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MULTIDIMENSIONAL POST-BRONCHODILATOR RESPONSE PHENOTYPES BEYOND THE FEV_1/FVC RATIO IN NIGERIAN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Ijeoma Blessing Anieto [1,*], Uchechukwu Dimkpa [1] and Ozioma Stella Okeke [2]

[1] Human Physiology Department, Faculty of Basic Medical Sciences, Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria.
[2] Physiology Unit, Federal Medical Centre, Asaba, Delta State, Nigeria.
* Corresponding Author

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ABSTRACT

Background: Bronchodilator responsiveness in chronic obstructive pulmonary disease (COPD) is heterogeneous, and assessment centred on forced expiratory volume in one second (FEV_1) may overlook changes in forced vital capacity (FVC) and mid-expiratory flow. We evaluated post-bronchodilator response patterns in Nigerian adults with COPD.

Methods: This cross-sectional study included 59 adults aged ≥35 years with post-bronchodilator FEV_1/FVC <0.70. Spirometry was performed before and 15 minutes after 400 µg salbutamol. Mutually exclusive patterns were combined flow–volume, flow-dominant, volume-dominant, exploratory $FEF_{25–75}$-defined response, or non-response. Conventional FEV_1 and FVC responses required increases of ≥12% and ≥200 mL; the exploratory $FEF_{25–75}$ response required an increase ≥20% without an FEV_1 or FVC response. The updated ERS/ATS definition was examined in a sensitivity analysis.

Results: Mean age was 61.7±12.5 years, and 36 participants (61.0%) were men. Changes were 0.158 L for FEV_1, 0.190 L for FVC, and 0.209 L/s for $FEF_{25–75}$ (all p<0.001). Patterns were combined flow–volume in 12 (20.3%), flow-dominant in eight (13.6%), volume-dominant in 13 (22.0%), exploratory $FEF_{25–75}$-defined in five (8.5%), and non-response in 21 (35.6%). Changes were correlated (Spearman ρ = 0.746–0.847; all p<0.001). Under the updated ERS/ATS definition, FEV_1 or FVC responsiveness decreased from 33/59 (55.9%) to 25/59 (42.4%); eight participants (13.6%) had an FVC-only response. Phenotype distribution differed across GOLD grades (Monte Carlo p<0.001), but not by biomass or tobacco exposure.

Conclusions: Bronchodilator-related changes extended beyond FEV_1. Joint assessment of FEV_1 and FVC identified complementary flow and volume responses, whereas $FEF_{25–75}$ provided an exploratory signal that requires validation. These patterns are descriptive and should not direct treatment without clinical validation.

Keywords: Bronchodilator Responsiveness; Chronic Obstructive Pulmonary Disease; Spirometry; FEV_1; Forced Vital Capacity; $FEF_{25–75}$; Small Airways; Nigeria

1 INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a heterogeneous condition arising from interacting abnormalities of the airways and alveoli that produce persistent, often progressive airflow obstruction. Spirometry remains essential for confirming COPD, conventionally using a post-bronchodilator FEV_1/FVC ratio below 0.70 in the appropriate clinical context. In contrast, post-bronchodilator FEV_1 percentage predicted is used to grade the severity of airflow limitation. [1] Although these measures support standardized diagnosis and staging, they do not fully describe the acute physiological effects of bronchodilation within an individual patient.

Bronchodilator responsiveness is particularly vulnerable to oversimplification. FEV_1 predominantly captures early forced expiratory flow, whereas FVC may increase when bronchodilation permits more complete lung emptying and reduces air trapping. [2–5] A patient may therefore exhibit a volume response despite a modest change in FEV_1. Conversely, FEF_{25-75} is influenced by flow during the middle portion of forced expiration and has been used as an exploratory marker of peripheral airway dysfunction. [6–8] Its high variability and dependence on FVC, however, preclude its interpretation as a stand-alone diagnostic measure. [9]

The 2005 ATS/ERS convention defined a significant FEV_1 or FVC response as an increase of at least 12% from baseline and 200 mL.[9] Updated ERS/ATS guidance expresses response relative to the predicted value (>10% of predicted), thereby reducing dependence on baseline lung function. [10] Because data collection and the prespecified phenotype framework for the present study used the earlier criterion, it was retained as the primary operational definition. Importantly, an acute bronchodilator response is neither required for COPD diagnosis nor sufficiently specific to distinguish COPD from asthma, and absence of a threshold response does not imply absence of clinical benefit. [1,10]

Evidence from sub-Saharan Africa remains limited, despite a distinct mix of tobacco, household-air-pollution, occupational and post-infectious risks. Nigerian population studies demonstrate a measurable burden of chronic airflow obstruction and substantial underdiagnosis. [11,12] Locally generated physiological data may therefore improve characterization of COPD in populations underrepresented in bronchodilator-response research.

We aimed to (1) quantify changes in FEV_1, FVC and FEF_{25-75} after salbutamol; (2) identify mutually exclusive multidimensional response phenotypes; (3) examine their distribution across GOLD airflow-limitation grades; and (4) explore associations with recorded biomass and tobacco exposure. We hypothesized that a meaningful proportion of participants would demonstrate an FVC-defined volume response not captured by the conventional FEV_1 criterion and that a smaller subgroup might demonstrate an exploratory FEF_{25-75}-defined response.

Key messages

- What is already known? COPD can show bronchodilator-related changes in expiratory flow, exhaled volume and small-airway indices even when airflow obstruction persists.
- What this study adds: Among 59 Nigerian patients with COPD, 13 (22.0%) demonstrated a guideline-supported FVC response without meeting the conventional FEV_1 response criterion. A further five participants (8.5%) met only an exploratory FEF_{25-75} threshold.
- Clinical implication: FEV_1 and FVC should be reported together after bronchodilation; FEF_{25-75} should be interpreted cautiously as an exploratory, volume-dependent index rather than an established treatment-selection biomarker.

2 METHODS

2.1 Study design and setting

This hospital-based cross-sectional analytical study was conducted in the respiratory clinic of Federal Medical Centre, Asaba, Delta State, Nigeria, a tertiary center serving urban and rural populations. Eligible participants completed clinical and exposure questionnaires and underwent pre- and post-bronchodilator spirometry during a single visit. Participants were consecutively recruited from the Respiratory Clinic of the Federal Medical Centre, Asaba, Nigeria, between 1 August 2024 and 31 March 2025.

2.2 Participants

Sixty adults aged ≥35 years were recruited consecutively. Inclusion required clinical stability, written informed consent, acceptable and repeatable spirometry, and COPD confirmed by a post-bronchodilator FEV_1/FVC ratio <0.70. Exclusion criteria included physician-diagnosed or suspected asthma/asthma-COPD overlap, COPD exacerbation within the preceding four weeks, active pulmonary tuberculosis, acute respiratory infection, hemodynamic instability, recent myocardial infarction or acute coronary syndrome, pneumothorax, pulmonary embolism, acute hemoptysis,

intracranial hypertension, retinal detachment, recent major surgery, hypertensive crisis, inability to maneuver safely, or spirometry not meeting acceptability criteria.

2.3 Ethical considerations

The Health Research Ethics Committee of Federal Medical Centre, Asaba approved the study (NHREC/TR/FMCASABA-HREC/31/7/24/173). All participants provided written informed consent. Data were handled confidentially, and participation was voluntary.

2.4 Measurements and exposure assessment

A structured interviewer-administered questionnaire captured sociodemographic information, respiratory history, occupational exposure, tobacco smoking and household cooking fuel use. For the present analysis, biomass exposure is indicative of recorded use of charcoal, wood or coal; polluting household fuel is indicative of biomass or kerosene; and tobacco exposure is indicative of cigarette smoking as no other smoked products were recorded. Exposure variables were categorical; particulate matter concentration, cooking-intensity measures and cigarette pack-years were unavailable and were not inferred.

2.5 Spirometry and bronchodilator protocol

Spirometry was performed using a MIR Spirolab device (MIR, Rome, Italy) calibrated with a 3-L syringe in accordance with manufacturer and ATS/ERS recommendations. Disposable mouthpieces and bacterial/viral filters were used. A trained physiologist performed testing, and a consultant pulmonologist reviewed maneuvers for acceptability and repeatability. Participants were seated upright and completed at least three forced expiratory maneuvers. The two highest FEV_1 and FVC values were required to agree within 150 mL.[3]

After baseline testing, 400 µg salbutamol was administered via a metered-dose inhaler with a spacer as four 100-µg actuations at approximately 30-second intervals. Spirometry was repeated after 15 minutes using the same quality criteria. Recorded indices were FEV_1 (L), FVC (L), FEV_1/FVC, FEF_{25-75} (L/s) and forced expiratory time. Absolute change was calculated as post-bronchodilator minus pre-bronchodilator value; percentage change was calculated relative to baseline.

2.6 Operational response phenotypes

Each participant was assigned to one mutually exclusive phenotype using a prespecified hierarchy: combined flow-volume > flow-dominant > volume-dominant > exploratory FEF_{25-75}-defined response > non-response. A conventional FEV_1 or FVC response required both an absolute increase ≥0.200 L and a relative increase ≥12%. The exploratory FEF_{25-75}-defined response criterion was defined as an increase in FEF_{25-75} ≥20% among participants who met neither the FEV_1 nor FVC criterion. The phenotypes were:

- Combined flow-volume: both FEV_1 and FVC met conventional criteria.
- Flow-dominant: FEV_1 met conventional criteria, but FVC did not.
- Volume-dominant: FVC met conventional criteria, but FEV_1 did not.
- Exploratory FEF_{25-75}-defined response: neither FEV_1 nor FVC met conventional criteria, but FEF_{25-75} increased ≥20%.
- Non-response: none of the three operational criteria were met.

The term 'phenotype' is used here as an operational description of the observed acute spirometric pattern, not as evidence of a stable biological endotype. FEF_{25-75} was treated as exploratory because it is variable and mathematically dependent on FVC.

As a sensitivity analysis, bronchodilator responsiveness was reclassified according to the updated ERS/ATS interpretive standard as an increase greater than 10% of the corresponding GLI Global race-neutral predicted value for FEV_1 or FVC. Predicted FEV_1 and FVC were calculated using the sex-specific GLI Global 2022 equations based on age and standing height. This criterion was not applied to FEF_{25-75} because GLI Global race-neutral predicted values are not currently available for this parameter.

2.7 Airflow-limitation grade

GOLD airflow-limitation grade was derived from post-bronchodilator FEV_1 percentage predicted. Predicted FEV_1 was calculated using the sex-specific GLI Global 2022 race-neutral spirometry equations, incorporating age in years and standing height in centimeters. [13] Race or ethnicity was not included in the prediction model, equivalent to selecting the race-neutral option or setting ethnicity to zero in the GLI calculator. Post-bronchodilator FEV_1 percentage predicted was calculated as 100 × observed post-bronchodilator FEV_1 divided by GLI-predicted FEV_1. Among participants with

persistent post-bronchodilator airflow obstruction, airflow-limitation grades were classified as GOLD 1 (FEV_1 ≥80% predicted), GOLD 2 (50–79%), GOLD 3 (30–49%) or GOLD 4 <30%.[1] Classification was performed using unrounded percentage-predicted values.

2.8 Statistical analysis

Continuous variables are summarized as mean ± standard deviation (SD) and categorical variables as frequencies and percentages. Pre- and post-bronchodilator values were compared using paired t-tests, with mean changes, 95% confidence intervals, and standardized paired effect sizes (Cohen dz). Because change distributions departed from normality, Wilcoxon signed-rank tests were used as sensitivity analyses. Associations among spirometric changes were assessed with Spearman rank correlations. Phenotype distributions were compared across GOLD grades and exposure categories using Pearson chi-square statistics with Monte Carlo p-values (10,000 replicates) due to sparse expected cell counts. Any multidimensional response (the first four categories) was contrasted with non-response using binary logistic regression including biomass and tobacco exposure simultaneously; an interaction term was examined separately. Two-sided $p<0.05$ was considered statistically significant. Analyses were performed using IBM SPSS version 25 and independently audited with reproducible computational scripts.

3 RESULTS

3.1 Participant characteristics

Sixty participants were recruited; one record was excluded from the final COPD analysis due to failure of the post-BD obstruction criterion and incomplete data, leaving 59 participants with complete key spirometric data. Mean age was 61.7±12.5 years (range 35–83), 36 (61.0%) were men, and mean body mass index was 23.8±4.8 kg/m^2 (Table 1). All 59 met the post-bronchodilator fixed-ratio criterion for COPD. Seven (11.9%) had GOLD 1, 17 (28.8%) GOLD 2, 21 (35.6%) GOLD 3, and 14 (23.7%) GOLD 4 airflow limitation. Biomass exposure was recorded in 29 (49.2%), cigarette smoking in 19 (32.2%), and exposure to at least one polluting household fuel in 38 (64.4%).

Table 1: Participant characteristics (n=59)

Characteristic	Value
Age, years	61.7 ± 12.5
Age range, years	35–83
Male sex	36 (61.0)
Female sex	23 (39.0)
BMI, kg/m^2	23.8 ± 4.8
GOLD 1	7 (11.9)
GOLD 2	17 (28.8)
GOLD 3	21 (35.6)
GOLD 4	14 (23.7)
Recorded biomass exposure	29 (49.2)
Recorded cigarette smoking	19 (32.2)
Any polluting household fuel	38 (64.4)

Data are mean ± SD, range, or n (%). Biomass comprised charcoal/wood/coal; polluting household fuel comprised biomass or kerosene. GOLD grade was based on post-bronchodilator FEV_1 % predicted.

3.2 Changes in spirometric indices

All three prespecified indices increased after salbutamol (Table 2). Mean FEV_1 increased by 0.158 L (95% CI 0.095–0.221), FVC by 0.190 L (95% CI 0.088–0.292), and FEF_{25-75} by 0.209 L/s (95% CI 0.101–0.317); all paired-test p-values were <0.001. Sensitivity analyses using Wilcoxon signed-rank tests yielded the same inference (all $p<0.001$). Standardized paired effects were moderate (Cohen dz 0.49–0.65).

Table 2: Pre- and post-bronchodilator spirometric indices

Index	Pre-BD mean ± SD	Post-BD mean ± SD	Mean change (95% CI)	p value	Cohen dz
FEV_1, L	1.197 ± 0.702	1.354 ± 0.800	0.158 (0.095–0.221)	<0.001	0.65
FVC, L	2.119 ± 1.094	2.309 ± 1.115	0.190 (0.088–0.292)	<0.001	0.49
$FEF_{25–75}$, L/s	0.664 ± 0.503	0.873 ± 0.656	0.209 (0.101–0.317)	<0.001	0.50

BD, bronchodilator; CI, confidence interval. P-values are from paired t-tests. Wilcoxon sensitivity analyses were also significant at p<0.001 for all three indices.

3.3 Multidimensional response phenotypes

Thirty-three participants (55.9%) met the conventional response criterion for FEV_1 or FVC. Five additional participants (8.5%) met only the exploratory $FEF_{25–75}$ criterion, giving a total of 38 participants (64.4%) with at least one operational multidimensional response. The most frequent guideline-supported phenotype was volume-dominant (13/59; 22.0%), followed by combined flow–volume (12/59; 20.3%) and flow-dominant response (8/59; 13.6%). Thirteen participants (22.0%) therefore demonstrated an FVC response without an FEV_1 response. Separately, five participants (8.5%) met only the exploratory $FEF_{25–75}$ threshold. Twenty-one participants (35.6%) met none of the operational response criteria.

Table 3: Distribution and mean changes within multidimensional response phenotypes

Phenotype	n (%)	ΔFEV₁, L	ΔFVC, L	ΔFEF₂₅–₇₅, L/s	Physiological interpretation
Combined flow-volume	12 (20.3)	0.427	0.607	0.654	Flow and volume improvement
Flow-dominant	8 (13.6)	0.371	0.239	0.493	FEV_1 threshold met only
Volume-dominant	13 (22.0)	0.123	0.393	0.205	FVC threshold met only
Exploratory $FEF_{25–75}$-defined response	5 (8.5)	0.094	0.106	0.190	Exploratory $FEF_{25–75}$ threshold met only
Non-response	21 (35.6)	−0.041	−0.172	−0.147	No operational threshold met

Values are n (%) or phenotype-specific mean change. Phenotypes were mutually exclusive and hierarchical. The exploratory $FEF_{25–75}$-defined response category was exploratory and should not be interpreted as a validated clinical phenotype.

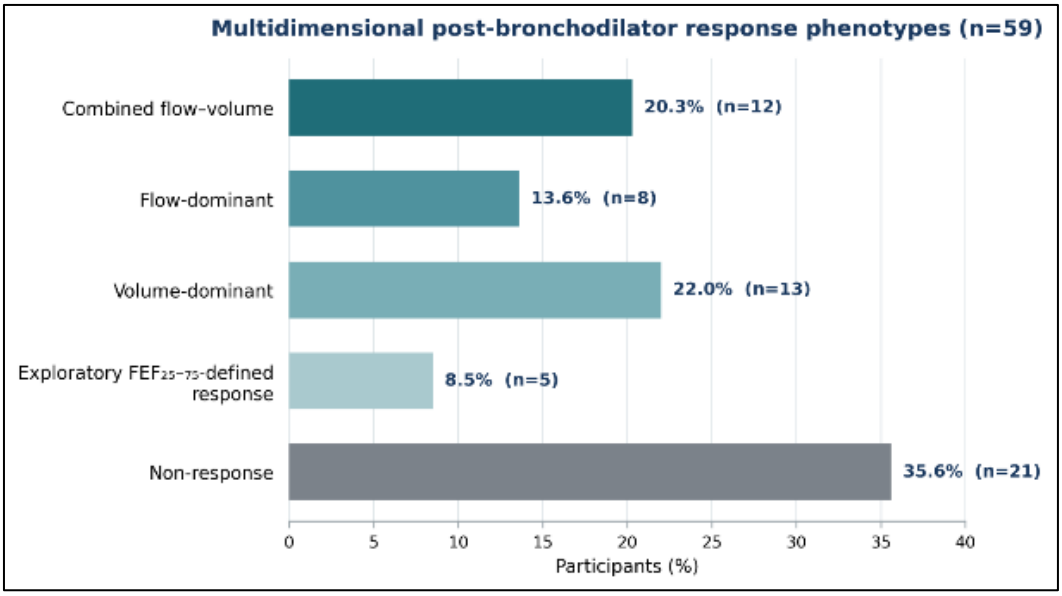

Figure 1: Distribution of multidimensional post-bronchodilator response phenotypes.

Categories are mutually exclusive. The exploratory $FEF_{25–75}$-defined response category does not represent a validated clinical phenotype.

3.4 Correlation among spirometric changes

Changes were strongly and positively correlated: ΔFEV_1 with ΔFVC (ρ=0.746), ΔFEV_1 with ΔFEF_{25-75} (ρ=0.847), and ΔFVC with ΔFEF_{25-75} (ρ=0.784); all $p<0.001$. These correlations indicate coordinated physiological improvement at the cohort level, whereas the threshold-based categories identify which component was predominant in an individual participant.

3.5 Sensitivity analysis using the updated ERS/ATS criterion

Application of the updated ERS/ATS >10%-of-predicted criterion reduced the prevalence of significant FEV_1 or FVC responsiveness from 33/59 (55.9%) under the historical criterion to 25/59 (42.4%). FEV_1 responsiveness decreased from 20 (33.9%) to 17 (28.8%), while FVC responsiveness decreased from 25 (42.4%) to 19 (32.2%). Under the updated criterion, 11 participants (18.6%) had combined FEV_1–FVC responses, six (10.2%) had FEV_1-only responses, and eight (13.6%) had FVC-only responses. All 25 participants meeting the updated definition also met the historical definition; eight participants classified as responsive under the historical definition were reclassified as non-responsive under the updated criterion (Table 4).

Table 4: Comparison of bronchodilator-response classifications using the historical and updated ERS/ATS criteria (n=59)

Response Classification	Historical Criterion, n (%)	Updated ERS/ATS Criterion, n (%)	Absolute difference, Percentage Points
FEV_1 response	20 (33.9)	17 (28.8)	−5.1
FVC response	25 (42.4)	19 (32.2)	−10.2
Any FEV_1 or FVC response	33 (55.9)	25 (42.4)	−13.5
Combined FEV_1–FVC response	12 (20.3)	11 (18.6)	−1.7
FEV_1-only response	8 (13.6)	6 (10.2)	−3.4
FVC-only response	13 (22.0)	8 (13.6)	−8.4
Neither FEV_1 nor FVC response	26 (44.1)	34 (57.6)	+13.5

Note: The combined, FEV_1-only, FVC-only, and neither-response pattern categories were mutually exclusive. The individual FEV_1-response and FVC-response rows were not mutually exclusive because participants with combined responses contributed to both.

3.6 Response phenotypes across GOLD grades

Response-pattern distribution differed across GOLD airflow-limitation grades (χ^2=33.55, 12 df; Monte Carlo $p<0.001$). Flow-dominant responses were concentrated in GOLD 1–2, whereas volume-dominant and exploratory FEF_{25-75}-defined responses occurred mainly in GOLD 3–4. No GOLD 4 participants had a combined or flow-dominant response (Table 5).

Table 5: Multidimensional response phenotype by GOLD airflow-limitation grade

Phenotype	GOLD 1 n=7	GOLD 2 n=17	GOLD 3 n=21	GOLD 4 n=14	Total
Combined flow-volume	3	5	4	0	12
Flow-dominant	4	3	1	0	8
Volume-dominant	0	1	5	7	13
Exploratory FEF_{25-75}-defined response	0	0	3	2	5
Non-response	0	8	8	5	21

$\chi^2(12)$=33.55; Monte Carlo $p<0.001$ (10,000 replicates). Sparse cells preclude stable cell-specific inference.

3.7 Exploratory exposure analyses

Any operational multidimensional response occurred in 20/29 (69.0%) participants with recorded biomass exposure and 18/30 (60.0%) without biomass exposure (Table 6). It occurred in 11/19 (57.9%) participants with tobacco exposure and 27/40 (67.5%) without tobacco exposure. In the mutually adjusted model, neither biomass (OR 1.52, 95% CI 0.51–4.47; p=0.450) nor tobacco exposure (OR 0.65, 95% CI 0.21–2.01; p=0.449) was associated with any operational multidimensional response. Phenotype distributions likewise did not differ significantly by biomass (Monte Carlo p=0.430) or tobacco exposure (p=0.507). The biomass×tobacco interaction was imprecise and non-significant (OR 0.70, 95% CI 0.07–6.73; p=0.755).

Table 6: Recorded biomass and tobacco exposure in relation to any operational multidimensional response

Exposure	Operational Responders/ Total (%)	Adjusted OR (95% CI)	p Value	Phenotype Monte Carlo p
Biomass: Exposed	20/29 (69.0)	1.52 (0.51–4.47)	0.450	0.430
Biomass: Unexposed	18/30 (60.0)	Reference	—	—
Tobacco: Exposed	11/19 (57.9)	0.65 (0.21–2.01)	0.449	0.507
Tobacco: Unexposed	27/40 (67.5)	Reference	—	—

ORs are mutually adjusted for biomass and tobacco exposure. Any operational multidimensional response included combined flow–volume, flow-dominant, volume-dominant, or exploratory FEF_{25-75}-defined response. This composite outcome therefore included both guideline-supported FEV_1/FVC responses and the exploratory FEF_{25-75} category.

4 DISCUSSION

4.1 Principal findings

This study demonstrates that spirometric change relating to the acute bronchodilator response in COPD is multidimensional. FEV_1, FVC and FEF_{25-75} improved significantly at the cohort level, yet participants crossed clinically defined thresholds in different combinations. Almost two-thirds met at least one operational response criterion, but only one-third met an FEV_1 criterion, either alone or together with FVC. The central guideline-supported observation was that 13 participants (22.0%) demonstrated an FVC response without meeting the FEV_1 response criterion. This confirms that an FEV_1-only assessment would have overlooked a meaningful volume-response component. Separately, five participants (8.5%) met only the exploratory FEF_{25-75} threshold; this finding should be regarded as hypothesis-generating rather than evidence of an established small-airway response phenotype.

4.2 Flow and volume responses represent complementary physiology

The volume-dominant phenotype was the most frequent guideline-supported responder pattern. This is physiologically plausible in COPD: airway narrowing, loss of elastic recoil and heterogeneous time constants promote premature airway closure and incomplete emptying during forced expiration. [2] Bronchodilation may extend expiratory emptying, reduce gas trapping and increase measured FVC without producing a proportional increase in FEV_1. Studies using lung volumes and respiratory mechanics similarly show that bronchodilators can reduce hyperinflation and improve exercise tolerance despite modest change in FEV_1. [4, 5] Our findings support reporting FVC alongside FEV_1, while recognizing that spirometry alone cannot prove a reduction in residual volume or hyperinflation. Confirmation would require inspiratory capacity and static lung-volume measurements.

Combined flow-volume responders showed the largest mean changes across all three indices, suggesting a broadly recruitable airway system. Flow-dominant responses were concentrated in milder GOLD grades, whereas volume-dominant responses clustered in severe and very severe airflow limitation. One plausible interpretation is that advanced disease constrains early expiratory flow but still permits improvement in lung emptying. This remains an inference: the cross-sectional design, small cells and absence of plethysmographic lung volumes inhibit mechanistic confirmation.

4.3 Small-airway signal and its limits

Five participants who did not meet either conventional FEV_1 or FVC response criterion demonstrated an increase of at least 20% in FEF_{25-75}. Small airways are a major site of resistance and pathological remodeling in COPD, and reduced

mid-expiratory flow has been linked to emphysema and disease severity. [6-8] Nevertheless, FEF_{25-75} varies substantially, depends on the measured FVC, and lacks a universally accepted bronchodilator-response threshold. [9, 10] An apparent change can partly reflect the different lung-volume range over which flow is measured after bronchodilation. Accordingly, the present ≥20% threshold should be viewed as hypothesis-generating. Replication should incorporate z-scores, isovolume comparisons, oscillometry, multiple-breath washout or imaging where available.

4.4 Coordinated improvement and categorical heterogeneity

The strong correlations among ΔFEV_1, ΔFVC and ΔFEF_{25-75} show that bronchodilator-related improvements tended to occur together. This does not conflict with the categorical phenotypes. Correlation evaluates whether continuous changes move in the same direction across participants; classification identifies which prespecified threshold or combination was crossed. A volume-dominant responder, for example, may have modest FEV_1 and mid-flow improvements while only FVC crosses its response threshold. The two approaches are therefore complementary: one identifies coordinated physiology, the other summarizes its predominant expression.

4.5 Disease severity and exposure context

The association between phenotype and GOLD grade is potentially important, but it requires cautious interpretation. The absence of flow-dominant and combined responses in GOLD 4 and the accumulation of volume responses in GOLD 3–4 suggest severity-dependent expression. Yet sparse counts, multiple categories and potential mathematical coupling among baseline function, percentage change and GOLD classification can exaggerate apparent separation. A larger cohort should model continuous post-bronchodilator FEV_1 z-score, baseline lung function and absolute change rather than relying primarily on cross-tabulation.

Neither recorded biomass nor tobacco exposure was significantly associated with any operational multidimensional response or phenotype distribution. The confidence intervals were wide and compatible with clinically meaningful effects in either direction. These null findings should not be interpreted as evidence that exposure history is physiologically irrelevant. Exposure classification lacked cumulative cigarette pack-years, lifetime primary fuel, cooking duration, ventilation characteristics, and direct $PM_{2.5}$ measurement. Misclassification and limited power are therefore likely. Future work should quantify exposure dose and examine sex-specific patterns, because household-air-pollution and smoking exposures may be socially patterned.

4.6 Clinical and research implications

Three practical implications follow. First, post-bronchodilator reports in COPD should retain both FEV_1 and FVC rather than reducing response to a single binary label. Second, response categories should be described as acute spirometric patterns and should not be used to exclude COPD, diagnose asthma, predict long-term treatment benefit, or define stable endotypes without longitudinal evidence. Third, FEF_{25-75} may enrich research phenotyping but should remain secondary to reproducible, guideline-supported measures.

The updated ERS/ATS >10%-of-predicted definition was used in a sensitivity analysis to assess the robustness of response prevalence and phenotype classification. [10] Application of the updated ERS/ATS >10%-of-predicted criterion reduced the prevalence of guideline-supported FEV_1 or FVC responsiveness from 55.9% to 42.4%. Nevertheless, separate flow and volume response patterns persisted, including an FVC-only response in 13.6% of participants. Thus, the absolute prevalence of responsiveness was criterion-dependent, but the principal observation that FEV_1 alone did not capture all guideline-supported responses remained robust.

4.7 Strengths and limitations

Strengths include standardized pre- and post-testing, a uniform 400-µg salbutamol protocol, consultant review of spirometry quality, complete key measurements, mutually exclusive prespecified response categories, effect-size reporting, non-parametric sensitivity analyses and Monte Carlo inference for sparse tables. The study also contributes data from a Nigerian tertiary-care population that is underrepresented in physiological research in COPD.

The study is limited by its single-center, cross-sectional design, modest sample, and consecutive clinic sampling, which constrain generalizability and causal inference. Phenotypes were assigned from a single test, and their temporal stability is unknown. The historical ≥12% and ≥200 mL criterion differs from current ERS/ATS guidance. FEF_{25-75} is variable and volume-dependent, and the ≥20% threshold is not validated for clinical classification. Lung volumes, inspiratory capacity, oscillometry, diffusing capacity, symptom response, and longitudinal outcomes were not measured; therefore, reductions in air trapping or clinical benefit cannot be directly claimed. Sparse GOLD-by-phenotype cells limit subgroup inference. Exposure variables were coarse and did not quantify cumulative dose. COPD was defined using the GOLD fixed-ratio criterion; because a lower-limit-of-normal sensitivity analysis was unavailable, age-related misclassification, particularly among older participants, cannot be excluded. GLI-derived FEV_1 calculations were independently reproduced for all participants. Nevertheless, predicted values were based on age recorded in

completed years rather than exact age on the testing date. However, sensitivity analysis showed that plausible age variation did not alter any GOLD grade.

5 CONCLUSION

In this cohort of Nigerian adults with COPD, bronchodilator-related changes were not confined to FEV_1. Joint evaluation of FEV_1 and FVC identified distinct flow, volume and combined response patterns. Notably, 13 participants (22.0%) demonstrated a guideline-supported FVC response without meeting the FEV_1 response criterion. A further five participants (8.5%) met only the exploratory FEF_{25-75} threshold, a finding that requires independent validation. These findings support multidimensional reporting of post-bronchodilator spirometry while underscoring that operational response phenotypes are descriptive, not yet treatment-directing. Larger, multicenter longitudinal studies incorporating current response criteria, static lung volumes, symptom outcomes and quantitative exposure assessment are needed to establish reproducibility and clinical relevance.

STATEMENTS ON COMPLIANCE WITH ETHICAL STANDARDS

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Disclosure of conflict of interest

The authors declare no conflicts of interest.

Statement of ethical approval

Approved by the Health Research Ethics Committee of Federal Medical Centre, Asaba (NHREC/TR/FMCASABA-HREC/31/7/24/173).

Statement of informed consent

Written informed consent was obtained from all participants.

Availability of data and materials

The de-identified dataset generated and analyzed in this study is available from the corresponding author upon reasonable request. Access will be subject to approval by the relevant institutional and ethical authorities and to compliance with participants' consent and data-protection requirements.

Author contributions

IBA: Conceptualization, methodology, investigation, participant recruitment, data collection, and writing—original draft. **UD**: Methodology, formal analysis, validation, interpretation, supervision, and writing—review and editing. **OSO**: Methodology, data interpretation, writing—review and editing. All authors read and approved the final manuscript and agreed to be accountable for the integrity of the work.

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