

Online Supplement

Forced Expiratory Flow at 25%-75% Links COPD Physiology to Emphysema and Disease Severity in the SPIROMICS Cohort

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Variable		Unadjusted for %predFEV ₁ ^a		Adjusted for %predFEV ₁ ^b	
		OR (95% CI)	P value	OR (95% CI)	P value
Categorical	Emph	1.754 (1.671, 1.840)	<0.0001	1.760 (1.605, 1.929)	<0.0001
	BDR (FVC or FEV ₁)	1.545 (1.485, 1.607)	<0.0001	1.160 (1.074, 1.252)	<0.0001
	mMRC	1.271 (1.227, 1.316)	<0.0001	0.922 (0.865, 0.983)	0.013
	CB	1.078 (1.047, 1.109)	<0.0001	0.981 (0.923, 1.041)	0.523
Variable		Estimate (95% CI)	P value	Estimate (95% CI)	P value
Continuous	PRM ^{fSAD}	2.586 (2.445, 2.726)	<0.0001	1.394 (1.335, 1.655)	<0.0001
	Emph-C	1.497 (1.403, 1.592)	<0.0001	0.619 (0.453, 0.786)	<0.0001
	TLC	84.918 (71.072, 98.764)	<0.0001	132.677 (105.060, 160.295)	<0.0001
	RV	166.623 (156.228, 177.018)	<0.0001	72.334 (53.975, 90.693)	<0.0001
	RV/TLC	0.023 (0.021, 0.024)	<0.0001	0.0021 (-0.001, 0.005)	0.126
	Pi10	0.002 (0.001, 0.003)	<0.0001	-0.006 (-0.008, -0.004)	<0.0001
	CAT	0.733 (0.647, 0.818)	<0.0001	-0.114 (-0.285, 0.058)	0.195
	6MWD	-7.418 (-8.685, -6.150)	<0.0001	1.500 (-1.039, 4.040)	0.247
	SGRQ score	2.370 (2.163, 2.577)	<0.0001	-0.302 (-0.708, 0.104)	0.145

e-Table S1: Prebronchodilator analysis of %predFEF₂₅₋₇₅% and clinical parameters. ^aAdjusted for smoking pack year history. ^bAdjustment includes percent predicted FEV₁ (%predFEV₁) and its square. Emph = emphysema (binary variable below -950HU), BDR = bronchodilator response, FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, mMRC = modified Medical Research Council score (Binary variable grouped as MRC score 0-1 for no clinically significant dyspnea and 2-4 for significant dyspnea), CB = Chronic bronchitis. PRM^{fSAD} = parametric response mapping functional small airways disease, TLC = total lung capacity, Emph-C = emphysema as a continuous variable, Pi10 = airway thickness relative to reference airway of 10mm, RV = residual volume, RV/TLC = ratio of residual volume to total lung capacity, CAT = COPD assessment test score, 6MWD = 6-minute walk distance, SGRQ = St. George's Respiratory Questionnaire dyspnea score. OR = Odds ratio, CI = Confidence Interval. Boldface indicates a result that retains significance and relationship integrity after adjustment for %predFEV₁. Values are presented per 10% reduction in %predFEF₂₅₋₇₅.

Variable		Unadjusted for %predFEV ₁ ^a		Adjusted for %predFEV ₁ ^b	
		OR (95% CI)	P value	OR (95% CI)	P value
Categorical	Emph	1.663 (1.593, 1.736)	<0.0001	1.534 (1.425, 1.650)	<0.0001
	BDR (FVC or FEV ₁)	1.347 (1.308, 1.387)	<0.0001	1.444 (1.365, 1.527)	<0.0001
	mMRC	1.237 (1.201, 1.275)	<0.0001	0.934 (0.896, 0.984)	0.0078
	CB	1.065 (1.040, 1.092)	<0.0001	1.042 (0.997, 1.089)	0.0673
Variable		Estimate (95% CI)	P value	Estimate (95% CI)	P value
Continuous	PRM ^{fSAD}	2.273 (2.154, 2.392)	<0.0001	0.873 (0.668, 1.078)	<0.0001
	TLC	75.054 (63.184, 86.924)	<0.0001	59.768 (38.386, 81.150)	<0.0001
	RV	146.206 (137.365, 155.048)	<0.0001	17.255 (2.415, 32.095)	0.0227
	Emph-C	1.318 (1.237, 1.398)	<0.0001	0.002 (-0.130, 0.134)	0.9783
	RV/TLC	0.020 (0.019, 0.021)	<0.0001	0.001 (-0.002, 0.003)	0.6007
	Pi10	0.002 (0.001, 0.002)	<0.0001	-0.004 (-0.006, -0.003)	<0.0001
	CAT	0.647 (0.574, 0.720)	<0.0001	-0.019 (-0.147, 0.110)	0.7731
	6MWD	-6.724 (-7.810, -5.639)	<0.0001	1.532 (-0.377, 3.442)	0.1159
	SGRQ score	2.086 (1.910, 2.263)	<0.0001	-0.108 (-0.409, 0.193)	0.4815

e-Table S2: Postbronchodilator analysis of %predFEF_{25-75%} and clinical parameters using a linear model. ^aAdjusted for smoking pack year history. ^bAdjustment includes percent predicted FEV₁ (%predFEV₁). Emph = emphysema (binary variable below -950HU), BDR = bronchodilator response, FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity, mMRC = modified Medical Research Council score (Binary variable grouped as MRC score 0-1 for no clinically significant dyspnea and 2-4 for significant dyspnea), CB = Chronic bronchitis. PRM^{fSAD} = parametric response mapping functional small airways disease, TLC = total lung capacity, Emph-C = emphysema as a continuous variable, Pi10 = airway thickness relative to reference airway of 10mm, RV = residual volume, RV/TLC = ratio of residual volume to total lung capacity, CAT = COPD assessment test score, 6MWD = 6-minute walk distance, SGRQ = St. George's Respiratory Questionnaire dyspnea score. OR = Odds ratio, CI = Confidence Interval. Boldface indicates a result that retains significance and relationship integrity after adjustment for %predFEV₁. Values are presented per 10% reduction in %predFEF₂₅₋₇₅

Variable		Unadjusted for %predFVC ^a		Adjusted for %predFVC ^b	
		OR (95% CI)	P value	OR (95% CI)	P value
Categorical	Emph	1.663 (1.593, 1.736)	<0.0001	1.761 (1.674, 1.853)	<0.0001
	BDR (FVC or FEV ₁)	1.347 (1.308, 1.387)	<0.0001	1.397 (1.351, 1.444)	<0.0001
Variable		Estimate (95% CI)	P value	Estimate (95% CI)	P value
Continuous	PRM ^{fSAD}	2.273 (2.154, 2.392)	<0.0001	2.151 (2.022, 2.279)	<0.0001
	TLC	75.054 (63.184, 86.924)	<0.0001	95.612 (82.905, 108.319)	<0.0001

e-Table S3: Postbronchodilator analysis of %predFEF_{25-75%} and strongest clinical associations with adjustment for %predFVC ^aAdjusted for age, sex, smoking pack year history. ^bAdjustment includes percent predicted forced vital capacity (%predFVC) and its square. Emph = emphysema (binary variable below -950HU), BDR = bronchodilator response, FEV₁ = forced expiratory volume in one second, FVC = forced vital capacity. PRM^{fSAD} = parametric response mapping functional small airways disease, TLC = total lung capacity. OR = Odds ratio, CI = Confidence Interval. Values are presented per 10% reduction in %predFEF₂₅₋₇₅.