (−4.11 to −2.34)
%	63 (48 to 74)	79 (76 to 83)	71 (68 to 75)*	50 (39 to 59)
FEF_{25-75}§				
z-score	−1.96 (−2.80 to −1.01)	−0.16 (−0.49 to 0.25)	−1.37 (−1.67 to −1.11)	−2.72 (−3.2 to −2.18)†
% Predicted	40.56 (21.08 to 67.58)	95.25 (83 to 110.51)	56.02 (47.76 to 63.70)	22.74 (14.80 to 33.76)†
FEF_{25-75}/FVC ratio	48.28 (27.25 to 79.86)	104.80 (90.10 to 122.99)	68.02 (59.16 to 79.86)*	28.73 (19.90 to 40.47)*†
FEV_3/FVC ratio	85.44 (74.22 to 92.26)	94.65 (92.10 to 96.83)	90.75 (87.73 to 93.46)*	75.13 (64.70 to 82.67)*†

Data are presented as median and IQR. In the groups' comparisons, the significance level for adjusted p value was set at 0.05.
*Significantly different from normal FEF_{25-75}/AL−.
†Significantly different from low FEF_{25-75}/AL−.
‡Significantly different from low FEF_{25-75}/AL+.
§Statistical test was only undertaken for differences between groups where a definition did cause the variable to differ.
AL, airflow limitation; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; FEV1, forced expiratory volume in 1 s; FEV3, FEV in 3 s; FVC, forced vital capacity.

z-score (r^2=0.17, p<0.001). FEF_{25-75} z-score also demonstrated strong relationship to FEV_3/FVC % (r^2=0.69, p<0.001; see figure 6).

In the multiple regression analyses (n=1458; accounting for pack-year history), FEF_{25-75} z-score showed strong relationship to FEV_1 z-score (r^2=0.90, p<0.001) and FEV_1/FVC (r^2=0.86, p<0.001), and weak relationship to FVC z-score (r^2=0.18, p<0.001). Pack-years was not a statistically significant predictor in any of the regression models.

In the multiple regression analysis for ex-smokers (n=616; accounting for years since quitting smoking), FEF_{25-75} z-score showed a strong relationship to FEV_1 z-score (r^2=0.89, p<0.001) and FEV_1/FVC z-score (r^2=0.88, p<0.001), and a weak relationship to FVC z-score (r^2=0.22, p<0.001). Years since quitting was a significant predictor in all models (p<0.001 for all models, except in the model for FEV_1 z-score p=0.017).

FEF_{25-75} % predicted and FEF_{25-75}/FVC ratio also showed strong relationship to other spirometric measures, presented in online supplemental table E3. The relationships of FEF_{25-75} % predicted and FEF_{25-75}/FVC with FEV_1/FVC and FEV_1 % predicted are graphically shown in online supplemental figures E3 and E4.

The association of the presence of low FEF_{25-75} with low lung function measurements

A regression model was built to assess whether the presence of low FEF_{25-75} without AL was associated with lower lung function measurements (see table 4). In the univariate analysis, pack-years, sex, FEV_1 z-score, FVC z-score and FEV_1/FVC z-score were significant factors related to the presence of low FEF_{25-75}. All significant variables were included in the multivariate analysis except FVC z-score because of multicollinearity with other spirometric measures (VIF=30.94). The multivariate analysis demonstrated that females had a 33.22 times higher OR of having low FEF_{25-75} compared with males (95% CI, 8.19 to 134.72). The multivariate analysis also showed that the presence of low FEF_{25-75} was associated with a lower FEV_1 z-score and FEV_1/FVC z-score even when in the normal range. Of the significant factors in univariate analysis, pack-years was no longer significant in the multivariate analysis.

DISCUSSION

This cross-sectional study of commonly measure of SAF (FEF_{25-75}) in smokers suspected of having COPD highlights four important points.

First, low FEF_{25-75} (considered indicative of impairment in the small airways) is a constant feature of those who have developed AL, with and without correction for FVC.

Second, there was a significant reduction in FEF_{25-75} even in mild AL, suggesting a substantial disruption of SAF prior to crossing the AL diagnostic criteria. Indeed, once AL is established, there is a strong association between FEF_{25-75} z-score across AL severity.

Third, evidence of low FEF_{25-75} is common (51.4%) in symptomatic ever-smokers even without AL and is

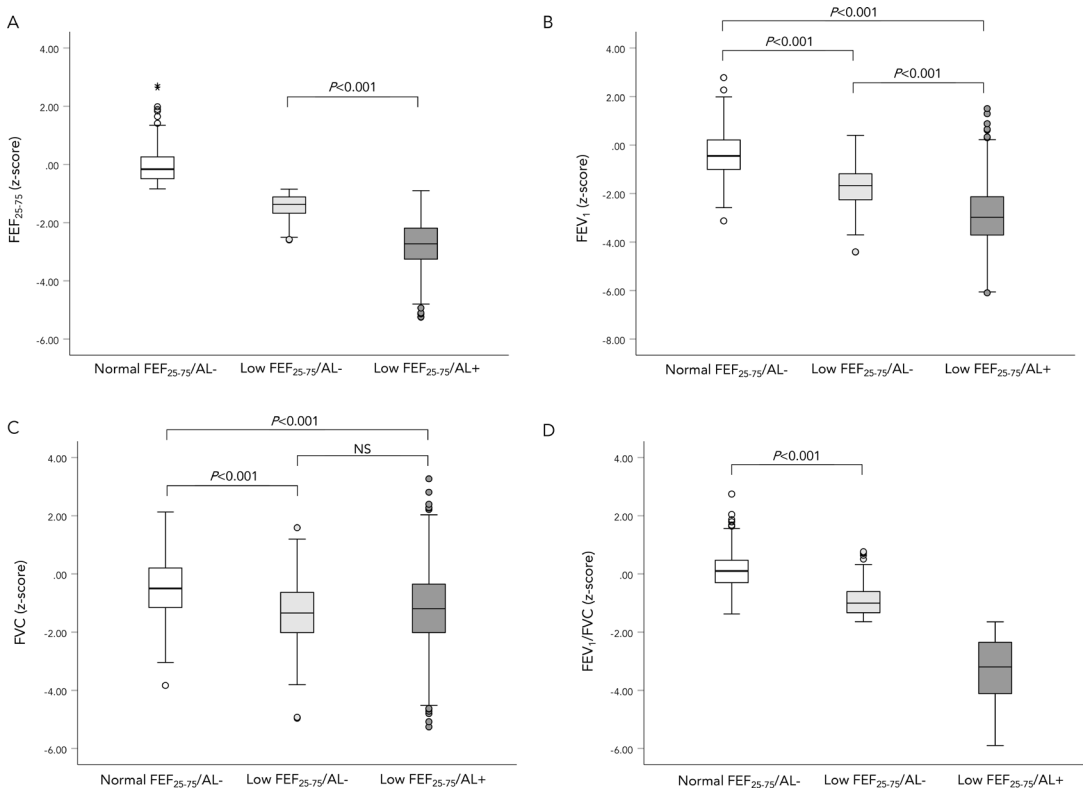

Figure 2 Distribution of spirometric measures across study groups. A box plot demonstrating the distribution of z-scores of spirometric measures across groups. The plot shows median, IQR, minimum and maximum. (A) The distribution of FEF_{25-75} z-score across groups. (B) The distribution of FEV_1/FVC z-score across groups. (C) The distribution of FEV_1 z-score across groups. (D) The distribution of FVC z-score across groups. For figures (A, D), statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p values are for the Mann-Whitney U test. For figures (B, C), the presented p values are for Mann-Whitney U test, and the Kruskal Wallis tests p values for both figures were<0.001. AL, airflow limitation; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; NS, not significant.

associated with lower lung function parameters (even while in the normal range) compared with those with normal FEF_{25-75} and normal FEV_1/FVC. This suggests that even when routine spirometry appears 'normal', those with low FEF_{25-75} may have physiological evidence suggesting decline compared with health. This group of patients likely have early lung injury reflecting small airway impairment. Our data support the notion that such patients may form a cohort that would benefit from close monitoring, to ascertain progression potentially leading to COPD and support to mitigate such an outcome.

Fourth, the relationship between FEF_{25-75} and FEV_1 and FEV_1/FVC is maintained even following adjustment for smoking history, indicating it is independent of cigarette load. Further, the logistic regression demonstrated that the presence of low FEF_{25-75} was associated with lower FEV_1 and FEV_1/FVC, after correcting for smoking status. This suggests there are a group of smokers who are pathophysiologically different, consistent with a 'susceptible' cohort. Further study is needed to understand the mechanisms underpinning this potential susceptibility.

In the regression model, sex was related to low FEF_{25-75} in the absence of AL, with females 33 times more likely to have low FEF_{25-75}, although with a wide 95% CI. In the AATD study by Stockley *et al* there was also a higher proportion of females with low FEF_{25-75} than males compared with those with normal spirometry and AL.[15] This study and the AATD study highlight that females have a greater likelihood of a low FEF_{25-75} in the absence of AL. Given that females with COPD have greater small airway impairments than males[28] and females are at higher risk of developing COPD than males with similar smoking histories,[29] our finding and those of Stockley *et al* indicate that low FEF_{25-75} (which is likely suggestive of impairment in the small airways) is likely to be greater in females before developing overt AL. Studies have reported that females have small tracheal cross-sectional area compared with males.[30 31] This may be similar throughout the bronchial tree explaining why females are most likely to have low FEF_{25-75} without AL than males. However, confirming this will require more comprehensive studies.

In the current study, age was higher in the low FEF_{25-75}/AL+ group than the normal FEF_{25-75}/AL− group and low FEF_{25-75}/AL− group, but was reduced in those with very severe AL compared with all other severities of AL. In a complex disease such as COPD, decline rates are variable. Age (as a surrogate of time) might account for some of the differences in baseline lung function between the

Table 3 Baseline demographics and FEF_{25-75} across AL severity

Variable	Mild n=177	Moderate n=111	Moderately severe n=120	Severe n=263	Very severe n=135
Age (years)	65 (57–75)	67 (60–75)	67 (58.50–74)	69 (61–73)	59 (53–64)*†‡§
Sex (male: female) n	92: 86	50: 61	72: 48	138: 125	73: 62
Smoking status (n, %)					
Current smokers	113 (63.5)	59 (53.2)	72 (60)	159 (60.5)	79 (58.5)
Ex-smokers	65 (36.5)	52 (46.8)	48 (40)	104 (39.5)	56 (41.5)
Pack-year	40 (26.75–55)	41 (25–53)	43 (29–60)	44 (30–62)	38 (23–63)
Years quit	12 (3–21.50)	9 (3–16)	9 (2.25–19.50)	7 (3–14)	5 (2–10)*
BMI (kg/m^2)	25.78 (22.96–28.68)	26.17 (21.29–30.42)	26.99 (22.85–30.36)	25.52 (21.92–30.66)	23.43 (19.62–28.73)‡
FEF_{25-75}					
z-score	−1.94 (−2.18 to −1.69)	−2.28 (−2.57 to −2.07)*	−2.56 (−2.82 to −2.32)*†	−3.01 (−3.26 to −2.78)*†‡	−3.77 (−4.11 to −3.52)*†‡§
% Predicted	40.50 (33.74 to 48.48)	32.50 (26.49 to 38.56)*	25.76 (21.40 to 29.61)*†	17.60 (13.95 to 21.62)*†‡	10.32 (8.76 to 13.67)*†‡§
FEF_{25-75}/FVC	41.93 (30.95 to 48.58)	38.11 (29.23 to 47.09)	31.61 (24.04 to 40.27)*†	23.28 (18.08 to 31.43)*†‡	15.68 (13.26 to 22.33)*†‡§

Data are presented as median and IQR unless otherwise stated. Severity of AL are stratified using FEV_1 z-score.
In the groups' comparisons, the significance level for adjusted p value was set at 0.05.
*Significantly different from mild.
†Significantly different from moderate.
‡Significantly different from moderately severe.
§Significantly different from severe.
AL, airflow limitation; BMI, body mass index; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; FEV3, forced expiratory volume in 3 s; FVC, forced vital capacity.

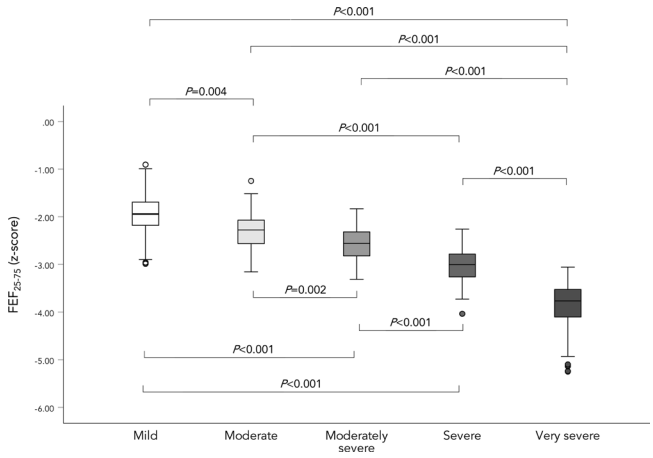

Figure 3 Distribution of FEF_{25-75} z-score across AL severity. A box plot demonstrating the distribution of FEF_{25-75} z-score across AL severity. The plot shows median, IQR, minimum and maximum. AL severity was assessed using FEV_1 z-score. The presented p values are for Mann-Whitney U test, and the Kruskal Wallis tests p value was <0.001 for all. AL, airflow limitation; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity.

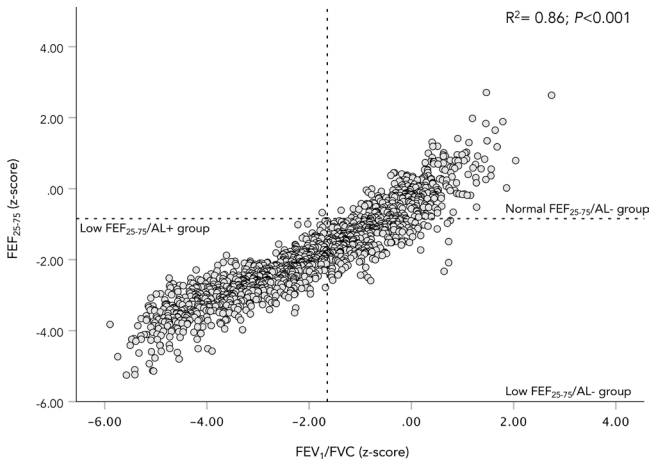

Figure 5 FEV_1/FVC z-score plotted against FEF_{25-75} z-score. A scatter plot showing the relationship between FEF_{25-75} z-score and FEV_1/FVC z-score. The plot is divided according to groups definition. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value. AL, airflow limitation; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; WLS, weight-least square.

low FEF_{25-75}/AL− group and low FEF_{25-75}/AL+ group. However, age was not a significant factor accounting for the presence of low FEF_{25-75} in multivariate regression modelling. The contribution of ageing on the presence of low FEF_{25-75} can only be confirmed by longitudinal follow-up, which would also enhance our understanding of the relationship between small and large airways function in COPD and might support new monitoring and treatment strategies.

Smoking exposure was similar between low FEF_{25-75}/AL− group and low FEF_{25-75}/AL+ group and did not differ across increasing AL severity (as grouped by FEV_1 z-score) nor was associated with low FEF_{25-75} in multivariate analysis. These results suggest that smoking exposure alone cannot explain the physiological differences between groups. Tsushima *et al* reported similar findings, demonstrating that smokers with COPD had similar pack-year history compared with those designated at-risk of COPD,[16] although Mirsadraee *et al* suggested this reflected a lower smoke exposure.[17] This latter study used GOLD criteria and % predicted to define groups while our study used the z-scores to define abnormality

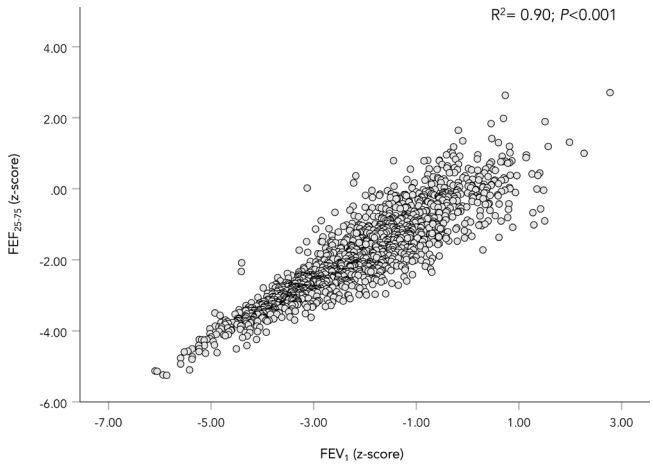

Figure 4 FEV_1 z-score plotted against FEF_{25-75} z-score. A scatter plot showing the relationship between FEF_{25-75} z-score and FEV_1 z-score. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value. FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in 1 s; WLS, weight-least square.

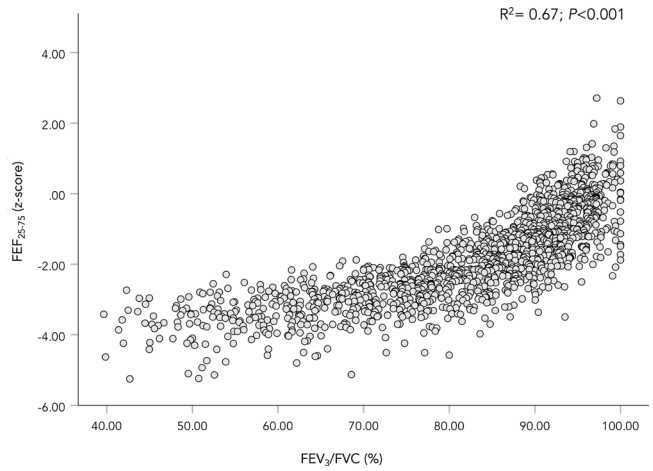

Figure 6 FEV_3/FVC plotted against FEF_{25-75} z-score. A scatter plot showing the relationship between FEF_{25-75} z-score and FEV_3/FVC. The coefficient of determination (r^2) for the WLS regression is shown in the figure along with its p value. FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in 1 s; FVC, forced vital capacity; WLS, weight-least square.

Table 4 Logistic regression of the association of the presence of low FEF_{25-75} with low lung function measurement in participants without AL

	Univariate			Multivariate*		
Variable	OR	95% CI	P value	OR	95% CI	P value
Age	1.004	0.991 to 1.018	0.55			
Pack-years	1.009	1.003 to 1.015	**0.002**	0.988	0.971 to 1.005	0.168
Smoking status†						
Current smokers	1.340	0.983 to 1.827	0.064			
Sex‡						
Female	1.383	1.016 to 1.883	**0.039**	33.225	8.194 to 134.723	**<0.001**
FEV_1 z-score	0.136	0.100 to 0.185	**<0.001**	0.001	0.00008 to 0.005	**<0.001**
FEV_1/FVC z-score	0.043	0.027 to 0.068	**<0.001**	0.00001	0.000001 to 0.0003	**<0.001**
FVC z-score	0.449	0.377 to 0.536	**<0.001**			

This tables demonstrate the logistic regression of the association of the presence of low FEF_{25-75} with low lung function measurements in participants without AL (n=651 (those normal FEF_{25-75} n=316 vs those with low FEF_{25-75} n=335)).
Low FEF_{25-75} was defined by z-score<−0.8435.
Statistically significant p values are written in bold.
*The multivariate regression model showed a Nagelkerke R^2=0.942 and Hosmer-Lemeshow p value=0.999.
†The reference category was ex-smokers.
‡The reference category was male.
AL, airflow limitation; BMI, body mass index; FEF25-75, forced expiratory flow between 25% and 75% of vital capacity; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity.

in FEV_1/FVC and FEF_{25-75}. The physiological criteria used may account for some differences in study findings.

The FEV_3/FVC has been used to detect mild lung injury in the absence of AL.[32] Morris *et al* reported that, compared with those with normal FEV_3/FVC, patients with a lower ratio had lower FEV_1, higher residual volume (RV)/total lung capacity (TLC), higher RV, higher TLC and lower transfer factor for carbon monoxide (TLco), potentially highlighting the presence of early physiological impairment including air trapping and impaired gas exchange.[32] Our study demonstrated that FEV_3/FVC was lower (although within normal range) in the low FEF_{25-75}/AL− group than in normal FEF_{25-75}/AL− group and was strongly associated with the FEF_{25-75} z-score, providing further support that the FEF_{25-75} z-score is likely detecting early lung pathology in this group. FEF_{25-75}/FVC has also been used in the early detection of COPD[17] and again this measure was also lower in low FEF_{25-75}/AL− group, further supporting the FEF_{25-75} z-score.

This study found that the use of ICS/LABA was as high in the low FEF_{25-75}/AL− group as in the low FEF_{25-75}/AL+ group, despite no AL in former group. This contradicts the recommendation by NICE guidelines that the use of ICS/LABA should be for those with spirometrically confirmed AL.[33] Therefore, the absence of AL in low FEF_{25-75}/AL− group raises concern regarding the reason for prescribing such high levels of ICS/LABA. ICS/LABA combinations contains high dose of ICS characterised by high potency, and adverse effects, including community-acquired pneumonia, glucose dysregulation and adrenal suppression.[34] There are two possible reasons why patients in low FEF_{25-75}/AL− group are prescribed ICS/LABA. First, the current study used the LLN to define AL, whereas the fixed 70% cut-off is still widely used in clinical practice. This could explain that some patients were given ICS/LABA following the confirmation of AL using the fixed ratio cut-off. Second, given the lack of evidence on how to treat patients with symptoms of COPD despite no AL, the patients might have experienced worse respiratory symptoms, requiring physicians to escalate therapy, by the addition of ICS. Whether using COPD medications (and especially ICS) to treat patients without AL is of benefit in the patients described here, requires appropriate randomised control trials. An RCT by Han *et al* is ongoing, which evaluates using LABA/LAMA in patients with COPD symptoms but no AL to determine whether such medication is effective in such patients[35] and the same should be done with ICS.

Several studies have assessed FEF_{25-75} in COPD. FEF_{25-75} % predicted was lower (though not necessarily abnormal) in patients at risk of developing COPD.[16] Correction of FEF_{25-75} for FVC also identifies early pathological changes prior to COPD development[17] and expiratory flow rates (including FEF_{25-75}) detected abnormality in those with normal FEV_1/FVC.[36] Our findings, together with other studies strengthen FEF_{25-75} (expressed as either % predicted or z-score) as a valuable marker of impairment in the small airways before classically defined AL is present.[15–17 21 36]

Concerns about the use of FEF_{25-75} in clinical management have been raised, for example, in a large cross-sectional study using FEF_{25-75} z-score.[37] That study concluded that FEF_{25-75} did not provide additional information to current spirometric measures used in clinical practice, which contrasts with the close relationship demonstrated in our study. However, the study by Quanjer *et al*[37] included a large and mixed population of participants including a variety of lung diseases. The lack of utility of a test in a general population does not negate its use in a selected one, a concept supported in the

study of a highly selected population (AATD), where low FEF_{25-75} % predicted in the absence of AL was associated with a reduced health status and a subsequent faster decline in lung function.[15] In addition, that study suggested that low FEF_{25-75} preceded the development of macroscopic emphysema, a classic component of the PiZZ genetic variant.

A 10-year longitudinal study demonstrated that non-AATD patients with low FEF_{25-75} z-score had a higher incidence rate of developing COPD than those with normal FEF_{25-75} z-score (41.8% vs 7.4%, p<0.001).[21] The authors used the same normality cut-off for as used in the current study.[21] Considering that small airways dysfunction seems to precede AL[15] and the fact that loss of >70% of small airways has to occur before COPD becomes detectable by FEV_1/FVC,[12] patients with FEF_{25-75} z-score<−0.8435 described by Kwon *et al* possibly had impairment in their small airways that would have worsened over time due to the continual exposure to risk factors, leading to the development of AL.[21]

Our study provides evidence to support the use of FEF_{25-75} (expressed as z-score) as an assessment tool in patients potentially at risk of developing COPD. We suggest that patients with FEF_{25-75} <-0.8453 should be considered a phenotypic group that likely reflects early impairment in the small airways. This group of patients should be monitored and early preventive measures (most importantly, smoking cessation) should be objectively supported and encouraged especially when there is progression. In this group, the reduction of environmental-related exposure (ie, pollution, work related exposure and biomass fuel exposure) may also be beneficial in stabilising progression to COPD. Moreover, pharmacological treatments such as extra-fine particles inhalers may be of particular use in this group, as they achieve higher deposition in the small airways.[38–40] However, this concept clearly requires further research to determine whether such treatments are of value for this group. Other measures of small airways have also demonstrated value in the early detection of COPD.[18 20 41] In this study, we chose FEF_{25-75} because of its availability already in routine physiological assessment.

Our study has limitations. It was a cross-sectional study but the value of FEF_{25-75} as a monitoring tool has also been demonstrated longitudinally[15 21 22] and our study provided a larger sample confirming the prevalence of low FEF_{25-75} in smokers with and without AL. FEF_{25-75} is a highly variable spirometric measure but we used FEF_{25-75} z-score to optimise the interpretive accuracy. This was also a retrospective study, meaning that available data were limited to routine lung function tests, although this is more representative of the real-world approach to such strategies. Studies have shown that RV/TLC is also a potential marker for SAF.[42–45] However, the data analysed in this study was limited to spirometric measures and did not include lung volumes such as RV and TLC. Therefore, further studies should evaluate whether low FEF_{25-75} is associated with low RV/TLC. We pragmatically used<−0.8453 z-score cut-off to define low FEF_{25-75}, which is different from the LLN for other lung function parameters. The ERS/ATS guidelines highlight that no satisfactory outcome-based thresholds for lung function have been defined and that further research is needed to establish a comprehensive disease-specific clinical approach to interpretation.[46] The chosen cut-off for our study has also been used by others and shown to significantly predict COPD development,[21] indicating it likely reflects early impairment in the small airways.

In conclusion, low FEF_{25-75} z-score is a physiological feature present in patients with AL and also in symptomatic patients in the absence of AL. These findings highlight the potential importance of FEF_{25-75} as marker of small airways impairment, and importantly, in the detection of early pathological features of COPD. FEF_{25-75} is part of routine lung function assessment, and therefore, closely monitoring patients with low FEF_{25-75} and considering early interventions may be central to improving health and prognosis.

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Contributors NYA was the study's guarantor, responsible for conducting the study, had access to the data, and controlled the decision to publish the study. NYA and ES designed and planned the study. NYA and MA analysed the data. NYA wrote the initial manuscript. ES, RAS and JS reviewed the data and revised the manuscript. All authors read and approved the final version of the manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval The data study was approved by the Health Research Authority (HRA – project number 274729) and the South Birmingham Research Ethics Committee (Reference number 20/WM/0024).

Provenance and peer review Not commissioned; externally peer reviewed.

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Small airway function measured using forced expiratory flow between 25% and 75% of vital capacity and its relationship to airflow limitation in symptomatic ever-smokers: A cross-sectional study

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Supplementary Tables

Table E1. List of medications used in the included participants

Variable	Total n= 1458	Normal FEF_{25-75}/AL- *n = 316*	Low FEF_{25-75}/AL- *n = 335*	Low FEF_{25-75}/AL+ *n = 806*
SABA	891 (61.1)	128 (40.5)	186 (55.7)*	576 (71.4)*†
SAMA	51 (3.5)	2 (0.6)	10 (3)	39 (4.8)*
SABA/SAMA	1 (0.1)	0 (0)	0 (0)	1 (0.1)
ICS	85 (5.8)	17 (5.4)	22 (6.6)	45 (5.6)
LABA	24 (1.6)	1 (0.3)	3 (0.9)	20 (2.5)*
ICS/LABA	405 (27.8)	33 (10.4)	70 (21)*	302 (37.4)*†
LAMA	353 (24.2)	20 (6.3)	47 (14.1)*	286 (35.4)*†
LABA/LAMA	36 (2.5)	2 (0.6)	9 (2.7)	25 (3.1)
ICS/LABA/LAMA	7 (0.5)	0 (0)	0 (0)	7 (0.9)
Systematic CS	55 (3.8)	2 (0.6)†‡	15 (4.5)	38 (4.7)
Antibiotic	28 (1.9)	1 (0.3)	8 (2.4)	19 (2.4)
Montelukast	25 (1.7)	3 (0.9)	4 (1.2)	18 (2.2)
CV Medications	687 (47.1)	183 (57.9)†‡	160 (47.9)	343 (42.5)
GI Medications	381 (26.1)	97 (30.7)	96 (28.7)	187 (23.2)*
Domiciliary Oxygen	19 (1.3)	2 (0.6)	5 (1.5)	12 (1.5)
Mucolytic	101 (6.9)	3 (0.9)	14 (4.2)*	88 (10.9)*†
Theophylline	15 (1.0)	0 (0)	1 (0.3)	14 (1.7)

Legend: Data is presented in n (%); *Significantly different from group 1; †Significantly different from group 2; ‡Significantly different from group 3. Significance level was set at $P<0.05$

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; AL, airflow limitation; SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal.

Table E2. List of medications used across airflow limitation severity.

Variable	Mild *n = 178*	Moderate *n = 111*	Moderately severe *n = 120*	Severe *n = 263*	Very severe *n = 135*
Medications (n, %)					
SABA	103 (57.9)	77 (69.4)	83 (69.2)	197 (74.9)*	116 (85.9)*†‡
SAMA	5 (2.8)	4 (3.6)	7 (5.8)	15 (5.7)	8 (5.9)
SABA/SAMA	0 (0)	0 (0)	0 (0)	1 (0.4)	0 (0)
ICS	10 (5.6)	5 (4.5)	6 (5)	17 (6.5)	8 (5.9)
LABA	4 (2.2)	2 (1.8)	2 (1.7)	9 (3.4)	3 (2.2)
ICS/LABA	43 (24.2)	29 (26.1)	41 (34.2)	112 (42.6)*†	77 (57)*†‡
LAMA	40 (22.5)	40 (36)	29 (24.2)	114 (43.3)	63 (46.7)*‡
LABA/LAMA	3 (1.7)	4 (3.6)	1 (0.8)	12 (4.6)	5 (3.7)
ICS/LABA/LAMA	1 (0.6)	1 (0.9)	1 (0.8)	1 (0.4)	3 (2.2)
Systematic CS	6 (3.4)	4 (3.6)	6 (5)	14 (5.3)	8 (5.9)
Mucolytic	10 (5.6)	8 (7.2)	8 (6.7)	36 (13.7)	26 (19.3)*‡
Antibiotic	1 (0.6)	2 (1.8)	3 (2.5)	7 (2.7)	6 (4.4)
Montelukast	1 (0.6)	0 (0)	2 (1.7)	9 (3.4)	6 (4.4)
CV Medications	89 (50)	44 (39.6)	60 (50)	109 (41.4)	41 (30.4)*‡
GI Medications	44 (24.7)	36 (32.4)	30 (25)	56 (21.3)	22 (16.3)†
Domiciliary Oxygen	0 (0)	4 (3.6)	1 (0.8)	4 (1.5)	3 (2.2)
Theophylline	0 (0)	1 (0.9)	1 (0.8)	7 (2.7)	5 (3.7)

Legend: Data is presented in n (%). *Significantly different from mild; †Significantly different from moderate; ‡Significantly different from moderately severe; §Significantly different from severe. Significance level was set at $p<0.05$.
Abbreviations: SABA, short-acting beta-2 agonist; SAMA, short-acting muscarinic antagonist; ICS, inhaled corticosteroid; LABA, long-acting beta-2 agonist; LAMA, long-acting muscarinic antagonist; CS, corticosteroid; CV, Cardiovascular; GI, gastrointestinal

Table E3. The relationship of FEF_{25-75} and FEF_{25-75}/FVC with spirometric measures (n=1458)

Spirometric measures	FEF_{25-75} % predicted		FEF_{25-75}/FVC	
	r^2	*P value*	r^2	*P value*
FEV_1 (% predicted)	0.71	<0.001	0.47	<0.001
FVC (% predicted)	0.13	<0.001	0.006	<0.001
FEV_1/FVC (%)	0.83	<0.001	0.92	<0.001
FEV_3/FVC (%)	0.70	<0.001	0.82	<0.001

Legend: This tables presents the relationship of FEF_{25-75} % predicted and FEF_{25-75}/FVC with other spirometric measures. The relationship was assessed using curvilinear regression analysis.
Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expiratory volume in the first second; FVC, forced vital capacity; FEV_3, forced expiratory volume in three seconds.

Supplementary Figures

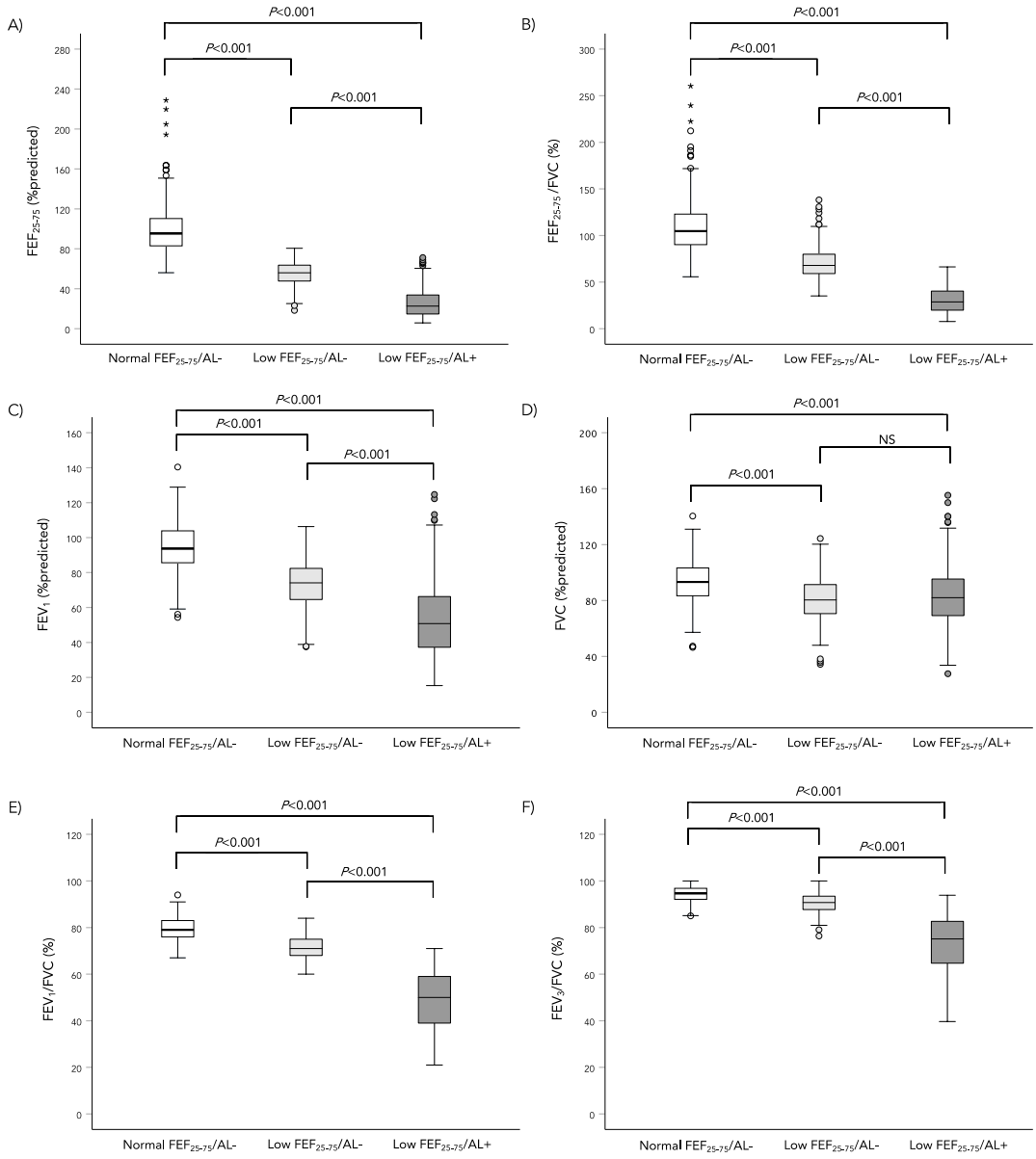

Figure E1. **Distribution of %predicted or ratio of spirometric measures across study groups**.

Legend: A box plot demonstrating the distribution of the % predicted or ratio of spirometric measures across study groups. The plot shows median, interquartile range, minimum and maximum. A) The distribution of

FEF_{25-75} % predicted across groups. B) The distribution of FEF_{25-75}/FVC ratio across groups. C) The distribution of FEV_1 % predicted across groups. D) The distribution of FVC % predicted across groups. E) The distribution of FEV_1/FVC ratio across groups. F) The distribution of FEV_3/FVC ratio across groups. For groups' comparisons, Kruskal-Wallis H test was performed, and for statistically significant test, a post-hoc Dunn's test was applied. The presented *P* values were adjusted using the Bonferroni method to account for multiple comparisons. For figures A and E, statistical test was only done for differences between groups where a definition did cause the variable to differ, and the reported p-values are for the Mann-Whitney U test. For figures B, C, D and F, the presented p-values are for post-hoc Dunn's test, and the Kruskal Wallis tests p-values for all figures were <0.001.

Abbreviations: FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_3, forced expiratory volume in the first 3 seconds; AL, airflow limitation; NS, not significant.

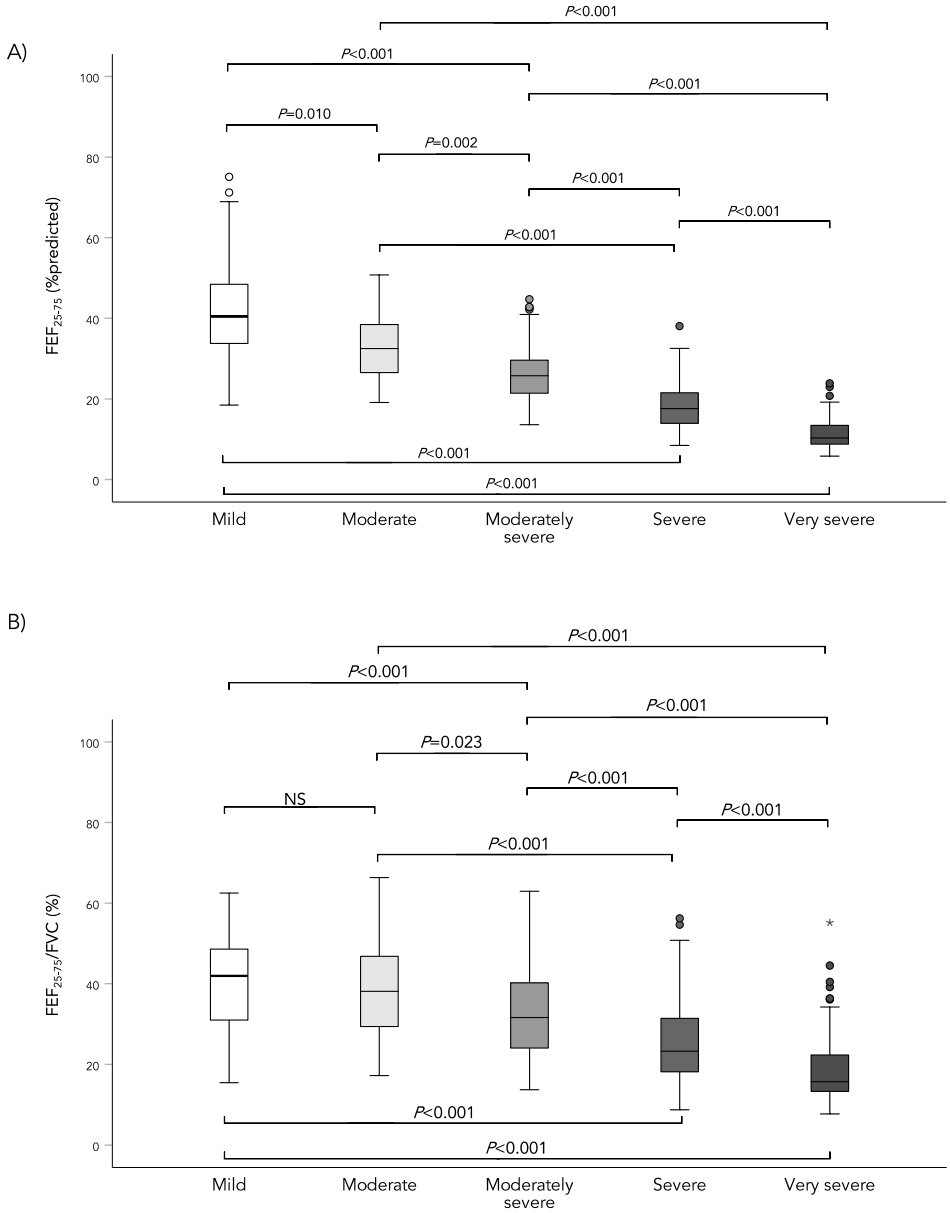

Figure E2. **Distribution of FEF_{25-75} and FEF_{25-75}/FVC across AL severity**.

Legend: A box plot demonstrating the distribution of FEF_{25-75} and FEF_{25-75}/FVC across AL severity. The plot shows median, interquartile range, minimum and maximum. A) The distribution of FEF_{25-75} % predicted across severity. B) The distribution of FEF_{25-75}/FVC ratio across severity. AL severity was assessed using FEV_1 z-score. For groups' comparisons, Kruskal-Wallis H tests was performed, and for statistically significant test, a

Alobaidi NY, *et al. BMJ Open Resp Res* 2022; 9:e001385. doi: 10.1136/bmjresp-2022-001385

post-hoc Dunn's test was applied. The presented *P* values were adjusted using the Bonferroni method to account for multiple comparisons. The p-values for Kruskal-Wallis H tests for both figures were <0.001.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FVC, forced vital capacity; NS, not significant; AL, airflow limitation.

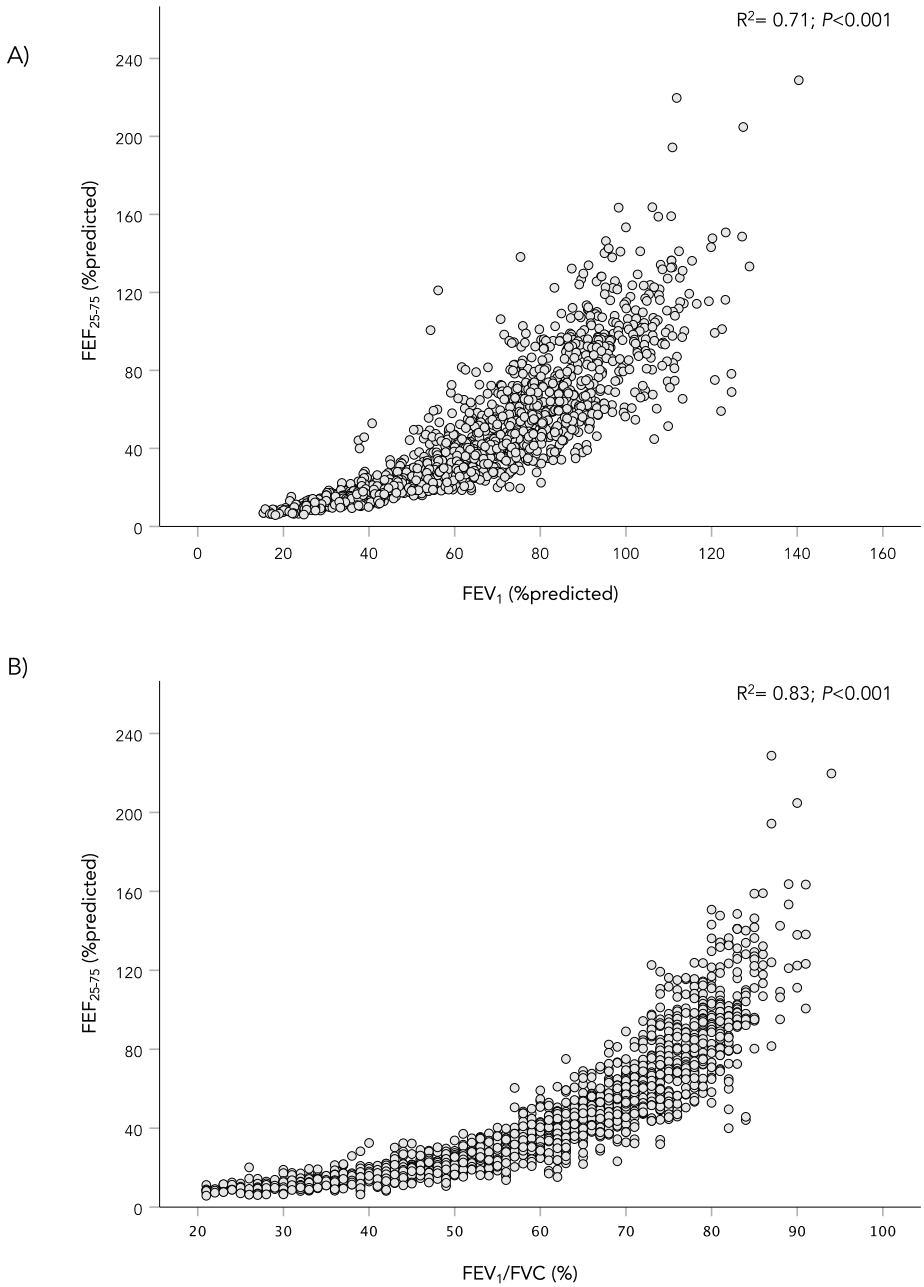

Figure E3. FEV_1 % predicted and FEV_1/FVC plotted against FEF_{25-75} % predicted.

Legend: A) A scatter plot showing the relationship between FEF_{25-75} % predicted and FEV_1 % predicted. B) A scatter plot showing the relationship between FEF_{25-75} % predicted and FEV_1/FVC %. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.

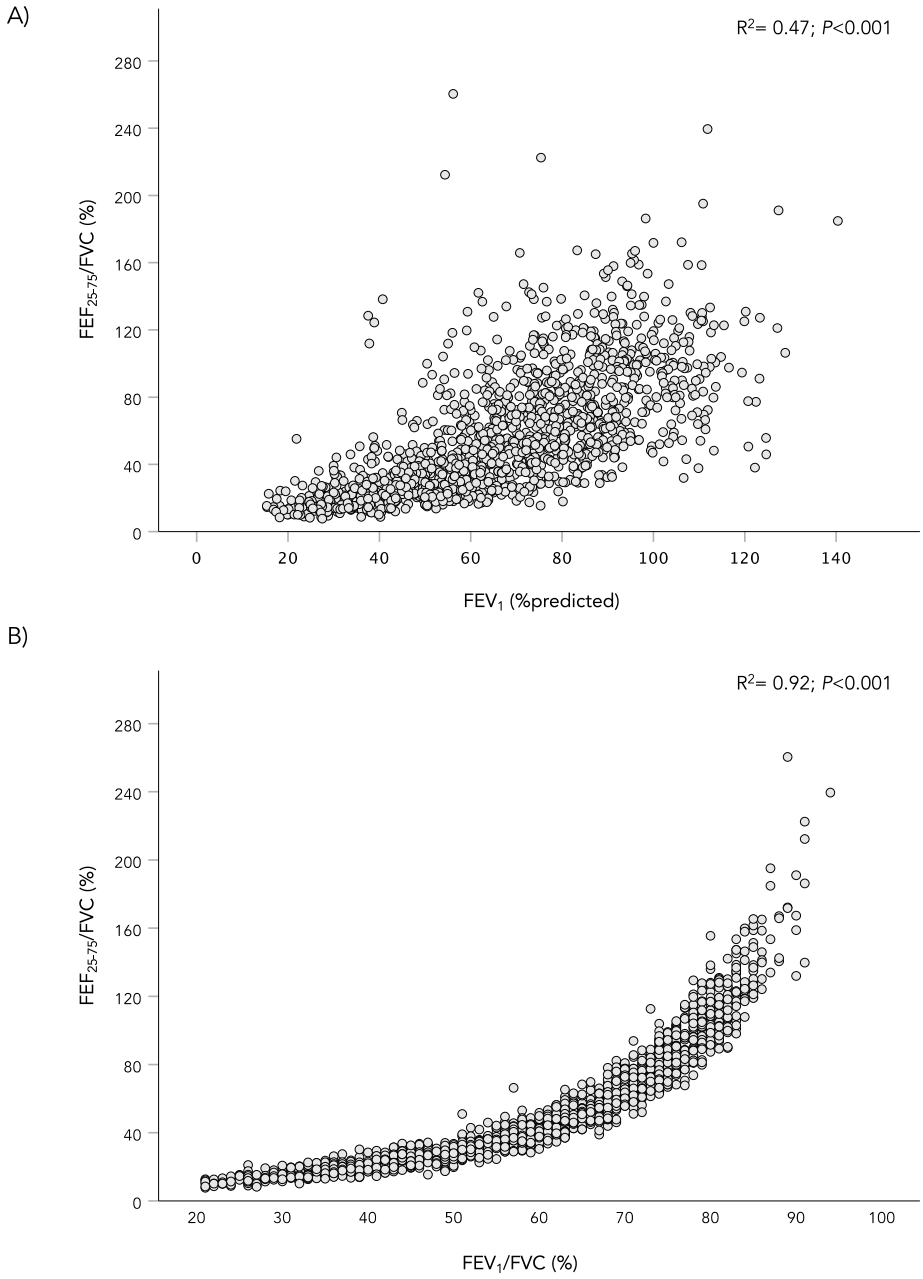

Figure E4. FEV_1 % predicted and FEV_1/FVC plotted against FEF_{25-75}/FVC.

Legend: A) A scatter plot showing the relationship between FEF_{25-75}/FVC and FEV_1 % predicted. B) A scatter plot showing the relationship between FEF_{25-75}/FVC and FEV_1/FVC. The coefficient of determination (r^2) for the curvilinear regression is shown in the figure along with its *P* value.

Abbreviations: FEF_{25-75}, forced expiratory flow between 25% and 75% of vital capacity; FEV_1, forced expired volume in the first second; FVC, forced vital capacity.