Brief Report
Bronchodilator Response in COPD: Definitions, Reference Equations, and Race

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Running Head: **Bronchodilator Response in COPD**

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Abbreviations**:** COPD: chronic obstructive pulmonary disease, BDR: bronchodilator response, ATS: American Thoracic Society, ERS: European Respiratory Society, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, GLI: global lung initiative, SPIROMICS: Subpopulation and Intermediate Markers in COPD Study, BioLINCC: Biologic Specimen and Data Repository Information Coordinating Center, SGRQ-C: St. George's Respiratory Questionnaire: COPD, 6-MWD: six-minute walk distance

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Introduction

Bronchodilator response (BDR) is a portion of spirometry which assesses changes in pre- to post-bronchodilator expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC). This test is frequently obtained in patients with respiratory complaints and is often used to help differentiate chronic obstructive pulmonary disease (COPD), asthma, or COPD-asthma overlap syndrome. BDR is frequently positive in patients with COPD and its definition has changed. The 2021 ATS/ERS guidelines now define a positive BDR as >10% change in FEV1 and/or FVC relative to an individual's predicted value [1]. This predicted value depends on the reference equation applied. Current ATS/ERS guidelines recommend a race neutral reference equation, Global Lung Initiative (GLI)-Global [2]. Although studies have compared BDR definitions in patients with COPD, none have used GLI-Global as the reference equation. In a cohort of participants with COPD, we compared the frequency of a positive BDR between the 2005 and 2021 definitions, using both GLI race-specific and race-neutral reference equations, stratified by race.

Methods

We performed a cross-sectional secondary analysis of the Subpopulation and Intermediate Markers in COPD Study (SPIROMICS). SPIROMICS was a multicenter cohort study of participants with or at risk for COPD from 2010-2015. Participants were aged 40-80. Participants could have a previous history of asthma but not a primary diagnosis of asthma. Participants completed pre- and post- bronchodilator spirometry, questionnaires, and a six-minute walk test at the baseline visit.

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We included participants in SPIROMICS with COPD at the baseline visit, defined as FEV1/FVC < 0.7. We excluded races other than White and Black due to low sample size. For each patient we determined BDR based on the 2005 (BDR-05) or two 2021 definitions (BDR-21). The 2005 definition for positive BDR is an increase in post-bronchodilator forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC) greater than or equal to 12% and 200mL compared with pre-bronchodilator raw values [3] . The 2021 ATS/ERS guidelines define positive BDR as >10% change in FEV1 and/or FVC relative to an individual's predicted value [1]. The two 2021 BDR definitions used GLI-race specific and GLI-global reference equations, respectively. Participant race was self-reported. The predicted values were obtained from the GLI calculator (https://glicalculator.ersnet.org/index.html). SPIROMICS data was obtained via the NHLBI Biologic Specimen and Data Repository Information Coordinating Center (BioLINCC).

Our primary outcome was frequency of positive BDR according to each definition, stratified by race. Subsequent analyses used BDR-21 with GLI-global reference ranges, based on current ATS recommendations. We tested the overall agreement between definitions using the Kappa statistic. We subsequently defined four strata: BDR-05 + / BDR-21 +, BDR-05 - / BDR-21 -, BDR-05 +/ BDR-21 -, BDR-05 - / BDR-21 +. Across these strata we compared spirometry values, St. George's Respiratory Questionnaire-COPD (SGRQ-C), and 6-MWD. Continuous variables were compared using Anova or T-test for normally distributed variables and Wilcoxon Rank Sum Test or Kruskal-Wallis for nonparametric variables. Categorical variables were compared with chi-squared tests. Statistical Analysis was completed using SAS 9.4 (SAS Inc., Cary, NC). IRB approval was granted by Emory University.

Results

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There were 1688 participants analyzed. 1428 (84.6%) were White and 260 (15.4%) were Black. 745 (52.2%) White participants had positive BDR-05 and 672 (47.1%) had positive BDR-21. 145 (55.8%) Black participants had positive BDR-05 and 96 (36.9%) had positive BDR-21. White and black participants had different frequency of positive BDR using BDR-21 with GLI-Global reference equations (p=0.003), but not the other definitions (see Figure 1). The Kappa statistic for agreement between BDR-05 and BDR-21 was 0.8 (95%CI: 0.77-0.83) for White and 0.61 (95% CI: 0.53-0.71) for Black participants.

Black participants with BDR-05 + / BDR-21 - had a lower percent predicted FEV1 (37.82, IQR: 32.17; p=0.002) than either concordant positive BDR (50.90, IQR: 28.11) or concordant negative BDR (57.36, IQR: 32.24). A similar pattern was noted for FVC, see Table 1. 56.9% of Black participants with BDR-05 + / BDR-21 - had GOLD stage 3 or 4 severity, compared with 35.8% of those with concordant positive and 33.3% with concordant negative BDR. There were no differences in 6-MWD (p=0.48) or SGRQ-C (p=0.59), see Table 1.

White participants with BDR-05 + / BDR-21 - had lower percent predicted FEV1 (47.67, IQR 24.82; p<0.001) than concordant positive BDR (64.00, IQR: 32.59), concordant negative BDR (FEV1 70.33, IQR 38.74), or BDR-05 - / BDR-21 + (99.10, IQR: 31.53). 59.3% of White participants with BDR-05 + / BDR-21 - had COPD severity grades 3 or 4, compared with 33.0% with concordant positive BDR, 29.6% concordant negative BDR, and 5.7% with BDR-05 - / BDR-21 +. White participants with BDR-05 + / BDR-21 - had higher SGRQ-C (45.5, IQR: 28.7; p<0.001) than the other 3 BDR strata. There were no differences in six-minute walk distance, p=0.86 (see Table 1).

Discussion

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In this study, fewer Black than White patients with COPD had positive BDR-21 using race neutral spirometry reference equations. This difference is not present with BDR-21 using race specific reference ranges or with BDR-05. Across both races, participants with positive BDR-05 but negative BDR-21 had lower spirometry values and more severe GOLD stages.

The strengths of this study are the well phenotyped, large size of the SPIROMICS cohort. The primary limitation is that our analysis was limited to White and Black participants, due to low numbers in other race groups. Our findings may not be applicable to other racial/ethnic groups.

Multiple studies have compared BDR definitions in COPD cohorts [4-8]. Fortis et al. found an increase in BDR-21 compared with BDR-05, from 32.5% to 44.6%. This study excluded participants with self-reported asthma and used race-specific GLI reference ranges for BDR-21. Beasley et al. showed a decrease in positive BDR from 24.7% by BDR-21 to 18.0% by BDR-05. The directionality of BDR changes in our study aligns with Beasley, however our overall number of BDR positive participants is higher. This difference is possibly due to the inclusion of patients with self-reported history of asthma.

There has been significant debate in the pulmonary community regarding the impact of race-specific versus race-neutral reference ranges, and this study adds to that literature [2,9,10]. We tested the BDR definitions on the same participants, who therefore acted as their own controls. Using race-neutral GLI reference ranges, compared with race-specific GLI reference ranges, Black participants had a decrease in the frequency of positive BDR of 6.6% (43.5% to 36.9%) while White participants had an increase of 2.6% (44.5% to 47.1%). This directionality is due to the fact that the predicted spirometry values for FEV1 and FVC, which forms to the denominator of the BDR equation, is relatively higher for Black individuals and lower for White individuals

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using GLI-Global compared with GLI-race specific equations (see Table 1)[10]. The BDR changes therefore reflect definitional rather than physiologic or biologic differences and, as there is no gold standard, an optimal BDR definition should correlate with patients related outcomes. While in line with current ATS guidelines, applying the 2021 definition for BDR with GLI-global reference ranges leads to higher identified BDR in White participants compared with Black participants and may introduce disparities in the diagnosis and care of patients with respiratory complaints and airway-based diseases if BDR is used as a criteria for concurrent asthma diagnosis, specific inhaler therapies, or clinical trial inclusion criteria in patients with COPD [1,2].

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Data Sharing: deidentified SPIROMICS data is available via request through NHLBI BioLINCC or direct request from SPIROMICS study PI's. We obtained the data through the BioLINCC request but in accordance with that agreement are not able to share data directly, however SPIROMICS data is readily available to all through the above mechanisms.

Conflicts of Interest: STR, VNL, and JAK declare that there are no conflicts of interest in relation to this manuscript.

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Table 1. Clinical Characteristics, Spirometry, Symptoms, and Functional Status for Participants by 2005 and 2021 BDR Categorizations[$], Stratified by Race

		Black, (n=260)[a]				White (n=1428)				
		BDR-05 Categorization / BDR-21 Categorization								
		+/+	-/-	+/-	Total	+/+	-/-	-/+	+/-	Total
Frequencies, N		95	114	50	260	637	648	35	108	1428
Clinical Characteristics N (%) or Mean (STD)	Age	61.3 (7.8)	60.7 (8.6)	61.5 (7.5)	6.1 (8.1)	65.7 (7.7)	66.4 (7.7)	68.4 (7.5)	63.8 (7.8)	66.0 (7.7)
	BMI	26.5 (6.0)	26.8 (6.0)	26.6 (6.3)	26.6 (6.1)	27.6 (5.2)	27.3 (5.0)	26.7 (4.3)	27.1 (5.3)	27.4 (5.1)
	Active Smoking	54 (56.8)	57 (51.4)	21 (42.9)	133 (51.8)	204 (32.5)	195 (30.6)	6 (17.1)	31 (29.8)	436 (31.0)
	History of asthma	41 (43.2)	39 (34.8)	20 (41.7)	100 (39.1)	148 (23.8)	107 (16.9)	2 (5.7)	20 (19.4)	277 (19.9)
	GOLD Severity Stage 3 or 4	34 (35.8)	38 (33.3)	29 (58.0)	101 (38.9)	210 (33.0)	192 (29.6)	2 (5.7)	64 (59.3)	468 (32.8)
	Use of Inhaled Bronchodilators	79 (83.2)	84 (73.7)	40 (83.3)	204 (79.1)	425 (67.6)	380 (59.3)	17 (48.6)	88 (82.2)	910 (64.5)
	Use of Inhaled Corticosteroids	53 (56.4)	55 (48.3)	29 (60.4)	137 (53.3)	297 (46.9)	270 (42.1)	10 (29.4)	70 (66.0)	647 (45.7)
Spirometry Median (IQR)	Pre Bronchodilator Raw FEV1	1.13 (0.59)	1.43 (1.26)	0.85 (0.81)	1.21 (0.91)	1.30 (0.84)	1.66 (1.24)	2.25 (1.25)	1.17 (0.80)	1.44 (1.07)
	Post Bronchodilator Raw FEV1	1.41 (0.82)	1.50 (1.27)	1.01 (0.87)	1.41 (0.96)	1.63 (1.01)	1.77 (1.26)	2.42 (1.46)	1.39 (0.92)	1.68 (1.13)
	FEV1 Predicted Value, GLI-Global	2.74 (0.69)	2.87 (0.96)	2.83 (0.83)	2.79 (0.79)	2.76 (0.89)	2.71 (0.95)	2.69 (0.78)	2.99 (0.67)	2.77 (0.90)

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	FEV1 Predicted Value, GLI-Race Specific	2.48 (0.63)	2.58 (0.86)	2.53 (0.73)	2.52 (0.72)	2.92 (0.98)	2.86 (1.03)	2.81 (0.85)	3.1 (0.69)	2.92 (1.01)
	FEV1 % Predicted, GLI-Global	50.90 (28.11)	57.36 (34.24)	37.82 (32.17)	50.90 (32.50)	64.00 (32.59)	70.33 (38.74)	99.10 (31.53)	47.67 (24.82)	65.40 (36.43)
	Pre Bronchodilator Raw FVC	2.44 (1.01)	2.78 (1.47)	2.21 (1.42)	2.55 (1.28)	2.81 (1.25)	3.10 (1.64)	3.96 (1.64)	2.78 (1.33)	2.95 (1.51)
	Post Bronchodilator Raw FVC	2.90 (1.04)	2.87 (1.51)	2.48 (1.30)	2.80 (1.27)	3.40 (1.38)	3.23 (1.70)	4.39 (1.71)	3.03 (1.26)	3.31 (1.53)
	FVC Predicted Value, GLI-Global	3.46 (0.99)	3.70 (1.33)	3.59 (1.29)	3.57 (1.13)	3.61 (1.18)	3.59 (1.30)	3.50 (1.07)	3.90 (0.92)	3.60 (1.26)
	FVC Predicted Value, GLI-Race Specific	3.15 (0.84)	3.30 (1.16)	3.20 (1.06)	3.21 (0.97)	3.82 (1.33)	3.73 (1.42)	3.68 (1.18)	4.15 (0.93)	3.82 (1.35)
	FVC % Predicted, GLI-Global	86.35 (24.89)	81.04 (26.71)	67.03 (24.24)	80.43 (26.94)	98.31 (26.91)	95.90 (28.94)	121.44 (19.13)	80.29 (19.88)	96.72 (28.99)
	FEV1/FVC	0.49 (0.18)	0.59 (0.20)	0.45 (0.25)	0.51 (0.21)	0.51 (0.19)	0.58 (0.21)	0.62 (0.18)	0.46 (0.16)	0.53 (0.21)
Outcomes Median (IQR)	SGRQ-C	43.6 (27.3)	42.3 (32.3)	44.3 (23.5)	43.4 (28.2)	35.5 (28.9)	34.2 (27.9)	27.2 (29.0)	45.5 (28.7)	35.5 (29.4)
	6-MWD	380.5 (163.1)	402.3 (147.0)	402.6 (181.4)	390.0 (153.0)	402.3 (130.6)	402.0 (164.6)	399.0 (143)	387.1 (127.0)	399.1 (142.3)

Table 1 Figure Legend.
$: 2021 BDR definition in this table uses GLI-global predicted values for the denominator of the equation
a: BDR-05 - / BDR-21 + was excluded as there was only 1 participant in that strata

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Abbreviations: BDR: bronchodilator response, GOLD: Global Initiative for Chronic Obstructive Lung Disease, BMI: body mass index, FEV1: forced expiratory volume in 1 second, FVC: forced vital capacity, SGRQ-C: St. George's Respiratory Questionnaire for COPD, 6-MWD: Six-minute walk distance

Missing: age: none; BMI: none; smoking status: 5 black, 29 white; history of asthma: 12 Black, 101 White; chronic bronchitis: 12 black, 51 white; GOLD stage severity: 1 black, 4 white; FEV1: none; FEV1% predicted: none; FVC: none; FVC % predicted: none; FEV1/FVC: none; SGRQ-C: 20 black, 91 white; 6-MWD: 22 black, 68 white; Inhaled bronchodilators at baseline: 20 white, 3 black; inhaled corticosteroids at baseline: 4 black, white 17

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Figure 1

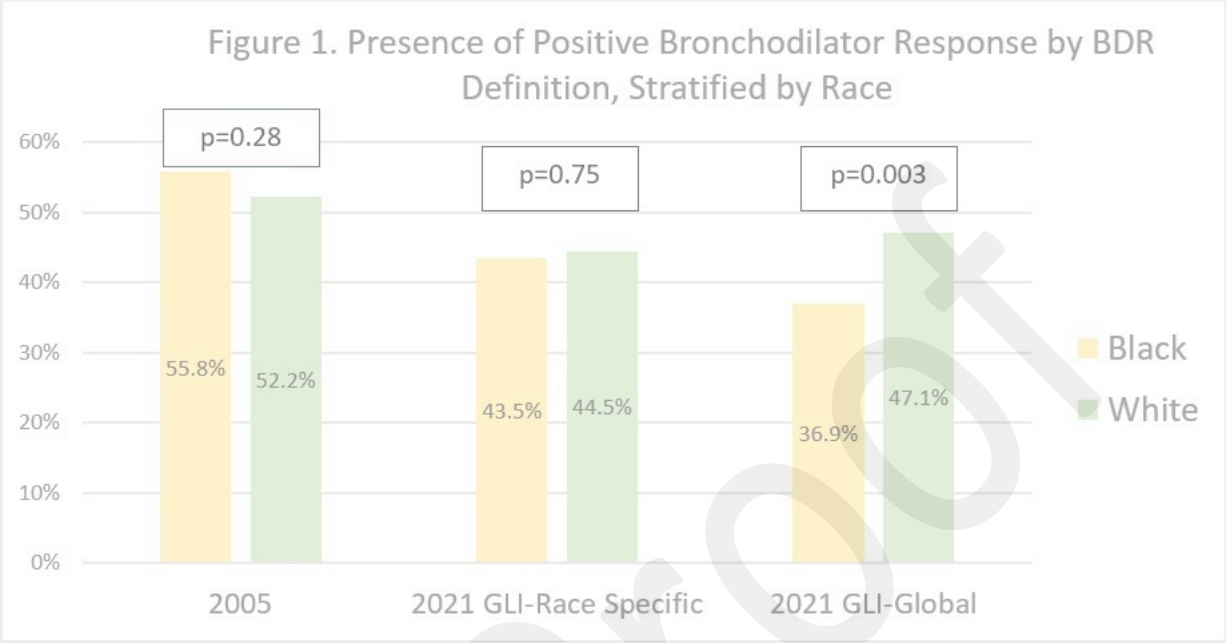

Table 1 Legend:

Abbreviations: BDR: bronchodilator response, GLI: global lung initiative

BDR definitions: BDR 2005: increase in forced expiratory volume in 1 second (FEV1) and/or forced vital capacity (FVC) greater than or equal to 12% and 200mL; BDR 2021: >10% change in FEV1 and/or FVC relative to an individual's predicted value.

Statistical tests: Chi-squared.

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