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RESEARCH ARTICLE

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Quantitative CT measures of pulmonary vascular volume distribution in pulmonary hypertension associated with COPD: Association with clinical characteristics and outcomes

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Abstract

To determine whether quantitative computed tomography (qCT)-derived metrics of pulmonary vascular volume distribution could distinguish chronic obstructive pulmonary disease (COPD) subjects with associated pulmonary hypertension (PH) from those without and to characterize associations of these measurements with clinical and physiological characteristics and outcomes. We collected retrospective CT, pulmonary hemodynamic, clinical, and outcomes data from subjects with COPD and right-heart catheterization-confirmed PH (PH-COPD) and control subjects with COPD but without PH. We measured the volumes of pulmonary vessels < 5 and $>10\,mm^2$ in cross-sectional area as a percentage of total pulmonary vascular volume (qCT-derived volume of pulmonary vessels $< 5\,mm^2$ in cross-sectional area as a volume fraction of total pulmonary blood volume [BV5%] and qCT-derived

Abbreviations: A, aorta; BMI, body mass index; BV10, qCT-derived volume of pulmonary vessels $> 10\,mm^2$ in cross-sectional area; BV10%, BV10 as a volume fraction of total pulmonary blood volume; BV5, qCT-derived volume of pulmonary vessels $< 5\,mm^2$ in cross-sectional area; BV5%, BV5 as a volume fraction of total pulmonary blood volume; BV5–10, qCT-derived volume of pulmonary vessels between 5 and $10\,mm^2$ in cross-sectional area; BV5%–10%, BV5–10 as a volume fraction of total pulmonary blood volume; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CSA, cross-sectional area; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; E/A, the ratio of the early (E) to late (A) ventricular filling velocities; E/e', the ratio of early diastolic mitral inflow velocity to early diastolic mitral annulus velocity; FEV_1, forced expiratory volume in 1 s; FRI, Functional Respiratory Imaging; FVC, forced vital capacity; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; HR, hazard ratio; HU, Hounsfield unit; ICD, international classification of diseases; iVaw, qCT-derived volume of the airways >1 mm in diameter; iVlobe, qCT-derived volume of the lungs; LA, left atrium; LAS%, low attenuation score, the volume fraction of qCT-derived lung volume with attenuation values < -950 Hounsfield units following application of a binomial blur filter; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; NYHA, New York Heart Association; PA, pulmonary artery; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PH, pulmonary hypertension; PH-COPD, pulmonary hypertension associated with COPD; PVR, pulmonary vascular resistance; qCT, quantitative computed tomography; RAP, right atrial pressure; RHC, right heart catheterization; RIMP, right ventricular index of myocardial performance; SD, standard deviation; SVV, small vessel volume; TAPSE, tricuspid annular plane systolic excursion; TBV, total pulmonary blood volume; WU, wood units.

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volume of pulmonary vessels > 10 mm^2 in cross-sectional area [BV10] as a volume fraction of total pulmonary blood volume [BV10%], respectively) using Functional Respiratory Imaging (FRI), an automated qCT platform, and compared them between PH and control arms and between subjects with mild-moderate PH and those with severe disease. Correlations of hemodynamics with pulmonary function and associations with survival were tested. Forty-five PH-COPD and 42 control subjects were studied. BV5% was lower in PH subjects (32.2% vs. 37.7%, $p = 0.003$), and BV10% was higher (50.2% vs. 43.5, $p = 0.001$). Subjects with severe PH did not differ from those with mild-moderate PH in qCT. Pulmonary vascular volumes were not associated with pulmonary function. BV10 was associated with mean pulmonary artery pressure ($r = 0.3$, $p = 0.05$). Associations with survival were observed for BV5% (hazard ratio 0.63, $p = 0.02$) and BV10% (hazard ratio 1.43, $p = 0.03$) in the PH-COPD arm, but not for controls. qCT-derived measures of pulmonary vascular volume may have diagnostic and prognostic significance in PH-COPD and should be investigated further as screening and risk stratification tools

KEYWORDS
COPD, pulmonary hypertension, quantitative computed tomography, vascular pruning

BACKGROUND

Pulmonary hypertension (PH), frequently found in the context of chronic obstructive pulmonary disease (PH-COPD), is thought to have a multifactorial origin, with hypoxia, left heart disease, destruction of the vascular bed due to emphysema, and pulmonary arterial remodeling all playing a role.[1,2] PH-COPD remains a highly morbid condition, associated with worse hypoxia, more significant dyspnea, shorter 6-min walk distances, worse survival compared with COPD patients with similar degrees of airflow obstruction, and greater risk of severe exacerbations.[3–5] Detection of PH in COPD with echocardiography is technically fraught due to lung hyperinflation.[6,7] Right heart catheterization (RHC) is infrequently performed in COPD patients due to its invasive nature and the paucity of treatment options available should PH be confirmed.[2,8] There remains a substantial unmet need for diagnostic and prognostic tools to manage PH-COPD.

Advances in this area have come from quantitative computed tomography (qCT). It is now possible to automatically segment the pulmonary vascular tree and thus quantify the loss of small peripheral vessels and dilation of proximal vessels. Reduced small vessel volume (SVV) or vessels that have a surface of less than 5 mm^2 is characteristic of pulmonary arterial hypertension (PAH) and correlates with the extent of emphysema and various markers of clinical severity in subjects with COPD, including those with Global Obstructive Lung Disease stages 4 versus 1 and markers of functionality such as 6-min walk distance.[9–11] Recently, Alkhanfar et al. demonstrated that subjects with severe PH-COPD had lower SVV compared with PH-COPD subjects with mild-moderate PH and that SVV was negatively correlated with mean pulmonary artery pressure (mPAP).[12]

Our study aims were (1) determine whether qCT-measured vascular volume distribution differed between COPD subjects with and without PH; (2) characterize the relationship of these metrics to conventional metrics of disease severity and clinical outcomes, particularly survival; and (3) characterize how these measurements differed between mild-to-moderate and severe PH. We hypothesized that reduced SVV would be associated with the presence and severity of PH, as well as with worse outcomes.

METHODS

Subject selection

Patients 18 years of age and older who had consented to participate in research and were seen at Mayo Clinic Florida, Arizona, and Rochester after January 2000 were

queried by I2B2 software and included based on international classification of diseases (ICD)9/ICD10 diagnoses COPD with exacerbation, COPD with acute lower respiratory tract infection, COPD unspecified, and or other obstructive pulmonary disease.

PH arm

Subjects were queried for the availability of any of the following: a combined right and left heart catheterization, combined right and left heart catheterization including intraprocedural injection for left ventriculography, combined right and left heart catheterization including intraprocedural injection for left ventriculography imaging supervision and interpretation, combined RHC and retrograde left heart catheterization for congenital cardiac anomalies, RHC, or RHC for congenital cardiac anomalies. The selected subjects were required to have had a CT thorax without contrast material, CT thorax with and without contrast material, or CT thorax within 30 days of the RHC. Subjects were included in the PH group if they met the above criteria and had any diagnosis of primary PH, other secondary PH, PH not otherwise specified, PH due to lung disease or hypoxia, or PH unspecified. We reviewed the pulmonary hemodynamics assessed via RHC to ensure all subjects had mPAP > 20 mmHg. They were further subdivided into severe (mPAP ≥ 35 or mPAP ≥ 25 mmHg with a cardiac index < 2.0 L/min/m^2) and mild-moderate PH.

Control arm

Subjects without PH were required to have had an echocardiogram with normal right ventricular systolic pressure measurement and normal right heart function, confirming the exclusion of PH within 30 days of a CT.

Technical requirements for CT data

All CT scans were required to have been reconstructed with section thickness ≤1.5 mm, with contiguous or overlapping sections, and the entire lung within the field of view.

Data collection

CT images, demographic data, and relevant clinical and physiologic variables were collected, including hemodynamic, echocardiographic, laboratory, functional, and pulmonary function test variables from the medical record. We used ACCURINT® software to query patients who died after being lost to follow-up.

QCT analysis

Deidentified CT data was provided to FLUIDDA and postprocessed using Functional Respiratory Imaging (FRI), an automated qCT pipeline developed by FLUIDDA. We performed manual segmentation of the hilum to include extra-parenchymal hilar vessels in the vessel analysis. The following outcome measures resulted:

qCT-derived volume of pulmonary vessels < 5 mm^2 in cross-sectional area (BV5), qCT-derived volume of pulmonary vessels between 5 and 10 mm^2 in cross-sectional area (BV5–10), qCT-derived volume of pulmonary vessels > 10 mm^2 in cross-sectional area (BV10) (mL): The volume of pulmonary vessels < 5 mm^2, between 5 and 10, and >10 mm^2 in cross-sectional area (CSA), respectively. See Figure 1 for a graphic depiction of the denoted volumes.

BV5 as a volume fraction of total pulmonary blood volume (BV5%), BV5–10 as a volume fraction of total pulmonary blood volume (BV5%–10%), BV10 as a volume fraction of total pulmonary blood volume (BV10%) (%):

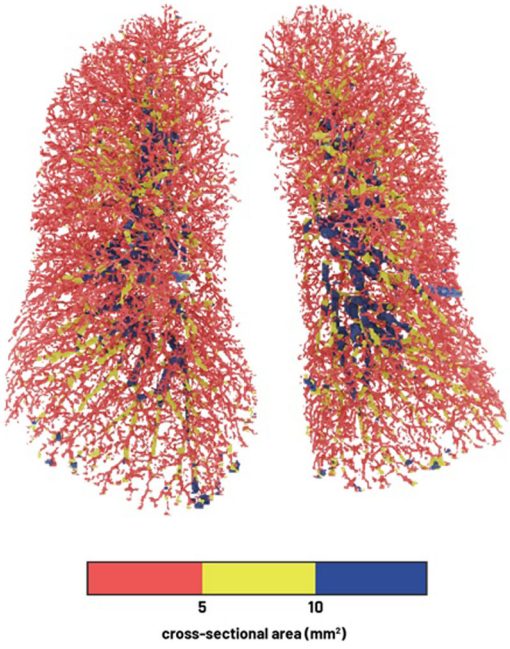

FIGURE 1 Vascular tree, color-coded by vessel cross-sectional area, for example, healthy volunteer adapted from Lins et al. Quantitative computed tomography (qCT)-derived volume of pulmonary vessels < 5 mm^2 in cross-sectional area denotes the cumulative volume of red vessels, qCT-derived volume of pulmonary vessels between 5 and 10 mm^2 in cross-sectional area yellow vessels, and qCT-derived volume of pulmonary vessels > 10 mm^2 in cross-sectional area blue vessels.

BV5, BV5–10, and BV10 expressed as a percentage of total pulmonary blood volume.

qCT-derived volume of the airways > 1 mm in diameter (iVaw) (mL): The volume of airways (>1 mm in diameter).

qCT-derived volume of the lungs (iVlobe) (L): The volume of the lungs.

Low attenuation score, the volume fraction of qCT-derived lung volume with attenuation values < −950 Hounsfield units following application of a binomial blur filter (LAS%) (%): Percent of lung volume affected by emphysema.

Fractal dimension: The fractal dimension of the segmented vasculature is computed using the box-counting method as a measure of vascular complexity.[13]

Full details of the FRI process can be found in the Supporting Information.

Statistics

Relevant demographic, clinical, physiological, echocardiographic, and qCT variables were compared between PH and no-PH (control) arms using Wilcoxon Rank Sum tests for ordinal variables and χ^2 or Fischer exact tests appropriate for nonordinal variables. We made comparisons between severe and mild-moderate PH using only qCT variables. Unless otherwise noted, listed measures of central tendency are presented as median (interquartile range).

We assessed Spearman rank correlations between qCT and pulmonary function variables for all subjects pooled, PH, and control arms. We performed a similar correlation analysis for qCT variables and pulmonary hemodynamics.

We assigned associations with survival using Cox proportional hazard models for pulmonary function and qCT parameters as continuous predictors in the PH and control arms separately and for the pooled cohort. Pulmonary hemodynamics were assessed only in the PH arm. The qCT variables of highest interest were used to stratify subjects for Kaplan–Meier estimates of overall survival to be computed, using cut-points derived using the Contal–O'Quigley method for PH and control arms separately and for the pooled cohort.[14] Median follow-up to overall survival was computed using the reverse Kaplan–Meier method.

RESULTS

Subjects

Sixty-three subjects met PH-COPD criteria; 18 were excluded as their CT did not meet the technical requirements. Six hundred and twenty patients met the criteria for no PH-COPD, and 45 were included as controls—three were later excluded because of scan quality issues. Cohort demographic and clinical characteristics are shown in Table 1, with physiological and pulmonary hemodynamic variables in Supporting Information S5: Tables 1 and 2.

Twenty-five subjects (56%) in the PH-COPD arm met the mild-moderate PH criteria, while the remaining 20 (44%) met the severe PH criteria. Within the PH arm, 22 subjects (48.9%) had additional features of postcapillary PH, with 5 (22.7%) of those having features of isolated postcapillary PH and 17 (77.3%) features of combined pre- and postcapillary PH (using a pulmonary vascular resistance [PVR] threshold of 2 wood units [WU]). Two (4.4%) subjects had PVR ≤ 2 WU and normal pulmonary capillary wedge pressure (PCWP), and one subject (PVR > 2 WU) did not have a PCWP measurement recorded.

Group comparisons

PH versus no PH

Compared with non-PH controls, subjects with PH-COPD were significantly more likely to have historical diagnoses of cardiac comorbidities (heart disease 73.3% vs. 50%, $p = 0.03$, heart failure with preserved ejection fraction 44.4% vs. 21.4%, $p = 0.02$) as well as kidney disease defined per medical record history (57.8% vs. 31%, $p = 0.01$). They were functionally more impaired in terms of the New York Heart Association (NYHA) functional class ($p < 0.001$). There were no significant differences in forced expiratory volume in 1 s (FEV_1)%, FEV_1/forced vital capacity (FVC), or diffusion capacity for carbon monoxide (DLCO)% between the two groups, though there was a trend towards milder obstruction (higher FEV_1/FVC) in the PH-COPD arm ($p = 0.09$). Table 1 and Supporting Information S5: Table 1 shows the complete group comparison.

All qCT metrics except BV10 differed significantly between PH and control groups. BV5 and BV5% were lower in the PH-COPD group [105.6 (81.3–131.4) mL vs. 131.7 (103.3–154.4 mL, 30.2 (25.5–38.5)% vs. 38.6 (34.0–43.0)%, $p = 0.002$ and $p = 0.003$, respectively], and BV10% was higher (50.5 (41.8–58.9)% vs. 42.4(37.9–48.4)%, $p = 0.001$). BV5–10 and BV5%–10% were lower in the PH group as well [58.1 (49.8–64.3) mL vs. 63.9(55.2–73.3), 16.8 (15.4–19.3)% vs. 18.7 (17.0–20.4)%, $p = 0.01$ for both]. The vessel fractal

TABLE 1 Group comparison of baseline demographic and clinical characteristics of subjects with PH-COPD and controls.

	PH-COPD, $N = 45$	COPD, $N = 42$	p Value
Female, n (%)	22 (48.9)	15 (35.7)	0.18
Age, years, mean (SD) [range]	64.8 (13) [30–85]	67.7 (9.8) [36–86]	0.42
Ethnicity, n (%)			
White	40 (90.9)	40 (97.6)	0.32
African American	2 (4.5)	1 (2.4)	
Asian	2 (4.5)	0 (0)	
Missing	1	1	
BMI, mean (SD)	38.3 (63.9)	28.9 (5.5)	0.85
Comorbidities, n (%)			
Diabetes	20 (44.4)	12 (28.6)	0.13
Hypertension	31 (68.9)	35 (83.3)	0.12
Heart disease	33 (73.3)	21 (50.0)	0.03
Atrial fibrillation	23 (51.1)	17 (40.5)	0.32
HFpEF	20 (44.4)	9 (21.4)	0.02
HFrEF	10 (22.2)	6 (14.3)	0.34
Mitral valve disease	17 (37.8)	8 (19)	0.053
Kidney disease	26 (57.8)	13 (31)	0.01
Cancer	14 (31)	19 (45)	0.17
Thyroid disease	4 (8.9)	7 (16.7)	0.28
Autoimmune disease	1 (2.2)	0 (0)	0.33
NYHA functional class, n (%)			<0.001
1	0 (0)	7 (17)	
2	11 (26)	27 (66)	
3	28 (65)	6 (15)	
4	4 (9)	1 (2)	
Missing	2	1	
6-min walk distance, n (%)			0.37
<440 m	14 (70)	9 (90)	
≥440 m	6 (30)	1 (10)	
Missing	25	32	

Abbreviations: HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; NYHA, New York Heart Association; PH-COPD, pulmonary hypertension associated with chronic obstructive pulmonary disease.

dimension was also lower compared with the control arm [1.72 (1.68–1.74) vs. 1.74 (1.72–1.76), $p = 0.007$].

iVlobe and iVaw were both lower in the PH arm [4.0 (3.5–4.7) L vs. 4.9 (4.2–6.7) L, 40.9 (32.4–49.7) mL vs. 50.6 (36.4–64.4) mL, $p < 0.001$ and $p = 0.01$, respectively]. Finally, LAS% was lower in the PH group than in the control group [0.1 (0.0–1.5)% vs. 2.3 (0.4–6.0) %, $p < 0.001$]. All between-group comparisons of qCT variables can be found in Table 2.

TABLE 2 Group comparison of quantitative CT measurements between subjects with PH-COPD and controls.

	PH-COPD, $n = 45$, median (IQR)	COPD, $n = 42$, median (IQR)	p Value
BV5, mL	105.6 (81.3–131.4)	131.7 (103.3–154.4)	0.002
BV5%	30.2 (25.5–38.5)	38.6 (34.0–43.0)	0.003
BV10, mL	167.6 (129.1–206.5)	140.7 (114.3–191.4)	0.24
BV10%	50.5 (41.8–58.9)	42.4 (37.9–48.4)	0.001
BV5–10, mL	58.1 (49.8–64.3)	63.9 (55.2–73.3)	0.01
BV5%–10%	16.8 (15.4–19.3)	18.7 (17.0–20.4)	0.01
LAS%	0.1 (0.0–1.5)	2.3 (0.4–6.0)	<0.001
IVLobe, L	4.0 (3.5–4.7)	4.9 (4.2–6.7)	<0.001
iVaw, mL	40.9 (32.4–49.7)	50.6 (36.4–64.4)	0.01
Fractal dimension	1.72 (1.68–1.74)	1.74 (1.72–1.76)	0.007

Abbreviations: BV10%, BV10 as a volume fraction of total pulmonary blood volume; BV10, qCT-derived volume of pulmonary vessels > 10 mm^2 in cross-sectional area; BV5%, BV5 as a volume fraction of total pulmonary blood volume; BV5, qCT-derived volume of pulmonary vessels < 5 mm^2 in cross-sectional area; BV5%–10%, BV5–10 as a volume fraction of total pulmonary blood volume; BV5–10, qCT-derived volume of pulmonary vessels between 5 and 10 mm^2 in cross-sectional area; CI, cardiac index; COPD, chronic obstructive pulmonary disease; CT, computed tomography; DLCO, diffusion capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; LAS%, low attenuation score, the volume fraction of qCT-derived lung volume with attenuation values < −950 Hounsfield units following application of a binomial blur filter; mPAP, mean pulmonary artery pressure; PCWP, pulmonary capillary wedge pressure; PVR, pulmonary vascular resistance; qCT, quantitative computed tomography.

Mild-moderate versus severe PH

Neither qCT vessel nor emphysema measures differed significantly between mild-moderate and severe PH, though LAS% was lower in the severe than the mild-moderate group [0.0 (0.0–0.2)% vs. 0.7 (0.0–2.9)%, $p = 0.08$]. These comparisons are shown in Supporting Information S5: Table 3.

Pulmonary function and pulmonary hemodynamics

No significant correlations were observed between qCT vessel parameters and pulmonary function, considering the PH and control arms separately and pooled. In the PH-COPD arm, a borderline significant negative

association between BV10% and DLCO% was observed ($r = -0.2$, $p = 0.09$). The control arm had a significant positive association between BV5%–10% with FEV_1% and FEV_1/FVC. The complete results of this analysis can be seen in Supporting Information S5: Table 4.

The correlations between vascular parameters and pulmonary hemodynamics were significant for a positive association between BV10 and mPAP ($r = 0.3$, $p = 0.05$). The results of this analysis are shown in Supporting Information S5: Table 5.

Survival

Median follow-up to overall survival was 9.5 years for the pooled cohort, 9.5 years for the PH-COPD arm, and 11 years for the control arm. Median survival was 5.9 years in subjects with PH and 11.1 years in those without PH. There were 30 recorded deaths in the PH group (66.67%) and 17 (40.04%) among the controls.

Univariate Cox proportional hazard ratios (HRs)

The presence of PH was associated with a significantly greater risk of death (HR: 2.32, $p = 0.007$), as was increased age (HR: 1.42 per 10 years, $p = 0.003$). Lower FEV_1% and FEV_1/FVC were associated with increased risk of death in the pooled cohort and the control arm but not in the PH group (FEV_1: HR: 0.78 and HR:0.55 per 10%, $p = 0.001$, and $p < 0.001$, for

TABLE 3 Univariate Cox hazard regression for pooled, control, and PH-COPD arms, respectively.

	All subjects, $n = 87$		COPD (no PH), $N = 42$		PH-COPD, $n = 45$	
	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value	Hazard ratio (95% CI)	*p* Value
Baseline characteristics						
Presence of PH	2.32 (1.27–4.27)	0.007	n/a	n/a	n/a	n/a
Age (per 10 years)	1.54 (1.16–2.05)	0.003	n/a	n/a	n/a	n/a
Physiological and hemodynamic characteristics						
FEV_1%, per 10%	0.78 (0.68–0.9)	0.001	0.55 (0.4–0.76)	<0.001	0.88 (0.74–1.05)	0.16
FEV_1/FVC, per 10	0.8 (0.66–0.97)	0.03	0.56 (0.38–0.81)	0.002	0.87 (0.7–1.09)	0.22
DLCO%, per 10%	0.74 (0.62–0.87)	<0.001	0.73 (0.57–0.93)	0.009	0.73 (0.56–0.95)	0.02
mPAP	n/a	n/a	n/a	n/a	1.01 (0.97–1.05)	0.68
PVR	n/a	n/a	n/a	n/a	1.05 (0.99–1.12)	0.11
PCWP	n/a	n/a	n/a	n/a	0.97 (0.91–1.03)	0.26
Cardiac index	n/a	n/a	n/a	n/a	1.02 (0.67–1.53)	0.94
Quantitative CT						
BV5, per 10 mL	0.96 (0.88–1.06)	0.42	1.18 (0.98–1.41)	0.07	0.95 (0.85–1.07)	0.4
BV5%, per 10%	0.6 (0.44–0.84)	0.003	0.89 (0.47–1.68)	0.71	0.63 (0.42–0.93)	0.02
BV10, per 10 mL	1.07 (1.02–1.12)	0.005	1.05 (0.98–1.13)	0.18	1.09 (1.02–1.17)	0.02
BV10%, per 10%	1.49 (1.15–1.94)	0.003	1.13 (0.65–1.96)	0.67	1.43 (1.031.99	0.03
BV5–10, per 10 mL	1.13 (0.92–1.39)	0.23	1.41 (1.02–1.94)	0.04	1.25 (0.89–1.76)	0.2
BV5%–10%, per 10%	0.52 (0.2–1.35)	0.18	0.75 (0.12–4.5)	0.75	0.68 (0.22–2.12)	0.51
Fractal dimension, per 0.1	0.46 (0.21–1.02)	0.06	2.05 (0.35–11.93)	0.43	0.52 (0.22–1.24)	0.43
LAS%, per 10%	1.15 (0.86–1.54)	0.35	4.09 (1.85–9.04)	0.001	0.97 (0.68–1.37)	0.847

Abbreviations: BV10%, BV10 as a volume fraction of total pulmonary blood volume; BV10, qCT-derived volume of pulmonary vessels > 10 mm2 in cross-sectional area; BV5%, BV5 as a volume fraction of total pulmonary blood volume; BV5, qCT-derived volume of pulmonary vessels < 5 mm2 in cross-sectional area; BV5%–10%, BV5–10 as a volume fraction of total pulmonary blood volume; BV5–10, qCT-derived volume of pulmonary vessels between 5 and 10 mm2 in cross-sectional area; CT, computed tomography; IQR, interquartile range; iVaw, qCT-derived volume of the airways > 1 mm in diameter; iVlobe, qCT-derived volume of the lungs; LAS%, low attenuation score, the volume fraction of qCT-derived lung volume with attenuation value < −950 Hounsfield units following application of a binomial blur filter; PH-COPD, pulmonary hypertension associated with chronic obstructive pulmonary disease; qCT, quantitative computed tomography.

overall and control, respectively; FEV_1/FVC: HR: 0.8 and HR: 0.56 per 10, $p = 0.03$, and, $p = 0.002$ for overall and control, respectively). Lower DLCO% was a significant predictor of mortality in general and both subgroup analyses (HR: 0.74, HR: 0.73, and HR: 0.73 per 10%, $p < 0.001$, $p = 0.009$, $p = 0.02$ for overall, control, and PH, respectively). Notably, no hemodynamic variable was significantly associated with survival in those patients with PH-COPD and who had RHC.

Lower BV5% was associated with increased risk of death in both the overall pooled analysis (HR: 0.6 per 10%, $p = 0.003$) and in the PH subgroup analysis (HR: 0.63 per 10%, $p = 0.02$), as was higher BV10 and BV10%. Curiously, near-significant and significant associations between *increased* BV5 and BV5–10 (but not BV5% or BV5%–10%) and risk were observed in the control arm ($p = 0.07$ and 0.04, respectively). A lower fractal dimension was not associated with an increased risk of death in the overall cohort ($p = 0.06$). LAS% was strongly associated with risk in the control arm (HR: 4.09, $p = 0.001$) but not in the overall analysis or the PH-COPD arm. The complete results of the univariate Cox analysis can be found in Table 3.

Kaplan–Meier estimate for overall survival

Survival as a function of PH status is shown in Figure 2. Cut-points for Kaplan–Meier analysis and associated univariate Cox HRs are shown in Supporting Information S4: Table 6 using BV5, BV5%, BV10, BV10%, and LAS%. Resultant survival curves are shown in Figures 2 and 3 and Figures S1 and S2. Of note, a BV5% < 40% was associated with an 8.41 increased risk of death in the PH arm.

LIMITATIONS

Resource constraints and data availability limited our sample size, so we could not include enough pre- and postcapillary PH to analyze the groups separately. Data were retrospective and based on ICD codes, raising the possibility of inaccurate diagnoses, though PH diagnoses were confirmed with RHC data, obstruction by pulmonary function tests, and emphysema radiographically. Other obstructive lung diseases could have been included such as chronic bronchitis, bronchiectatic airway disease, or chronic asthma. CT data were not

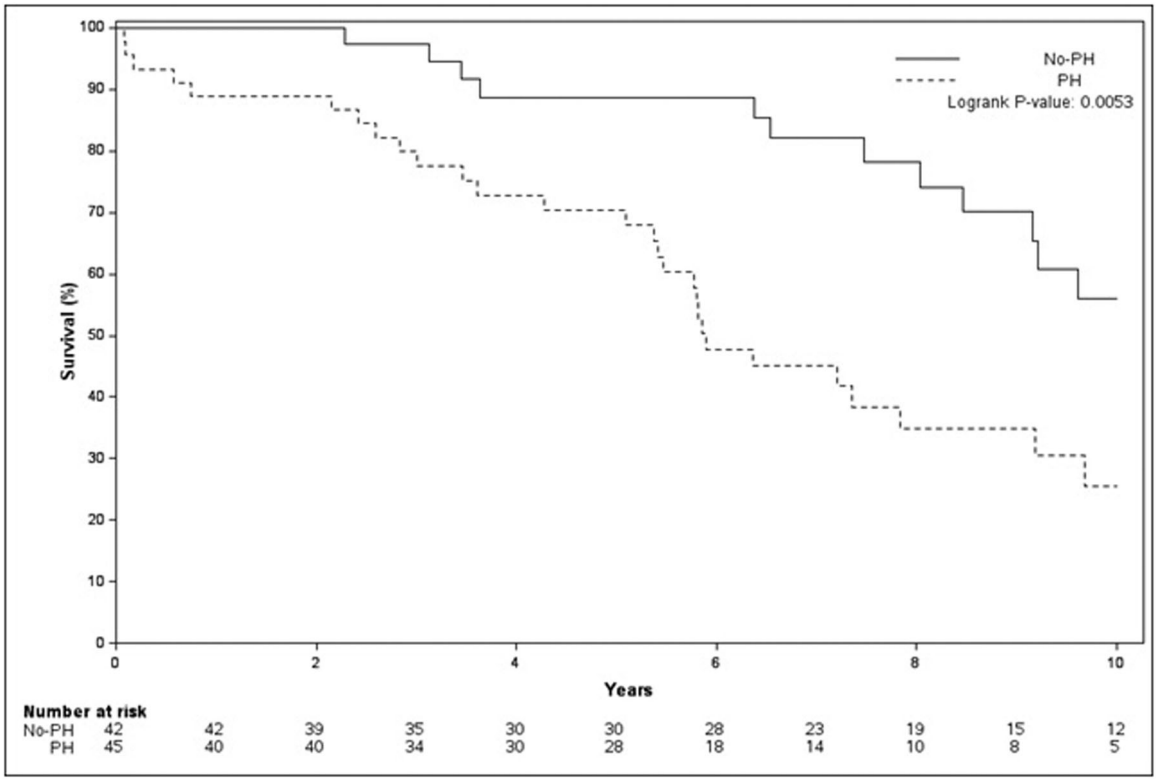

FIGURE 2 Kaplan–Meier survival curves comparing survival of subjects with pulmonary hypertension (PH) ($n = 45$) and no-PH controls ($n = 42$).

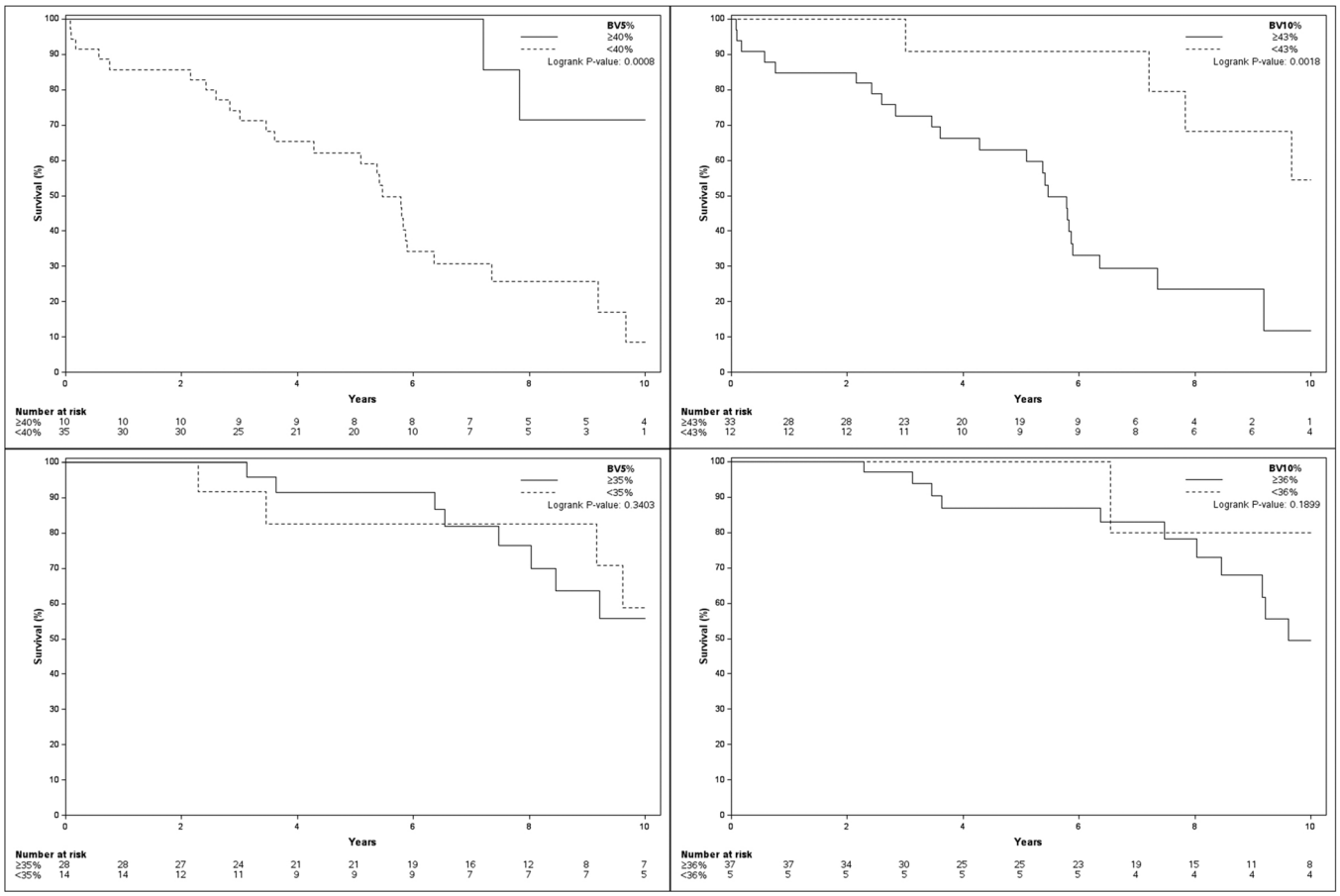

FIGURE 3 Kaplan–Meier survival curves for pulmonary hypertension associated with chronic obstructive pulmonary disease ($n = 45$, top row) and control ($n = 42$, bottom row) arms, stratified according to quantitative computed tomography (qCT)-derived volume of pulmonary vessels < 5 mm^2 in cross-sectional area as a volume fraction of total pulmonary blood volume (left) and qCT-derived volume of pulmonary vessels > 10 mm^2 in cross-sectional area as a volume fraction of total pulmonary blood volume (right) with cut points determined using the Contal–O'Quigley method.

standardized, and reconstructions varied considerably concerning the reconstruction algorithm, use of contrast, and indication for scans; we controlled this variability to the extent possible by imposing specific technical requirements. Nevertheless, more control subjects (40%) had contrast scans than PH subjects (20%). While there is limited data available regarding the impact of contrast on these measurements, one large ($n = 508$) retrospective study of subjects hospitalized with acute respiratory complaints observed no difference ($p = 0.23$) in BV5% between subjects whose scans had been acquired with contrast and those without, so the impact of this imbalance is likely small.[15] Patients with increased pulmonary venous pressures were included, representing a significant portion of the cohort; while imperfect, this also reflects the reality of limitations in measuring wedge pressures in patients with comorbid respiratory and cardiac disease.

DISCUSSION

The present is the first study where a comparison of blood vessel characteristics by qCT and clinical parameters was made between patients with COPD and PH demonstrated by RHC versus COPD without PH.

Radiographic pulmonary vessel measurements have been studied for decades.[16] An increase in the ratio of the diameter of the pulmonary artery to the ascending aorta (PA:A) in COPD is linked to the risk of severe exacerbations, worse survival, and increased mPAP, and outperforms echocardiography at diagnosing PH in this group.[7,17,18] qCT has made possible automatic measurement of small vessel characteristics, which have been shown to correlate with the extent of emphysema, lower resting oxygen saturation, more significant symptom burden, and increased right ventricular volume absent known PH.[9,11] Rahaghi et al. showed that subjects with (PAH) had significantly reduced BV5 and increased

large vessel volume compared with healthy volunteers, a signature "redistribution" from small to large vessels which is now thought to characterize PH.[10]

Loss of SVV on qCT is often referred to as "pruning," suggesting obliteration of distal arterioles and capillaries. However, current CT resolution visualizes only the largest arterioles, and the capillary bed is not directly resolvable. Vessel CSA is also variable—proximal artery dilation is characteristic of PH, resulting in vessels typically smaller than 5 mm^2 in CSA growing above that cut-off, ultimately leading to an apparent "loss" of SVV. Pruning is likely a contributor to reduced SVV but not the only mechanism.

Our results suggest that, like PAH, PH-COPD is characterized by reduced BV5(%) and increases in BV10% compared to non-PH controls. These differences were most striking when expressed as volume fractions due to the complementarity of change in small and large vessels; we also speculate that normalized volumes are more robust to normal anatomic variability. Notably, the non-PH subjects had more emphysema, which is associated with reduced BV5.[9] Figure 4 shows example vessel trees from PH and non-PH subjects, color-coded according to vessel size. Figure 5 depicts the same control subject; an area of focal pruning, reflecting emphysema, is indicated, and the same vessel tree with emphysema overlaid in gray is shown alongside. We conjecture that loss of SVV due to emphysema is phenotypically distinct from loss associated with PH due to its spatially limited extent and lack of concomitant proximal vessel dilatation. Likewise, vessel fractal dimension, a measure of vascular tree complexity, was significantly lower in the PH subjects. These findings point to the possible utility of qCT to improve PH screening in COPD populations. We also note that despite similar pulmonary function between arms, PH subjects had significantly lower qCT-derived measurements of lung and airway volumes. The significance of this finding needs to be clarified. However, we speculate that it reflects the impact of cardiomegaly compressing lung tissue and airways based on visual examination of the images.

Consistent with our hypotheses, lower BV5% and higher BV10% were associated with worse survival in both the PH-COPD and pooled groups. We contemplate that the survival effect in the pooled group was driven by the strong association of low BV5% and high BV10% with the presence of PH, which was strongly associated with worse survival. This signal was still significant within the PH-COPD group, suggesting that these measurements capture physiologically relevant processes not reflected in hemodynamic severity. No hemodynamic variable was associated with survival, and qCT was not generally correlated with hemodynamics. This differs from findings reported by Alkhafar et al. and may be explained by the lack of a standardized imaging protocol in our study, variability that is known to affect blood vessel measurements, the inclusion of subjects with elevated pulmonary venous pressures, and the user-dependent nature of RHC

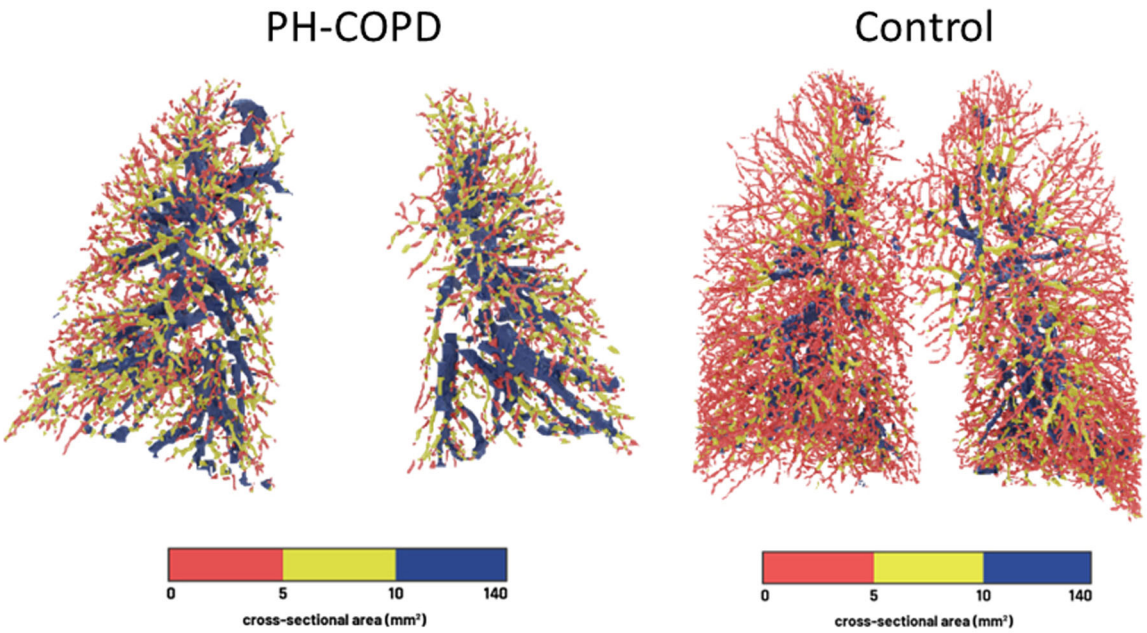

FIGURE 4 Vascular trees, color-coded by vessel cross-sectional area, for a subject with pulmonary hypertension (PH) associated with chronic obstructive pulmonary disease (PH-COPD) (left and a control subject (right). Note the paucity of small vessels (red) and prominence of large vessels (blue) in the subject with PH.

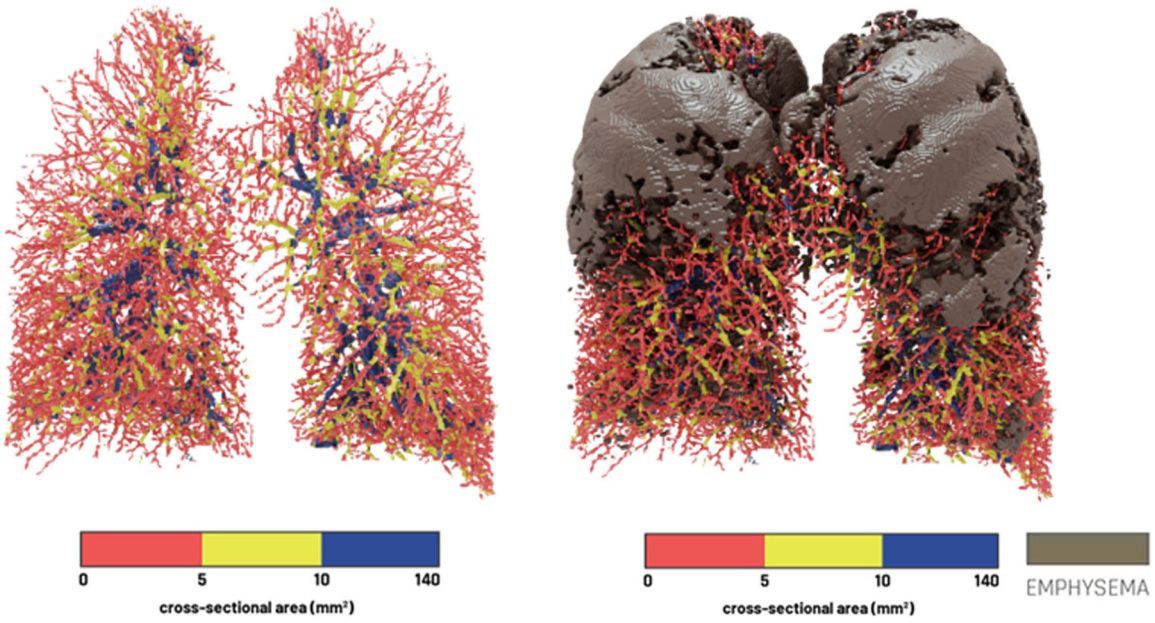

FIGURE 5 Vascular trees, color-coded by vessel cross-sectional area, for the same control subject shown in Figure 4 on the left, with the same vascular tree shown on the right with regions of emphysema depicted in gray. Note how emphysema coincides spatially with focal regions of low small vessel density (red).

readings, which in our case were collected over more than two decades.[12] Also, unlike Alkhanfar, we did not find significant differences in vessel characteristics between severe and mild-moderate PH despite severe PH being overrepresented in our cohort. This may stem from the fact that the authors of that paper analyzed the pulmonary arteries only, whereas our data included the pulmonary veins. Because pruning of distal vessels and dilatation of proximal vessels occur primarily within the arterial compartment, we speculate that the magnitude of effects would have been larger were arterial and venous components separated. Intriguingly, subjects with severe PH had *less* emphysema than those with non-severe PH, though the difference did not quite reach significance ($p = 0.08$). The extent of emphysema was also not associated with outcomes in the PH group, in stark contrast to the control group. This reinforces the idea that PH in COPD, particularly severe, progressive PH, is at least partly independent of COPD disease severity; additional work is needed to untangle this interplay.[19]

Despite the limitations, these strong results motivate additional studies of this quantification modality in larger, protocolized observational cohorts. In particular, they point to the possible utility of vascular volume quantification as a risk stratification tool, potentially helpful both in clinical decision-making and as a cohort enrichment tool in events-driven clinical trials and a noninvasive screening tool for PH in COPD.

AUTHOR CONTRIBUTIONS

Hector R. Cajigas and Ben Lavon co-primary authors contributed to the original idea, design, manuscript preparation, and editing. Patrick Muchmore, William Harmsen, and Sydney Pulsifer contributed to statistical method design and analysis. Joana Costa, Charles Mussche, and JanDe Backer contributed to imaging processing, editing, and design.

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CONFLICT OF INTEREST STATEMENT

B. L., P. M., C. M., J. C., and J. D. B. are FLUIDDA Inc. employees who funded this project through an unrestricted grant. The remaining authors declare no conflict of interest.

ETHICS STATEMENT

This study followed ethical principles according to the Declaration of Helsinki and US Food and Drug Administration guidelines (Code of Federal Regulations Title 21, part 812; and Good Clinical Practices recommended by the International Organization for Standardization ISO 14155:2011). The study was approved by the Mayo Clinic Institutional Review Board.

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REFERENCES

1. García AR, Piccari L. Emerging phenotypes of pulmonary hypertension associated with COPD a field guide. Curr Opin Pulm Med. 2022;28:343–51.
2. Blanco I, Tura-Ceide O, Peinado V, Barberà JA. Updated perspectives on pulmonary hypertension in COPD. Int J Chron Obstruct Pulmon Dis. 2020;15:1315–24.
3. Cuttica MJ, Kalhan R, Shlobin OA, Ahmad S, Gladwin M, Machado RF, Barnett SD, Nathan SD. Categorization and impact of pulmonary hypertension in patients with advanced COPD. Respir Med. 2010;104(12):1877–82.
4. Kessler R, Faller M, Weitzenblum E, Chaouat A, Aykut A, Ducoloné A, Ehrhart M, Oswald-Mammosser M. "Natural history" of pulmonary hypertension in a series of 131 patients with chronic obstructive lung disease. Am J Respir Crit Care Med. 2001;164(2):219–24.
5. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 1999;159(1):158–64.
6. Arcasoy SM, Christie JD, Ferrari VA, Sutton MSJ, Zisman DA, Blumenthal NP, Pochettino A, Kotloff RM. Echocardiographic assessment of pulmonary hypertension in patients with advanced lung disease. Am J Respir Crit Care Med. 2003;167(5):735–40.
7. Iyer AS, Wells JM, Vishin S, Bhatt SP, Wille KM, Dransfield MT. CT scan-measured pulmonary artery to aorta ratio and echocardiography for detecting pulmonary hypertension in severe COPD. Chest. 2014;145(4):824–32. https://doi.org/10.1378/chest.13-1422
8. Nathan SD, Barbera JA, Gaine SP, Harari S, Martinez FJ, Olschewski H, Olsson KM, Peacock AJ, Pepke-Zaba J, Provencher S, Weissmann N, Seeger W. Pulmonary hypertension in chronic lung disease and hypoxia. Eur Respir J. 2019;53(1):1801914.
9. Estépar RSJ, Kinney GL, Black-Shinn JL, Bowler RP, Kindlmann GL, Ross JC, Kikinis R, Han MK, Come CE, Diaz AA, Cho MH, Hersh CP, Schroeder JD, Reilly JJ, Lynch DA, Crapo JD, Wells JM, Dransfield MT, Hokanson JE, Washko GR. Computed tomographic measures of pulmonary vascular morphology in smokers and their clinical implications. Am J Respir Crit Care Med. 2013;188(2):231–9.
10. Rahaghi FN, Nardelli P, Harder E, Singh I, Sánchez-Ferrero GV, Ross JC, San José Estépar R, Ash SY, Hunsaker AR, Maron BA, Leopold JA, Waxman AB, San José Estépar R, Washko GR. Quantification of arterial and venous morphologic markers in pulmonary arterial hypertension using CT imaging. Chest. 2021;160(6):2220–31.
11. Washko GR, Nardelli P, Ash SY, Vegas Sanchez-Ferrero G, Rahaghi FN, Come CE, Dransfield MT, Kalhan R, Han MK, Bhatt SP, Wells JM, Aaron CP, Diaz AA, Ross JC, Cuttica MJ, Labaki WW, Querejeta Roca G, Shah AM, Young K, Kinney GL, Hokanson JE, Agustí A, San José Estépar R. Arterial vascular pruning, right ventricular size, and clinical outcomes in chronic obstructive pulmonary disease. A longitudinal observational study. Am J Respir Crit Care Med. 2019;200(4):454–61.
12. Alkhanfar D, Shahin Y, Alandejani F, Dwivedi K, Alabed S, Johns C, Lawrie A, Thompson AAR, Rothman AMK, Tschirren J, Uthoff JM, Hoffman E, Condliffe R, Wild JM, Kiely DG, Swift AJ. Severe pulmonary hypertension associated with lung disease is characterised by a loss of small pulmonary vessels on quantitative CT. ERJ Open Res. 2022;8(2):00503–2021.
13. Helmberger M, Pienn M, Urschler M, Kullnig P, Stollberger R, Kovacs G, Olschewski A, Olschewski H, Bálint Z. Quantification of tortuosity and fractal dimension of the lung vessels in pulmonary hypertension patients. PLoS One. 2014;9(1):e87515.
14. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. Comput Stat Data Anal. 1999;30(3):253–70.
15. Morris MF, Pershad Y, Kang P, Ridenour L, Lavon B, Lanclus M, Godon R, De Backer J, Glassberg MK. Altered pulmonary blood volume distribution as a biomarker for predicting outcomes in COVID-19 disease. Eur Respir J. 2021;58(3):2004133.
16. Ng CS, Wells AU, Padley SPG. A CT sign of chronic pulmonary arterial hypertension: the ratio of main pulmonary artery to aortic diameter. J Thorac Imaging. 1999;14(4):270–8.
17. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, Regan E, Bailey WC, Martinez FJ, Westfall E, Beaty TH, Curran-Everett D, Curtis JL, Hokanson JE, Lynch DA, Make BJ, Crapo JD, Silverman EK, Bowler RP, Dransfield MT. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med. 2012;367(10):913–21.
18. LaFon DC, Bhatt SP, Labaki WW, Rahaghi FN, Moll M, Bowler RP, Regan EA, Make BJ, Crapo JD, Estepar RSJ, Diaz AA, Silverman EK, Han MK, Hobbs B, Cho MH, Washko GR, Dransfield MT, Wells JM, COPDGene Investigators. Pulmonary artery enlargement and mortality risk in moderate to severe COPD: results from COPDGene. Eur Respir J. 2019;55(2):1901812.
19. Kovacs G, Agusti A, Barberà JA, Celli B, Criner G, Humbert M, Sin DD, Voelkel N, Olschewski H. Pulmonary vascular involvement in chronic obstructive pulmonary disease. is there a pulmonary vascular phenotype? Am J Respir Crit Care Med. 2018;198(8):1000–11.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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