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Relationship between CT Findings and Pulmonary Hypertension in Mixed Connective Tissue Disease

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Abstract

Purpose: Studies on imaging findings in mixed connective tissue disease (MCTD) are limited. This study assessed the relationship between CT-derived parameters (pulmonary artery diameter [PAD] and lung parenchymal abnormalities [LPA]) and estimated pulmonary artery pressure (PAP) in patients with MCTD. **Materials and Methods:** This single-center retrospective study enrolled consecutive patients with MCTD who underwent CT and echocardiography within 6 months between December 2004 and November 2021. Chest CT was used to measure PAD (mm) and evaluate LPA (%). LPA was quantitatively assessed for reticular, ground-glass opacities, consolidation, or honeycombing. Peak tricuspid regurgitation velocity (TRV) on echocardiography was considered to reflect PAP. Correlation and partial correlation analyses were performed to assess the relationship between CT-derived parameters and peak TRV. **Results:** Overall, 116 patients (mean age 50.0 ± 17.0 years [SD]) with a median disease duration of 3.0 years had a median peak TRV of 2.28 m/sec and median PAD of 27.0 mm. Pulmonary hypertension was found in 18 (15.5%) patients. LPA was observed in 52 patients, with a median of 0.0% and a mean of 4.5% ± 8.9 [SD]. Peak TRV was correlated with PAD ($r = 0.58$, $p < 0.001$) and LPA ($r = 0.40$, $p < 0.001$). Peak TRV, adjusted for other CT parameters and confounding factors, showed a partial correlation with PAD ($r = 0.49$, $p < 0.001$) but was not correlated with LPA ($r = 0.19$, $p = 0.04$). **Conclusion:** A moderate positive correlation was observed in patients with MCTD between PAD and estimated PAP, irrespective of the presence of LPA, whereas LPA was not correlated with estimated PAP.

Keywords

Mixed Connective Tissue Disease, Pulmonary Hypertension, Interstitial

Lung Disease, Pulmonary Artery Diameter, Lung Parenchymal Abnormalities

1. Introduction

Mixed connective tissue disease (MCTD) is a systemic autoimmune disorder that often affects the lungs [1] [2]. In patients with MCTD, interstitial lung disease (ILD) occurs in 33% - 55%, and 4% - 43% develop pulmonary hypertension (PH) [1]-[9]. PH is a significant prognostic factor in patients with MCTD, making early detection and appropriate therapeutic intervention essential for improving patient outcomes [4]-[8].

In collagen vascular diseases, chest CT is commonly performed to evaluate ILD. Several studies have reported a correlation between pulmonary artery diameter (PAD) measured on chest CT and pulmonary artery pressure (PAP), indicating that CT is a valuable non-invasive imaging tool for not only assessing ILD but also for detecting PH [10]-[17]. However, some reports suggest that the correlation between PAD and PAP diminishes in the presence of ILD [16]-[19].

The clinical classification of pulmonary hypertension (PH) in collagen vascular diseases primarily includes pulmonary arterial hypertension (PAH, classified as group 1 by the 6th World Symposium on Pulmonary Hypertension) and PH associated with lung disease and/or hypoxia (group 3) [2] [5] [6] [20] [21]. In systemic sclerosis (SSc), a disease closely related to MCTD and similarly associated with a high prevalence of PH, chest CT often reveals relatively severe lung fibrosis and a high incidence of group 3 PH has been reported [5] [19] [21]-[23]. In contrast, there are very few studies reporting chest CT findings in MCTD, and imaging features related to PH in this condition remain insufficiently investigated. Therefore, the present study aims to quantitatively evaluate chest CT findings, including pulmonary artery diameter (PAD) and lung parenchymal abnormalities (LPA), and to clarify the relationship between these CT-derived parameters (PAD and LPA) and estimated pulmonary artery pressure (PAP) in patients with MCTD.

2. Materials & Methods

2.1. Patients

Our review committee approved this single-center retrospective study (IRB no. 2021-5649), and it complied with the Declaration of Helsinki's use of human data. This study included consecutive patients with MCTD who underwent both CT and echocardiography within six months between December 2004 and November 2021. Patients diagnosed with MCTD by specialists in autoimmune/collagen diseases were identified, and their imaging history was extracted from our institutional radiology database. We selected parameters from echocardiographic

examinations routinely performed on asymptomatic patients to estimate PAP and evaluate a broad range of patients with MCTD and not just those at high risk for PH. Patients with insufficient documentation to confirm Kasukawa's diagnostic criteria, an interval of more than six months between CT and echocardiographic examinations, CT scans unsuitable for LPA evaluation owing to acute exacerbations, or patients with incomplete echocardiographic records were excluded [24]. Finally, clinical information and imaging data from 116 patients (113 women, three men) were extracted from the center's medical records and radiology database (**Figure 1**). The disease duration was defined as the period from meeting the diagnostic criteria and diagnosis with MCTD to the CT examination.

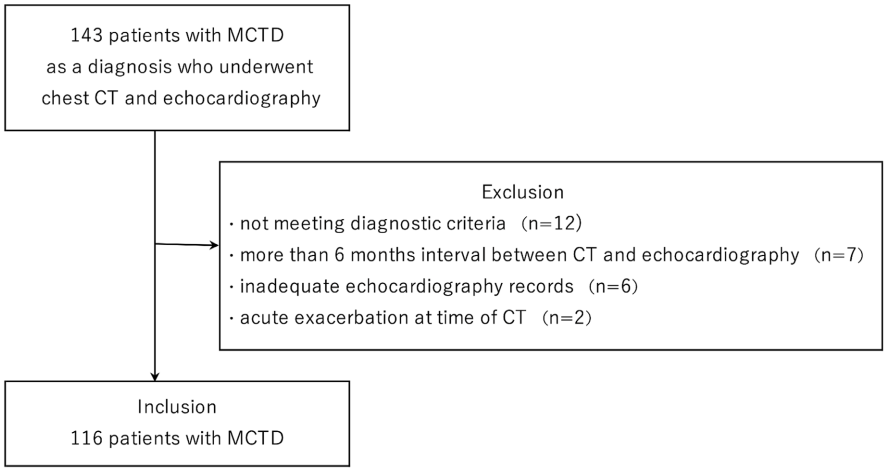


Figure 1. Flowchart detailing the patient enrollment procedure.

2.2. Echocardiography

Resting transthoracic echocardiography was performed using standard techniques. Based on the recommendations of the 2022 European Society of Cardiology/European Respiratory Society Guidelines for diagnosing and treating PH, peak tricuspid regurgitation velocity (TRV) measured via continuous wave Doppler was used as a variable to estimate PAP [24]. Echocardiographic PH was defined as a peak TRV of ≥2.9 m/sec. Echocardiography was performed by experienced and qualified sonographers and diagnosed by a cardiologist and Board Certified Fellow of the Japanese Society of Ultrasonics in Medicine. To ensure the reliability of this retrospective study, the author (Y.M.), a radiologist with 15 years of experience as a certified sonographer, reviewed the medical records and echocardiographic images in this study. Cases with inappropriate records were excluded (N = 6).

2.3. Chest CT

2.3.1. CT Acquisition

Chest CT examination was performed using various single- or multi-detector spiral CT scanners. Inspiratory non-contrast CT scans were acquired with patients

in the supine position. CT images were captured at 120 keV and 50 - 350 mA, and all images were reconstructed at a slice thickness of 0.5 - 2.0 mm using the standard reconstruction algorithm and standard window setting (mediastinal window settings: window level 40 Hounsfield Unit [HU], window width 350 HU, lung window settings: window level: –600 HU, window width: 1500 HU).

2.3.2. Image Interpretation

1) Diameter measurement of the vessels

Vessel diameters were measured by a radiologist (Y.M., with 3 years of experience in radiology) three months after data extraction, who was blinded to clinical information. PAD was measured at the thickest part of the slice, within 3 cm of the main pulmonary artery bifurcation, using the same method described by Tan *et al*. [11]. The ascending aorta diameter (AOD) was measured in the same slice as the PAD measurement (**Figure 2(a)**). The PAD to AOD ratio (PA/AO) was calculated for comparison [10] [12] [15].

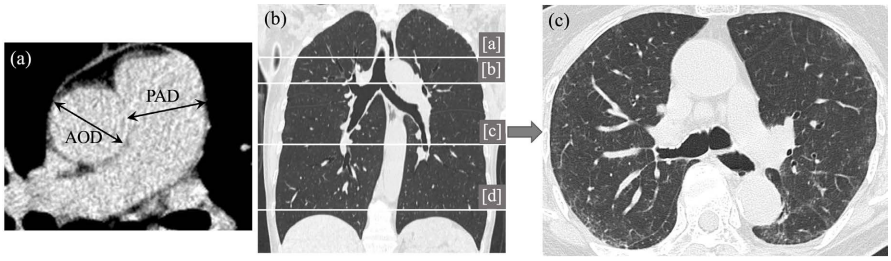


Figure 2. (a) Pulmonary artery diameter of 31.3 mm and ascending aorta diameter of 30.2 mm in a 57-year-old female. (b) Lung parenchyma abnormalities (LPA) were evaluated at the four levels of axial view shown in the figure. (c) Axial image obtained in a 72-year-old woman. The LPA was evaluated as 5% reticular, 5% ground glass opacities, with no consolidation or honeycombing; 10% LPA occupied the lungs at this level.

2) Visual quantitative assessment of lung parenchymal abnormalities

LPA was independently assessed under blinded conditions by two radiologists (Y.M. and S.M., with 3 and 30 years of interpretation experience, respectively) ≥ 3 months after clinical data extraction. Reticular patterns, ground-glass opacities, consolidation, and honeycombing were quantitatively evaluated as indicative findings of LPA. Each finding was classified according to the definitions in the Fleischner Society consensus statement glossary [25]. The measurements were carried out as described previously: the percentage occupied by LPA was visually assessed (units of 5%) in each axial image of four levels (a)-(d) set in advance, ensuring that the total area of reticular, ground-glass opacities, consolidation, honeycombing and normal lung parenchyma would be 100%; (a) Upper: above the aortic arch, (b) Middle: tracheal carina level, (c) Lower: between the tracheal carina level and 1 cm above the right diaphragmatic arch, (d) Bottom: 1 cm above the right diaphragmatic arch (**Figure 2(b)**) [26]. The LPA area was averaged by multiplying the volume difference between each zone by a correction coefficient (**Figure 2(c)**). Based on the previous report, the volume difference between the

upper, middle, lower, and bottom zones was estimated to be 1.0, 1.6, 1.3, and 1.3, respectively [26]. The average area of LPA was calculated accordingly. Subsequently, the average LPA (%) measured by two independent evaluators was calculated, and the average value was used as the LPA (%) parameter.

2.4. Statistical Analysis

No statistical sample size calculations were conducted. Categorical and continuous variables are expressed using descriptive statistics. A correlation analysis was performed to assess the relationship between CT-derived quantitative parameters and peak TRV using the Pearson correlation coefficient (r). A subgroup analysis was performed for correlation analysis, depending on the presence or absence of LPA. Partial correlation analysis adjusted for a confounding factor was also performed. The statistical significance level was set at 0.05 on both sides. None of the p-values were adjusted for multiplicity. The inter-rater reliability in terms of accurately identifying LPA was assessed using intraclass correlation coefficients. All statistical analyses were performed by Y.M. and validated by a statistical analyst (H.Y.) using JMP Pro version 15.2.0 (SAS Institute, Cary, NC, USA) and R version 4.2.3 (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

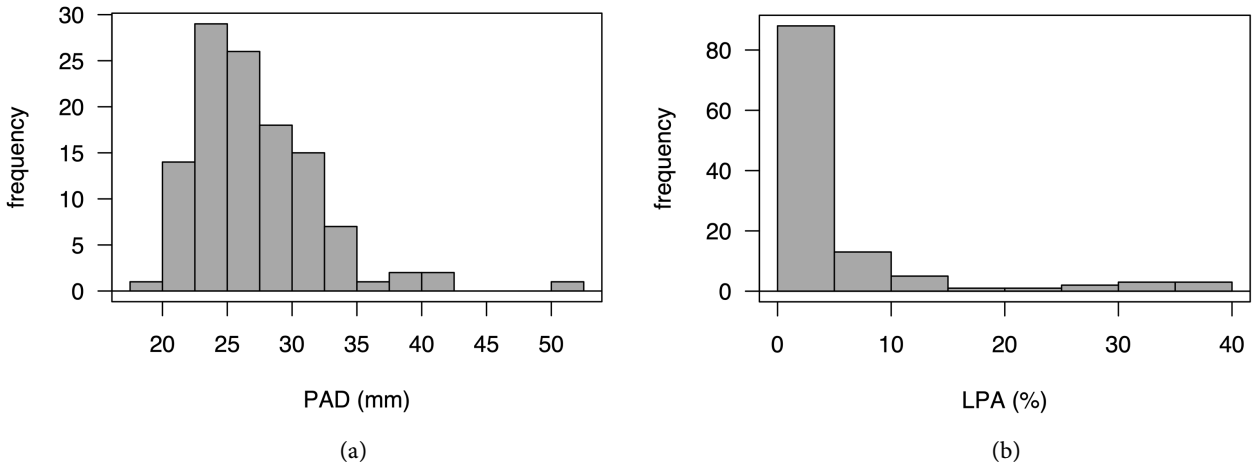
3.1. Patient Characteristics

We identified a total of 143 patients with MCTD who underwent chest CT and echocardiography at our facility between December 2004 and November 2021. After excluding 27 patients, 116 who met the inclusion criteria were included in the final analysis (**Figure 1**). **Table 1** shows the characteristics of the enrolled patients. The 116 patients (mean age 50.0 ± 17.0 [standard deviation] years, 113 women) had a mean disease duration at CT of 3.0 years (interquartile range [IQR]: 0.0 - 13.0). The median peak TRV was 2.28 m/sec (IQR: 2.05 - 2.66). Echocardiographic PH was observed in 18 (15.5%) patients. The diagnostic accuracy of echocardiographic PH was evaluated in 23 patients who underwent right-sided catheterization within two months before or after the echocardiographic examination for any reason. According to the diagnostic criteria for PH with mean PAP > 20 mmHg on right-sided catheterization, the sensitivity, specificity, and accuracy of peak TRV were 82.3%, 100%, and 87.0%, respectively. The median PAD was 27.0 mm (IQR: 23.8 - 30.0); mean, 27.3 ± 5.0 mm; skewness, 0.14; and kurtosis, −1.51. The median PA/AO ratio was 0.88 (IQR: 0.79 - 1.00); mean, 0.91 ± 0.02; skewness, 1.50; and kurtosis, 4.08. LPA was observed in 44.8% (52/116) patients, with a median of 0.0% (IQR: 0.0 - 5.0), a mean of 4.5% ± 8.9, skewness of 2.57, and kurtosis of 5.96 (**Figure 3**). Patients with no LPA accounted for 55.2% (64/116) of the cohort, those with ≤ 10% LPA accounted for 31.9% (37/116), and those with >30% LPA accounted for 6.0% (7/116; **Figure 3**). The intraclass correlation coefficient for LPA was 0.99 (95% confidence interval: 0.98 - 0.99).

Table 1. Patient characteristics and measurements.

Clinical characteristics and measurements	N = 116
Age, y	50.0 (17.0)
Female/Male sex, n	113/3
Duration of disease, y	3.0 (0.0 - 13.0)
Peak TRV, m/sec	2.28 (2.05 - 2.66)
PAD, mm	27.0 (23.8 - 30.0)
AOD, mm	30.3 (26.9 - 34.0)
PA/AO ratio	0.88 (0.79 - 1.00)
LPA, %	0.0 (0.0 - 5.0)
Lung function parameters	N = 77
FEV1.0, % predicted	80.6 (77.1 - 85.7)
VC, % predicted	90.5 (78.2 - 100.3)
FVC, % predicted	89.5 (79.9 - 101.1)
DLCO, % predicted	67.4 (52.5 - 81.9)
TLC, % predicted	94.2 (84.1 - 104.3)
Right-sided heart catheterization	N = 23
Mean PAP, mmHg	26.5 (19.8 - 34.5)
PAWP, mmHg	10.5 (6.8 - 12.3)

Data are presented as mean (standard deviation) or median (interquartile range). AOD, ascending aorta; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1.0, forced expiratory volume in one second; FVC, forced vital capacity; LPA, lung parenchymal abnormalities; PA/AO ratio, ratio of pulmonary artery diameter to aorta diameter; PAD, pulmonary artery diameter; PAP, pulmonary artery pressure; PAWP, pulmonary artery wedge pressure; TLC, total lung capacity; TRV, tricuspid regurgitant velocity; VC, vital capacity.



(a) (b)

Figure 3. Histograms showing the distribution of (a) pulmonary artery diameter (PAD) and (b) lung parenchymal abnormalities (LPA) on chest CT.

3.2. Assessment of Factors Influencing CT-Derived Imaging Parameters

Females comprised 97.4% (113/116) of the patients, therefore, an adjustment based on sex was considered impractical. The correlation coefficient for PAD, LPA and peak TRV with age was 0.29 (p = 0.002), 0.41 (p < 0.001), and 0.28 (p = 0.003), respectively. The correlation coefficient for PAD, LPA and peak TRV with disease duration was −0.02 (p = 0.87), 0.26 (p = 0.005), and 0.16 (p = 0.09), respectively (Table 2).

Table 2. Correlation between imaging parameters and possible confounding factors.

Parameters	Age		disease duration	
	r	*p*	r	*p*
PAD (mm)	0.29	0.002*	−0.02	0.87*
LPA (%)	0.41	<0.001*	0.26	0.005*
Peak TRV (m/sec)	0.28	0.003*	0.16	0.09

LPA, lung parenchymal abnormalities; PAD, pulmonary artery diameter; TRV, tricuspid regurgitant velocity; *$p < 0.05$.

3.3. Relationship between CT-Derived Imaging Parameters and Peak TRV

The peak TRV was correlated with PAD (r = 0.58, p < 0.001) and LPA (r = 0.40, p < 0.001; Figure 4, Table 3). Peak TRV was also correlated with PA/AO (r = 0.42, p < 0.001) but showed a stronger correlation with PAD. Many patients did not have LPA; therefore, a subgroup analysis according to the presence or absence of LPA was performed. The correlation coefficient between PAD and peak TRV was 0.49 (p < 0.001) for the without LPA group (N = 64) and 0.54 (p < 0.001) for the with LPA group (N = 52). The correlation coefficient between LPA and peak TRV was 0.35 (p = 0.01) for the with LPA group. The partial correlation coefficient between PAD and peak TRV, excluding the effects of LPA and age, was 0.49 (p < 0.001); between LPA and peak TRV, excluding the effects of PAD and age, was 0.19 (p = 0.04); and between age and peak TRV, excluding the effects of PAD and LPA, was 0.07 (p = 0.46; Table 3). Figure 5 shows the characteristic CT images of patients with MCTD that were determined to be indicative of PH.

Table 3. Correlation between CT imaging variables or age and peak TRV.

Parameters	Correlation analysis		Partial correlation analysis	
	r (95%CI)	*p*	r	*p*
PAD (mm)	0.58 (0.44 - 0.69)	<0.001*	0.49	<0.001*
LPA (%)	0.40 (0.23 - 0.54)	<0.001*	0.19	0.04*
Age (years)	0.28 (0.10 - 0.44)	0.003*	0.07	0.46

LPA, lung parenchymal abnormalities; PAD, pulmonary artery diameter; TRV, tricuspid regurgitant velocity; *$p < 0.05$.

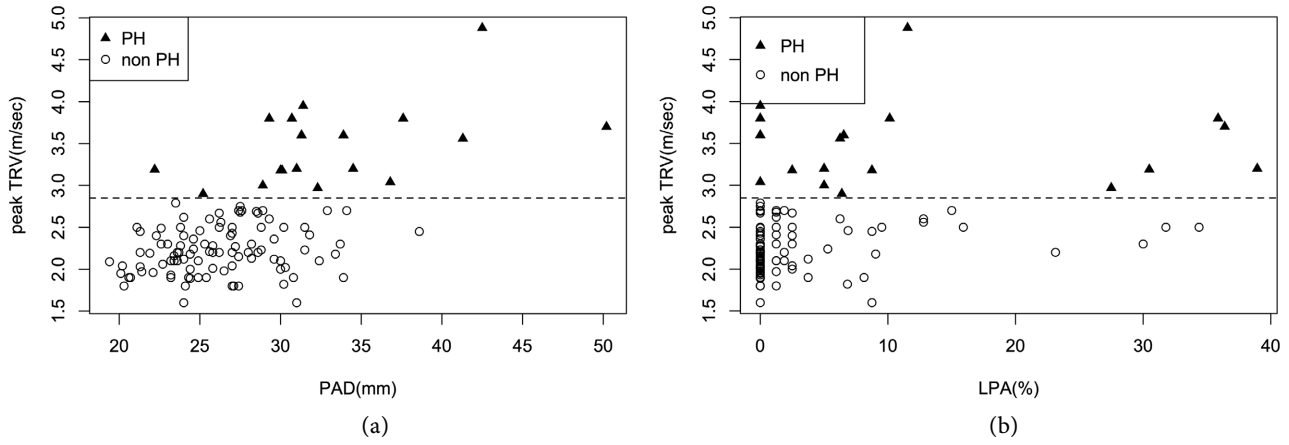


Figure 4. Scatterplots showing the correlation between peak TRV and (a) pulmonary artery diameter (PAD) and (b) lung parenchymal abnormalities (LPA). The dashed line shows peak TRV = 2.9 m/sec, and cases above the line indicate pulmonary hypertension (PH).

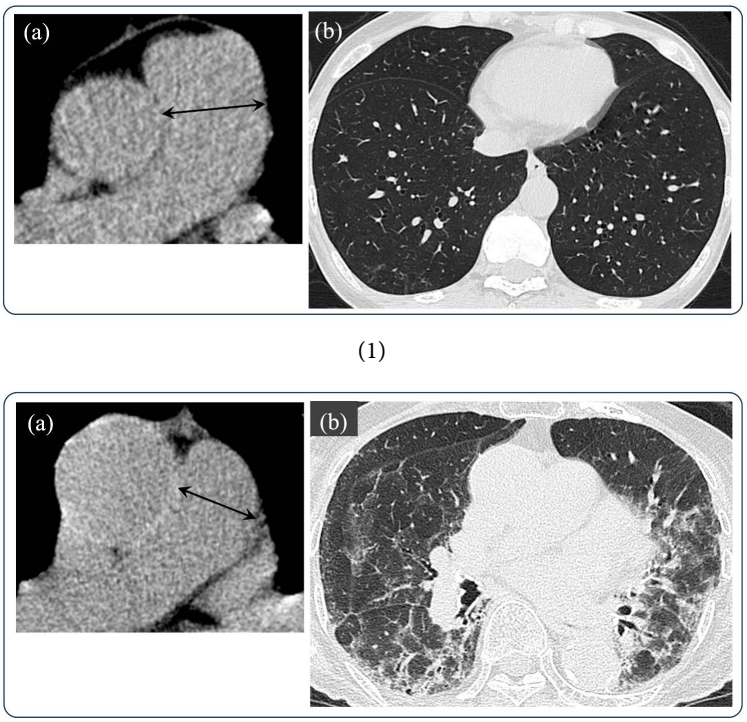


Figure 5. Characteristic CT images of MCTD with pulmonary hypertension. (1) CT images of a representative case of MCTD with PH. A 57-year-old woman with MCTD lasting 5 years. (a) PAD of 31.3 mm, (b) no LPA, and peak TRV of 3.6 m/sec. Most cases of PH in this study showed dilated PADs with no or mild LPA; (2) CT images of MCTD suggest group 3 PH. A 72-year-old woman with MCTD lasting 15 years. (a) PAD of 22.2 mm, (b) LPA occupancy of 30.5% in the lungs, and a peak TRV of 3.19 m/sec. Two cases of PH included in this study showed severe LPA without PAD dilatation, suggesting group 3 PH.

4. Discussion

To the best of our knowledge, this is the first study to assess the relationship

between CT findings quantitatively and estimated PAP in patients with MCTD. We found a positive correlation between PAD and estimated PAP on chest CT, irrespective of the presence of LPA. However, no correlation was observed between LPA and estimated PAP.

Pulmonary parenchymal disease in MCTD affects peripheral vessels < 100 μm in diameter as a result of fibrosis [23] [27]. A loss of >80% of normal lung structures in high-compliance pulmonary circulation causes PH [20] [28]. Arteriopathy with severe medial hypertrophy and intimal thickening of the muscular arteriole until it measures <600 μm in diameter causes lumen narrowing in pulmonary vascular disease in MCTD, resulting in higher vascular resistance and PAP, which progressively contributes to increased PAD [11]-[13] [15] [16] [23] [27] [29]. Moreover, lung disease is mainly identified in the form of pulmonary vascular disease causing PAH in autopsies of deceased patients who succumbed to MCTD [23] [27] [29]. Generally, PAH (group 1) gives rise to severe PH, whereas PH caused by lung parenchymal disease (group 3) results in mild PH [20] [21] [27]. Therefore, vascular disease (group 1) may be more common among deceased patients. However, even among the living patients in this study, many had no LPA. Additionally, most patients with LPA had relatively mild interstitial change. Moreover, in our partial correlation analysis excluding the effect of the other CT parameter, estimated PAP was found to correlate positively with PAD, but not with LPA. Therefore, LPA in MCTD does not appear to be severe enough to increase PAP; instead, vascular disease is more likely to play a dominant role as a risk factor for PH. However, it should be noted that the partial correlation between CT parameters and estimated PAP does not indicate a causal relationship because regression analysis was not performed in this study.

Limited reports are currently available in the literature regarding the onset period of PH in MCTD [3] [4] [6]-[8] [30] [31]. Although the average disease duration was relatively short, at only 3.0 years in this study, PH was observed in 15.5% of the patients. In our results, disease duration had a weakly positive correlation with LPA, but no association with PAD. Considering the time required for an increase in PAP caused by fibrosis progression, many patients with PH in this study may have actually had PAH (group 1). In a prospective study investigating the natural history of MCTD in Japan, over 30% of patients with PH developed PAH either before meeting the diagnostic criteria for MCTD or within one year following its diagnosis [31]. Similarly, four patients with PH in this study had no lung parenchymal change and were considered to have PAH (group 1). The mean disease duration of these four cases was 3.0 years; however, the exact time of PH occurrence remains unclear, since this was a cross-sectional study. Moreover, our findings suggest that PAH-associated PAD dilatation may occur independently of disease duration. Therefore, PAD dilatation should be carefully considered when interpreting chest CT scans for MCTD, regardless of disease stage.

Several studies have reported no or poor correlation between PAD on CT and PAP [16]-[19] [32] [33]. However, some of these studies investigated diverse

cohorts of participants with varying PH factors (groups 1-5) [11] [13] [16]. Group 3 PH is generally more frequent than group 1 PH in SSc. Moreover, rather than PAD, fibrosis is reportedly the most reliable independent predictor of PH on CT images [19]. Furthermore, no correlations between PAD and PAP were found in studies of advanced idiopathic pulmonary fibrosis or severe emphysema [18] [32] [33]. Dynamic changes in the pulmonary vascular bed may occur in group 3 PH because of functional factors such as hypoxia and vasoactive mediators, in addition to organic factors such as severe parenchymal destruction [28] [34]. Under these conditions, estimation of PAP from changes in central PAD is difficult, even if characteristic narrowing is observed in the remaining peripheral vessels [32]. Therefore, the moderate correlation observed between PAD and estimated PAP in this study supports the hypothesis that pulmonary vascular disease, rather than pulmonary parenchymal disease, may represent the predominant factor for PH in MCTD. However, further studies are warranted to determine the pathophysiological conditions under which PAD is helpful as an indicator of PH.

Nevertheless, our study has some limitations. First, it was based on single-center data from a tertiary medical institution, therefore, some selection bias may have been present regarding the homogenous ethnicity of the patient cohort. Second, regression analysis could not be performed because it was difficult to distinguish cause and effect between the PAP and CT findings. Third, adjustments for factors other than age could not be made when assessing the relationship between CT parameters and peak TRV. This was owing to the limited patient population, the high prevalence of the disease among the female patients of the cohort, and the difficulty of ascertaining past medical information.

5. Conclusion

A positive correlation was observed between PAD and estimated PAP, regardless of the presence or absence of LPA; however, LPA was not found to correlate with estimated PAP. Pulmonary hypertension in MCTD appears to be caused by disorders of pulmonary blood vessels, rather than being a secondary change caused by lung parenchymal abnormalities.

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Conflict of Interest

The authors of this manuscript declare no relationships with any companies whose products or services may be related to the subject matter of the article.

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