Prognostics significance of small pulmonary vessels alteration measured by chest CT in connective tissue diseases with PAH

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Abstract

Background

Pulmonary arterial hypertension (PAH) is characterized by structural alterations of the pulmonary vessels. Few studies have explored the clinical significance of quantitative assessment of pulmonary small vessels by chest CT. Our aim was to assess whether the prognosis of connective tissue diseases (CTD)-PAH patients could be assessed through pulmonary small vessels measured by chest CT.

Methods

42 CTD-PAH patients diagnosed based on right heart catheterization were retrospectively investigated. All patients underwent a chest CT within 1 month before and after RHC examination. Main pulmonary artery (MPA), the cross-sectional area of small pulmonary vessels $< 5 \text{ mm}^2$ as a percentage of total lung area ($\%CSA_{<5}$) were measured. The primary endpoint was a composite clinical worsening endpoint.

Results

After a median follow-up time of 30.5 (IQR, 8.5-45.25) months, endpoint events occurred in 16 (38.1%) patients after 19.5 (IQR 10.0-45.5) months. Cox univariate proportional hazard analysis showed that pulmonary vascular resistance, MPA diameter, and $\%CSA_{<5}$ were associated with the endpoint. A combination of MPA diameter and $\%CSA_{<5}$ was the independent risk factor for the prognosis (hazard ratio, 2.180 [95% CI, 1.405–3.383], $P = 0.001$). Kaplan-Meier analysis showed that CTD-PAH patients satisfying $\%CSA_{<5}$ less than 0.382 and MPA greater than 36.75 mm had the highest risk of experiencing the endpoint.

Conclusion

Among the pulmonary vascular indicators measured by chest CT, in addition to MPA, $\%CSA_{<5}$ may be a potential independent risk factor for poor long-term prognosis in Chinese CTD-PAH patients.

Introduction

Pulmonary arterial hypertension (PAH), is a progressive disorder of the pulmonary circulation characterized by vascular remodeling within precapillary pulmonary arterioles leading to an increase in pulmonary vascular resistance (PVR) and right ventricular failure[1]. Connective tissue diseases (CTD) is one of the common causes of PAH, rank only to congenital heart disease and idiopathic pulmonary arterial hypertension (IPAH) in China[2]. The survival rate of CTD patients with PAH is much lower than that of patients without PAH[3, 4], the prognosis of CTD-PAH and its response to targeted drugs are worse than IPAH[5–7].

Multi-parameters risk stratification plays an important role in judging the prognosis of patients with PAH and guiding treatment decisions[1]. At present, the indicators in risk stratification mainly come from the parameters of right heart catheterization (RHC), echocardiographic assessment of right heart function, and others such as

6-minute walking distance (6-MWD) and WHO function class. However, these indicators have a few limitations: RHC is an invasive diagnostic method and cannot be performed without an appropriate indication; besides, it is not feasible to be performed as a routine follow-up technique[8–11]. Echocardiography is limited by the operator experience and acoustic window, which substantially affect the accuracy and reproducibility of this approach[12, 13]. The 6-MWD cannot be applied to patients with severe illness or patients who have difficulty walking with lower limbs, and WHO function class is not absolutely objective[14].

As an objective and convenient method, chest CT can be used to evaluate the pulmonary parenchyma, pulmonary interstitial, and pulmonary vascular lesions, which is widely used in CTD patients[15]. A growing number of studies have shown that pulmonary vascular parameters measured on chest CT, including main pulmonary artery (MPA) diameter, the ratio of MPA to ascending aorta (MPA/AAO), have diagnostic and prognostic value in patients with PAH[16–21]. Our previous study showed that in patients with CTD-PAH, MPA greater than 37.7 mm was a potential independent risk factor of the poor long-term prognosis[22]. In addition, recent studies have shown that the cross-sectional area of small pulmonary vessels $< 5 \text{ mm}^2$ as a percentage of total lung area ($\% \text{CSA}_{\leq 5}$) plays an important role in diagnosis and severity assessment of PAH and COPD-related pulmonary hypertension[23–27]. However, the prognostic value of $\% \text{CSA}_{\leq 5}$ in PAH remains unknown. Therefore, here we will explore whether $\% \text{CSA}_{\leq 5}$ is associated with poor prognosis and can be used as a predictive indicator for screening high-risk populations of CTD-PAH patients.

Material And Methods

Subjects

In the present study, we retrospectively analyzed the medical records and clinical characteristics of CTD patients diagnosed with PAH by RHC hospitalized in the First Affiliated Hospital of Nanjing Medical University between January 1, 2010 and September 1, 2020. Inclusion criteria were listed as follows: (1) a confirmed diagnosis of PAH according to the 2015 guidelines[1]; (2) meeting the diagnostic criteria for each subcategory of CTD: Systemic lupus erythematosus (SLE) was diagnosed according to 1997 American Rheumatism Association (ACR) criteria[28], Sjogren's syndrome (SS) was diagnosed according to 2002 international classification criteria[29], systemic sclerosis (SSc) was defined according to 1980 ACR criteria[30]; mixed CTD (MCTD) was defined by Sharp's criteria[31]; (3) having undergone chest CT within 1 month before or after RHC and the patients' condition was stable during the two examination intervals. The exclusion criteria included: (1) congenital heart disease; (2) other causes of precapillary PH (such as PH due to respiratory diseases, chronic thromboembolic PH, or other miscellaneous causes of PAH); (3) significant valvular heart disease of more than moderate to severe or LV ejection fraction $< 50\%$ diagnosed by echocardiography; (4) coexisting pulmonary conditions on computed tomography scan affected quantitative CT measurements: moderate or severe pulmonary interstitial fibrosis, current pneumonia, massive pleural effusion.

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (number: 2018-SR-333). As all variables were obtained retrospectively from available clinical data, the need for patients to sign informed consent was waived.

CT measurement of pulmonary vessels

The diameter of the MPA and AAO was measured at the level of MPA bifurcation in its maximum dimension (Figure 2A)[32].

To measure the CSA of small pulmonary vessels, three slices were selected. Three plain CT axial slices: 1 cm above the upper margin of the aortic arch (upper slice), 1 cm below the carina (middle slice), and 1cm below the right inferior pulmonary vein (lower slice).

Subsequently, images were analyzed with semiautomatic quantitative image-processing Image J software (version 1.48; National Institutes of Health, Bethesda, MD, USA). %CSA_{<5} we calculated according to the method reported by Matsuoka et al[23]. On each CT slice, %CSA_{<5} was obtained with the “Analyze Particles” function to count and measure objects on binary images, the number of vessels at a specified size and the CSA of each size range were obtained. Notably, the vessels that ran obliquely or parallel to the slice were excluded using the “Circularity” function in Image J (Figure 2B-D)[24].

Clinical outcome

The primary endpoint was a composite clinical worsening endpoint (including all-cause mortality, worsening World Health Organization functional class, $\geq 15\%$ reduction in 6-MWD, all-cause hospitalization, or the introduction of parenteral prostacyclin analog therapy)[33]. The time of follow-up was calculated as the time from RHC examination to the end of the study (September 1, 2020) or to the composite endpoint of clinical deterioration, whichever came first. The follow-up data were obtained from hospital records. All patients were contacted to reconfirm survival status by telephone personal interview of the patient or family members at the end of the study.

Statistical Analyses

All statistical analyses were performed using Statistical Package for the Social Sciences (SPSS) (ver 25.0, International Business Machines, Inc. Armonk, New York, USA). Qualitative data were expressed as frequency (percentage) and compared using χ^2 test or Fisher exact test. Quantitative data were expressed as mean $\pm$ standard or median (interquartile range [IQR]) and compared among groups by Student’s-test or Mann-Whitney U test. The correlation between hemodynamic parameters and quantitative CT parameters was assessed by Pearson’s correlation coefficient. Receiver-operating characteristic curves were generated to assess the effectiveness of the %CSA_{<5} and MPA as targeting risk factors to predict the endpoint by evaluating the sensitivity and specificity of the scales. Results were expressed in terms of area under the curve (AUC) and 95% confidence interval for this area. We define the corresponding cutoff for each variable by the difference maximization method, and the patients were further divided into 3 groups according to the cutoff of the %CSA_{<5} and MPA. We use “pulmonary vasculature metrics” to define classification based on the cutoff values of %CSA_{<5} and MPA. The prognostic value of selected baseline parameters was tested using Cox’s univariate proportional hazards regression analysis, and the variables that were significant in the univariate model were then entered into a multivariate Cox model. The results were expressed as hazard ratios (HR) with 95% CI. Kaplan-Meier method was used to calculate time-to-event function among 3 groups and differences were assessed using the log-rank statistic. All P-values were two-sided and a P-value<0.05 was considered statistically significant.

Results

The baseline characteristics of CTD-PAH patients with or without endpoint events

According to the inclusion and exclusion criteria, a total of 42 patients were enrolled retrospectively (Figure 1). Baseline demographics, clinical characteristics, hemodynamic, echocardiographic, and chest CT parameters are provided in Table 1. After a median follow-up time of 30.5 (IQR, 8.5-45.25) months, endpoint events occurred in 16 (38.1%) patients after 19.5 (IQR 10.0-45.5) months. As shown in Table 1, patients with endpoint events were characterized by elevated PVR, larger MPA diameter, and smaller %CSA_{<5}.

Relationships between hemodynamic parameters and quantitative CT parameters

The parameter related to small vessels, %CSA_{<5} correlated negatively with mPAP and PVR and positively with CI (Figure 3). At the large vascular level, a positive correlation was found between mPAP and MPA/AAO (Supplement figure 1), MPA and PVR (Supplement figure 1).

Factors predicting endpoint events

ROC analysis showed that the optimal cutoff for %CSA_{<5} and MPA were 0.382 and 36.75 mm, respectively, and the areas under their corresponding ROC were 0.762 and 0.850. A cutoff value for %CSA_{<5} of 0.382 demonstrated a sensitivity of 96.2% and a specificity of 62.5%. A cutoff value for MPA of 36.75 mm demonstrated a sensitivity of 93.8% and a specificity of 65.4% (Supplement figure 2).

Univariate Cox regression analysis was performed to identify variables affecting prognosis. We identified that hemodynamic parameter, PVR, and morphological CT parameters including MPA and %CSA_{<5} might be used as risk factors to predict the occurrence of endpoint events. Furthermore, we selected variables with a p-value<0.2, age and disease duration as candidate variables and entered into a stepwise multivariate Cox regression (Table 2). In model 1, PVR showed an independent association with the endpoint after adjusted for clinical characteristics and hemodynamic parameters associated with the endpoint (1.523 [95% CI, 1.167-1.988], P=0.002). In model 2, MPA and %CSA_{<5} were predictors of the occurrence of the endpoint in CTD-PAH patients. In the model 3, the pulmonary vascular metric which was stratified by a combination of MPA and %CSA_{<5} was an independent risk factor predicting the presence of the endpoint (2.180 [95% CI, 1.405-3.383], P=0.001).

Survival Analysis

Patients were divided into three groups according to cut-off values of MPA and %CSA_{<5}: Group A: high-risk group, both smaller %CSA_{<5} (≤ 0.382) and larger MPA (≥ 36.75 mm); Group B: medium-risk group, smaller %CSA_{<5} (≤ 0.382) or larger MPA (≥ 36.75 mm); Group C: low-risk group, both larger %CSA_{<5} (> 0.382) and smaller MPA (< 36.75 mm). Kaplan-Meier analysis shown that the prognosis of group A was worse than that of group C (log-rank X^2 , 16.041; P=0.000) and group B (log-rank X^2 , 5.931; P=0.015), and that of group B was worse than that of group C (log-rank X^2 , 5.832; P=0.016) (Figure 4).

Discussion

In the current retrospective study, we found decreased small pulmonary vessels area ($\%CSA_{\leq 5}$) and increased MPA diameter were associated with poor long-term outcome in CTD-PAH patients. The prognosis of patients with CTD-PAH satisfying $\%CSA_{\leq 5}$ less than 0.382 and MPA greater than 36.75 mm is extremely poor.

We measured the pulmonary macrovascular diameter and $\%CSA_{\leq 5}$ in CTD-PAH patients on chest CT. The mean diameter of MPA was 35.49 mm, which was significantly larger than the normal value of the previously reported in the Chinese population[34] and the MPA value of patients with endpoint events was higher than that of patients without endpoint events, $\%CSA_{\leq 5}$ had a mean value of 0.79, similar to the previously reported values of healthy Chinese population[35], but the $\%CSA_{\leq 5}$ of CTD-PAH patients with endpoint events was significantly lower than that in the rest of the patients. Our results showed that in CTD-PAH patients, $\%CSA_{\leq 5}$ was negatively correlated with mPAP measured by RHC, consistent with previous studies. As early as 2009, Matsuoka et al found that in a population with severe emphysema and pulmonary hypertension, $\%CSA_{\leq 5}$ was negatively correlated with mPAP measured by RHC[23]. Subsequently, a negative correlation between $\%CSA_{\leq 5}$ and mPAP was also found in a study of 20 patients with PAH[27]. We speculate that the negative correlation between $\%CSA_{\leq 5}$ and mPAP may be related to the following two factors: first, impaired production of vasoactive mediators such as nitric oxide and prostacyclin in PAH patients, increased production of vasoconstrictors and proliferative mediators such as endothelin-1, ultimately lead to decreased vascular tone. This conjecture is supported by the significant negative correlation between $\%CSA_{\leq 5}$ and PVR shown in Figure 3; Then, among the 42 patients with CTD-PAH included in our study, their mean PVR and mPAP were higher, and in these patients with severe PAH, right heart function is impaired to a certain extent, which may cause a reduction in cardiac output leading to distal atelectasis of small pulmonary vessels. This hypothesis was also supported by the positive correlation between $\%CSA_{\leq 5}$ and CI shown in Figure 3, we can also see that the two echocardiographic parameters reflecting right ventricular function: TAPSE and FAC, were worse in patients with endpoint events than in those without an endpoint event, but unfortunately there was no statistical significance, possibly because of the small sample size of patients who underwent echocardiographic measurements of right ventricular function.

In this study, we documented that pulmonary vasculature metrics were associated with all-cause mortality and clinical worsening in patients with CTD-PAH in China. Several studies[22, 36-38] have shown that quantitative assessment of pulmonary large vessels can evaluate the prognosis of patients with PAH. Our results show that a combination of MPA diameter and $\%CSA_{\leq 5}$ could screen for patients with more severe disease and worse prognosis.

So far, few studies have used $\%CSA_{\leq 5}$ to evaluate the prognosis of CTD-PAH. Shimizu et al[27]. reported the value of $\%CSA_{\leq 5}$ in PAH patients was greater than that in the normal control group, but with the increase of mPAP, the value of $\%CSA_{\leq 5}$ decreased. In studies of COPD-related PH[23, 26, 35], the value of $\%CSA_{\leq 5}$ of COPD patients with severe PH was greater than that of COPD patients without severe PH, while mPAP was negatively correlated with $\%CSA_{\leq 5}$. In our study, $\%CSA_{\leq 5}$ of CTD-PAH patients without an endpoint event were larger than the overall mean. This may be because of thickening of the intima/media/adventitia of the pulmonary arteries in CTD-PAH patients; on the one hand, this may be explained by elevated pressure within the pulmonary arteries, which likely expanded these small arteries before the vascular tone has not decreased to a certain extent, leading to larger $\%CSA_{\leq 5}$. Therefore, this result suggests that $\%CSA_{\leq 5}$ may be more suitable as a

prognostic indicator than a diagnostic indicator of PAH. Our findings suggest that the quantitative evaluation of pulmonary small vessels by %CSA_{<5} combined with MPA has some value in improving risk stratification in patients with CTD-PAH.

Limitations

There are several limitations to this study. First, this was a single-centre retrospective study with a small sample size, there were also various deviations in the in-flow and discharge process. Second, Chest CT and RHC were not performed at the same time; however, we ensured that the interval between the two inspections did not exceed 1 month and during this period the patients' condition was stable. Third, since the specificity of the ROC analyses is not high for %CSA_{<5} and MPA, the cutoff value of %CSA_{<5} and MPA need to be further investigated in prospective, multicenter, and large sample size cohort. Fourth, we only demonstrated the relationship between pulmonary vasculature metrics in the baseline and prognosis, further studies are required to determine whether its change during follow up could reflect the prognosis of CTD-PAH patients.

Conclusions

%CSA_{<5} less than 0.382 in combination with MPA greater than 36.75 mm may be a potential risk factor of poor prognosis in Chinese CTD-PAH patients.

Abbreviations

6-MWD: 6-minute walking distance; %CSA_{<5}: the cross-sectional area of small pulmonary vessels <5 mm² as a percentage of total lung area; AAo: ascending aorta; CTD: connective tissue diseases; MPA: main pulmonary artery; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance; RHC: right heart catheterization; SS: Sjogren's syndrome; SLE: systemic lupus erythematosus; SSc: systemic sclerosis.

Declarations

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Data Availability statement

Data is available upon reasonable request. The authors commit to making the relevant anonymised patient data available for a specified purpose approved by the institution. All data relevant to the study are included in the article.

Acknowledgments

All authors declare that have made substantial contributions to all of the following: the conception and design of the study, or acquisition of data, or analysis and interpretation of data, drafting the article or revising it critically for important intellectual content, final approval of the version to be submitted.

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Ethics approval and consent to participate

This study was approved by the Medical Ethics Committee of the First Affiliated Hospital of Nanjing Medical University (number: 2018-SR-333). As all variables were obtained retrospectively from available clinical data, the need for patients to sign informed consent was waived.

Disclosures

All authors report no conflicts.

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Tables

Table 1 Clinical characteristics, hemodynamic parameters, echocardiographic RV parameters, and chest CT parameters of the overall population and patients with or without endpoint events.

	All patients(n=42)	Patients without endpoint events(n=26)	Patients with endpoint events(n=16)	P value
Age (years)	41.29±15.179	42.35±15.04	39.56±15.73	0.575
Gender, female (%)	40(95.20%)	26(100.00%)	14(88.50%)	0.065
Disease duration (months)	60.00(12.00-120.00)	78.00(24.75-120.00)	24.00(6.00-78.00)	0.062
PAH duration (months)	7.50(3.00-24.00)	9.00(3.00-30.00)	7.50(3.25-24.00)	0.549
Primary disease				0.503
SLE	16(38.10%)	10(38.50%)	6(37.50%)	
SS	15(35.70%)	9(34.60%)	6(37.50%)	
SSc	8(19.00%)	4(15.40%)	4(25.00%)	
MCTD	3(7.10%)	3(11.50%)	0(0)	
Systolic BP (mmHg)	120.48±14.59	120.92±13.02	119.75±17.28	0.804
Diastolic BP (mmHg)	77.95±9.64	77.31±11.26	79.00±6.36	0.538
Heart rate (bpm)	87.17±14.37	87.73±16.22	86.25±11.16	0.750
WHO class ($\geq$ II), n (%)	26(61.90%)	16(61.50%)	10(62.50%)	0.950
NT-proBNP (pg/ml) (n=39)	290.10(153.11-2782.34)	285.90(147.58-2320.75) (n=26)	598(178.15-2881.50) (n=13)	0.763
Combination PAH-targeted therapy*	19(45.20%)	14(53.80%)	5(31.30%)	0.153
Hemodynamic parameters				
mPAP (mmHg)	45.29±9.98	44.08±9.92	47.25±10.07	0.323
PAWP (mmHg)	8.51±3.72	8.79±3.89	8.13±3.67	0.590
PVR (wood)	9.90±4.85	7.43±2.79	13.28±4.65	0.000
PAC (ml/mmHg)	1.43±1.01	1.54±1.24	1.25±0.44	0.288
CO(L/min)	4.54±1.95	4.79±2.24	4.16±1.37	0.319
CI (L/min/m ²)	2.87±1.32	3.13±1.51	2.45±0.78	0.064
Echocardiographic RV parameters				
RAD (mm)	41.36±8.10	41.35±9.11	41.38±6.39	0.990
RVDd (mm)	42.71±7.39	41.88±7.55	44.06±7.15	0.360
TAPSE (mm) (n=26)	18.40±8.12	18.79±8.90(n=21)	16.78±1.69(n=5)	0.628

FAC (%) (n=23)	29.64±9.01	30.31±10.00(n=18)	27.26±3.48(n=5)	0.294
Chest CT parameters				
MPA (mm)	35.49±6.01	33.02±6.31	39.50±2.19	0.000
AAO (mm)	2.93±0.59	30.92±5.84	27.09±5.44	0.054
MPA / AAO	1.30±0.26	1.30±0.28	1.31±0.23	0.909
%CSA _{<5}	0.79±0.38	0.97±0.31	0.50±0.31	0.000

Abbreviations: MCTD, mixed connective tissue disease; SLE, systemic lupus erythematosus; SS, Sjogren syndrome; SSc, systemic sclerosis; BP, blood pressure; WHO, World Health Organization; NT-proBNP, N-terminal pro-brain natriuretic peptide; PAH, pulmonary arterial hypertension; mPAP, mean pulmonary arterial pressure; PAWP, pulmonary arterial wedge pressure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; CO, cardiac output; CI, cardiac index; RV, right ventricle; RAD, right atrial diameter; RVDd, right ventricular diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; CT, computed tomography; MPA: main pulmonary artery; AAO: ascending aorta; %CSA_{<5}, the cross-sectional area of small pulmonary vessels<5 mm² as a percentage of total lung area;

*Combination PAH-targeted therapy: At least 2 PAH-specific medications, including prostacyclin analogue, endothelin-1 antagonists, and phosphodiesterase 5 inhibitors.

Table 2 Univariate and Multivariate analyses to identify prognostic factors for the composite end point performed by the Cox proportional hazard regression model.

Variable	χ^2	P value	HR (95% CI)	Variable	P value	HR (95% CI)
Age (years)	0.016	0.899	0.967(0.965,1.032)	Model 1		
Disease duration (months)	0.888	0.354	0.996(0.988,1.004)	Age (years)	0.932	0.997(0.938,1.060)
PAH duration(months)	0.021	0.885	0.999(0.983,1.015)	Disease duration (months)	0.837	1.001(0.992,1.010)
WHO class ($\geq$ III),n (%)	1.015	0.644	1.274(0.457,3.548)	Pro-BNP (pg/ml)	0.942	1.000(1.000,1.000)
Combination PAH-targeted therapy	0.196	0.659	0.783(0.265,2.316)	PVR (wood)	0.002	1.523(1.167,1.988)
Pro-BNP (pg/ml) (n=39)	1.446	0.193	1.000(1.000,1.000)	CI (L/min/m ²)	0.942	0.969(0.411,2.284)
mPAP (mmHg)	1.195	0.278	1.027(0.979,1.078)	Model 2		
PVR (wood)	8.296	0.006	1.106(1.03,1.188)	Age (years)	0.440	1.019(0.971,1.070)
PAC (ml/mmHg)	0.003	0.957	1.015(0.591,1.744)	MPA (mm)	0.026	1.268(1.029,1.562)
CI (L/min/m ²)	2.998	0.095	0.628(0.363,1.085)	%CSA _{<5}	0.044	1.320(1.007,1.730)
MPA (mm)	8.756	0.002	1.297(1.104,1.524)	PVR (wood)	0.587	1.034(0.917,1.166)
MPA/AAO	0.659	0.418	2.512(0.272,3.372)	CI (L/min/m ²)	0.869	0.949(0.505,1.780)
%CSA _{<5}	14.078	0.001	1.428(1.151,1.771)	Model 3		
RAD (mm)	0.017	0.896	0.996(0.935,1.061)	Age (years)	0.186	1.031(0.986,1.077)
RVDd (mm)	0.242	0.623	1.018(0.948,1.093)	Pulmonary vasculature metrics	0.001	2.180(1.405,3.383)
TAPSE (mm) (n=26)	0.817	0.238	0.763(0.486,1.196)	PVR (wood)	0.325	0.935(0.819,1.069)
FAC	0.017	0.386	0.953(0.856,1.062)	CI (L/min/m ²)	0.659	0.863(0.449,1.661)

Abbreviations: PAH, pulmonary arterial hypertension; WHO, World Health Organization; NT-proBNP, N-terminal pro-brain natriuretic peptide; mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; PAC, pulmonary arterial compliance; CI, cardiac index; MPA: main pulmonary artery; AAO: ascending aorta; %CSA_{<5}, the cross-sectional area of small pulmonary vessels<5 mm² as a percentage of total lung area; RAD, right atrial diameter; RVDd, right ventricular diastolic diameter; TAPSE, tricuspid annular plane systolic excursion; FAC, fractional area change; Combination PAH-targeted therapy: At least 2 PAH-specific medications, including prostacyclin analogue, endothelin-1 antagonists, and phosphodiesterase 5 inhibitors.

Figures

Figure 1

Flowchart of patients’ screening. Abbreviations: CTD, connective tissue disease; PAH, pulmonary arterial hypertension; RHC, right heart catheterization; CT, computed tomography.

Figure 2

Measurement of %CSA, MPA, and AAO. Notes: (A) Measurement of MPA, AAO; (B) CT image of lung field segmented within the threshold values from -500 to -1,024 HU; (C) Binary image converted with window level of -720 HU from segmented image; (D) Pulmonary vessels are displayed in black. Abbreviation: CT, computed tomography; MPA, main pulmonary artery; AAO, ascending aorta; %CSA, the cross-sectional area of small pulmonary vessels as a percentage of total lung area.

Figure 3

Relationships between right heart catheterization parameters and %CSA<5. Abbreviations: mPAP, mean pulmonary arterial pressure; PVR, pulmonary vascular resistance; CI, cardiac index; %CSA<5, the cross-

sectional area of small pulmonary vessels<5 mm 2 as a percentage of total lung area;

Figure 4

Kaplan-Meier analysis of the clinical outcomes based on %CSA<5 and MPA diameter. Abbreviations: MPA: main pulmonary artery; %CSA<5, the cross-sectional area of small pulmonary vessels <5 mm 2 as a percentage of total lung area.

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