

- 1 Diagnosis of Chronic Thromboembolic Pulmonary Hypertension using
- 2 Quantitative Lung Perfusion Parameters Extracted from Dual-Energy Computed
- 3 Tomography Images
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ABSTRACT

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Purpose: To evaluate quantified iodine mapping parameters in dual-energy computed

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tomography (DECT) in normal patients vs those with chronic thromboembolic pulmonary

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hypertension (CTEPH) with and without pulmonary thromboembolism (PTE).

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Materials and Methods: Using automatically quantified iodine mapping in DECT, we

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evaluated lung relative average enhancement, standard deviation (SD), and the SD/lung

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relative average enhancement ratio. We compared the values for these parameters in

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normal patients vs those with CTEPH. We also performed a receiver operating

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characteristic (ROC) curve analysis to determine the diagnostic cutoffs for the

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parameters.

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Results: Patients constituted 41 patients (10 male [24.4%] and 31 female [75.6%];

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mean age [SD]: 70.0 years [13.3]) with CTEPH and 237 (92 male [38.8%] and 145

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female [61.2%]; mean age [SD]: 65.9 years [15.9]) normal patients. We found

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significant differences in lung relative average enhancement (34.9 ± 6.3 vs 26.9 ± 6.3 ;

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$P < 0.0001$), SD (11.6 ± 1.9 vs 14.7 ± 3.3 ; $P < 0.001$), and the SD/lung relative

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average enhancement ratio (33.7 ± 5.0 vs 55.7 ± 10.4 ; $P < 0.001$) between the normal

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and CTEPH groups, respectively. The ROC analyses demonstrated high discriminatory

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power (AUC = 0.99) for using the SD/lung relative average enhancement ratio to

1 differentiate between patients in the normal group and CTEPH group. At a threshold for
2 the area under the curve of 44.2, diagnostic sensitivity, specificity, positive predictive
3 value, and negative predictive value for the ratio were 92.7%, 97.5%, 86.5%, and
4 98.7%, respectively.

5 **Conclusions:** Patients with CTEPH were well-discriminated from normal patients using
6 the SD/lung relative average enhancement ratio.

7 **Key Words:** chronic thromboembolic pulmonary hypertension, dual-energy CT, lung
8 relative average enhancement, standard deviation, sensitivity

INTRODUCTION

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2 Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening
3 disease with a poor prognosis.¹ CTEPH is characterized by obstruction of the large
4 pulmonary arteries by acute and recurrent pulmonary thromboembolism (PTE).² These
5 changes lead to progressively elevated pulmonary arterial pressure and pulmonary
6 vascular resistance (PVR) and, consequently, right-sided heart failure.³ Therefore, it is
7 important to diagnose CTEPH early and start treatment. Dual-energy computed
8 tomography (DECT) pulmonary angiography has recently become an accepted technique
9 for diagnosing PTE. Post-processing software is used to subtract 80–100 kV from 140-kV
10 images to produce an iodine distribution map. Moreover, lung iodine distribution map,
11 CT, and CT angiography (CTA) images can be obtained in a single acquisition, which
12 permits evaluating pulmonary artery dilation and PTE. The lung iodine distribution map
13 shows the iodine-deficient areas of the lung field, and is useful for diagnosing PTE even if
14 the CTA image cannot identify thromboembolism in a pulmonary artery. However, the
15 iodine distribution map is affected by cardiac function and lung field condition (especially
16 emphysema),⁴ and it may overestimate increased and decreased pulmonary perfusion.
17 As a result, it is often difficult to determine whether decreased pulmonary perfusion is
18 due to PTE. Lung iodine distribution map quantification is performed for objective
19 evaluation, and it may reflect parenchymal arterial perfusion in patients with PTE.⁵ This

1 quantitative evaluation automatically displays the average increase (lung relative
2 average enhancement) and standard deviation (SD) in blood flow owing to the contrast
3 medium. Because this quantitative evaluation does not cause discrepancies between
4 observers, it may be possible to accurately evaluate increases, decreases, and variability
5 in blood flow in the lung fields of patients that cannot be evaluated visually. Perfusion of
6 the whole lung field in patients with CTEPH is decreased and uneven compared with that
7 in patients without CTEPH. We hypothesized that the average increase (lung relative
8 average enhancement) reflected the amount of lung perfusion, and that the SD reflected
9 the variability of pulmonary perfusion. SD is generally used as an index to evaluate
10 homogenization.⁶ Therefore, the objective of the present study was to examine the
11 clinical significance of lung relative average enhancement and SD for diagnosing patients
12 with CTEPH.

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MATERIALS AND METHODS

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Patient Population

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Our institutional review board approved this study and waived the need for

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written informed consent because the study design was retrospective.

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From April 2014 to October 2020, 746 patients underwent DECT pulmonary

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angiography in our hospital for the first time. Among them, 41 patients (10 male

1 [24.4%] and 31 female [75.6%]; mean age [SD]: 70.0 years [13.3]) were diagnosed as
2 having CTEPH (CTEPH group). All patients were diagnosed as having CTEPH using
3 standard criteria.⁷ Pulmonary hypertension was confirmed by right heart catheterization
4 (mean pulmonary arterial pressure \geq 25 mm Hg and pulmonary arterial wedge pressure
5 \leq 15 mm Hg at rest). Mismatch on ventilation/perfusion scintigraphy (usually
6 ventilation-perfusion (V/Q) single-photon emission CT) was defined as at least one large
7 perfusion defect in one segment or in two subsegments, or evidence of pulmonary
8 vascular lesions on CT and pulmonary angiography. These findings were obtained after at
9 least 3 months of effective anticoagulation. In the CTEPH group, 14 patients (6 male
10 [42.9%] and 8 female [57.1%]; mean age [SD]: 73.4 years [12.7]) had no PTE (no PTE
11 group), while 27 patients (4 male [14.8%] and 23 female [85.2%]; mean age [SD]:
12 68.3 years [13.3]) had PTE (PTE group). The diagnosis of PTE was according to the
13 detection of a pulmonary thrombus on pulmonary CTA images. The remaining 705
14 patients were not eligible to participate in this study if they had pleural effusion,
15 pneumonia, emphysema, or a history of lung surgery or PTE. Finally, a total of 237
16 patients (92 male [38.8%] and 145 female [61.2%]; mean age [SD]: 65.9 years [15.9])
17 were included in the normal group (Fig. 1). Two experienced radiologists with more than
18 10 years of experience in cardiothoracic CT independently analyzed the CT images. If
19 their diagnoses differed, they reviewed the data to reach a consensus.

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2 DECT Acquisition Protocol

3 All patients in this study were suspected of having venous thrombosis of the
4 lower extremities and thromboembolism of the pulmonary artery. They were examined
5 with a SOMATOM® Definition Flash dual-source CT scanner (Siemens Healthcare,
6 Forchheim, Germany) in the dual-energy mode. Studies were performed after
7 administering high-concentration iodine-based contrast medium (Omnipaque 350;
8 Daiichi-Sankyo, Tokyo) at 4.0 mL/s (total volume, 1.35 mL/kg) through a power injector
9 into a 20-G venous access catheter in an antecubital vein, with a 20-mL saline chaser at
10 4 mL/s.

11 CT scanning began 17 s from the start of the injection. To avoid streak artefacts
12 because of highly-concentrated contrast material in the subclavian vein or superior vena
13 cava, scans were acquired in the caudocranial direction so that the chaser bolus was
14 being injected by the time the scan reached the upper chest.

15 Other scan parameters were as follows: tube voltage, 140- and 100 kVp at 260
16 effective mAs; attenuation-based tube-current modulation; rotation time, 0.28 s; pitch,
17 0.7; and collimation, 128 × 0.6 mm. Coverage was from the lung apex to the lung base.
18 CT angiography images were reconstructed with a specific medium-soft convolution

1 kernel (D30), without edge modification, at a 2.0-mm slice thickness and 2.0-mm
2 increments.

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4 **Analysis of Dual-Energy Data**

5 Iodine distribution maps of the lungs were generated according to three-material
6 (soft tissue, air, and iodine) decomposition using a syngo Multimodality Workstation
7 (Siemens Healthcare GmbH, Erlangen, Germany) with specific dual-energy post-
8 processing software. CT values were automatically calculated in Hounsfield units (HU) for
9 several image patterns, namely the whole lung, right or left lung, and three right or left
10 regions (upper, middle, and lower). In this study, we evaluated whole-lung relative
11 average enhancement, SD, and SD/lung relative average enhancement ratio. The SD
12 summarizes the amount by which every value within a dataset varies from the lung
13 relative average enhancement; 68% of values are less than the SD away from the lung
14 relative average enhancement, 95% of values are less than 2 SD away from the lung
15 relative average enhancement, and 99% of values are less than 3 SD away from the
16 lung relative average enhancement.

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18 **Assessment of CTA Images**

19 CTA images were retrospectively assessed by the same two radiologists who

1 evaluated the CT images. The radiologists were blinded to the patients' clinical conditions
2 and worked independently. They viewed axial CTA images (soft tissue window setting)
3 and multiplanar reformatted (coronal) images, both of which had a slice thickness of 2.0
4 mm and a 2.0-mm slice interval. The radiologists evaluated the CT findings for chronic
5 PTE, including the presence of complete filling defects at the level of stenosed pulmonary
6 arteries, eccentric thromboembolism, or web.⁸ When different findings were obtained,
7 the radiologists reviewed the dataset to reach a consensus.

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9 **Statistical Analysis**

10 We used the D'Agostino–Pearson test to assess the normality of the data, and
11 we presented non-normally distributed variables as the median (range). Quantitative
12 results were expressed as the mean \pm SD or median (range). (The range provided in the
13 tables is the min–max range.)

14 Lung relative average enhancement, SD, and SD/lung relative average
15 enhancement ratio were analyzed using the paired t-test or the Wilcoxon signed-rank
16 test, as appropriate. Results were expressed as sensitivity, specificity, and overall
17 accuracy, with 95% confidence intervals (CI) calculated with the normal approximation
18 method.⁹

1 We created receiver operating characteristic (ROC) curves and determined the
2 threshold that led to the optimal values of probabilities in the presence or absence of
3 CTEPH. This optimal threshold was defined as the intersection of the ROC curve with the
4 bisecting line at which sensitivity equaled specificity.

5 For all tests, a two-sided P -value was used, and differences with a P -value of <
6 0.05 were considered statistically significant. Prism for Windows, version 8.3.0
7 (GraphPad, San Diego, CA) was used for all statistical analyses.

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RESULTS

10 World Health Organization (WHO) Classification

11 In the CTEPH group, patients had a WHO functional class of II ($n = 7$), III ($n =$
12 5), or IV ($n = 2$) in the no PTE group and II ($n = 11$), III ($n = 14$), or IV ($n = 2$) in the
13 PTE group (Table 1).

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15 Lung Relative Average Enhancement in Patients in the Normal Group, with 16 CTEPH no PTE Group, and with CTEPH PTE Group

17 Lung relative average enhancement was 34.9 ± 6.3 in the normal group and
18 26.9 ± 6.3 in the CTEPH group, with a significant difference between the groups ($P <$
19 0.0001). SD, showing the variation in lung relative average enhancement, was $11.6 \pm$

1 1.9 in the normal group and 14.7 ± 3.3 in the CTEPH group, with a significant difference
2 between the two groups ($P < 0.0001$). The SD/lung relative average enhancement ratio
3 was 33.7 ± 5.0 in the normal group and 55.7 ± 10.4 in the CTEPH group, with a
4 significant difference between the two groups ($P < 0.0001$) (Table 2) (Fig 2).

5 In comparison, lung relative average enhancement was 26.9 ± 8.6 in the CTEPH no PTE
6 group and 26.9 ± 4.6 in the CTEPH PTE group, with no significant difference between the
7 two groups ($P = 0.9582$). SD, showing the variation of lung relative average
8 enhancement, was 15.0 ± 3.8 in the CTEPH no PTE group and 14.6 ± 3.0 in the CTEPH
9 PTE group, with no significant difference between the two groups ($P = 0.6668$). The
10 SD/lung relative average enhancement ratio was 57.6 ± 10.7 in the normal group and
11 54.7 ± 10.1 in the CTEPH group, with no significant difference between the two groups
12 ($P = 0.4012$) (Table 3) (Fig. 3).

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14 **ROC Analysis in Patients in the Normal Group and CTEPH Group**

15 ROC analyses demonstrated moderate discriminatory power (area under the
16 ROC curve (AUC) = 0.82) for using lung relative average enhancement to differentiate
17 between patients in the normal group and CTEPH group. When an cut off value < 31.5
18 was used as the threshold for diagnosis, the sensitivity, specificity, positive predictive
19 value, and negative predictive value were 80.5%, 68.4%, 30.5%, and 95.3%,

1 respectively. ROC analyses demonstrated moderate discriminatory power (AUC = 0.79)
2 for using SD to differentiate between patients in the normal group and CTEPH group.
3 When an cut off value < 12.5 was used as the threshold for diagnosis, the sensitivity,
4 specificity, positive predictive value, and negative predictive value were 68.3%, 75.1%,
5 32.1%, and 93.2%, respectively. ROC analyses demonstrated high discriminatory power
6 (AUC = 0.99) for using the SD/lung relative average enhancement ratio to differentiate
7 between patients in the normal group and CTEPH group. When an cut off value < 44.2
8 was used as the threshold for diagnosis, the sensitivity, specificity, positive predictive
9 value, and negative predictive value were 92.7%, 97.5%, 86.5%, and 98.7%,
10 respectively (Fig. 4).

11 **Figure 5** shows lung iodine distribution map image in patient without CTEPH. Lung
12 iodine distribution map image shows slight iodine-deficient areas in the lung field.
13 However, SD/lung relative average enhancement ratio was 32.3, which was below the
14 cut off value of 44.2.

15 In comparison, **Figure 6** shows lung iodine distribution map image in patient with CTEPH
16 and no PTE. Lung iodine distribution map image also shows iodine-deficient areas in the
17 lung field, but it is difficult to determine whether pulmonary perfusion is decreased owing
18 to PTE because this cannot be detected in CTA. However, SD/lung relative average
19 enhancement ratio was 73.9, which was higher than the cut off value of 44.2.

DISCUSSION

1
2 CTEPH is caused by obstruction of the pulmonary vascular bed by repeated PTE
3 with organization. If treatment is delayed, increased vascular resistance with progressive
4 pulmonary hypertension can lead to right-sided heart failure and a poor prognosis.¹⁰
5 Therefore, early diagnosis of CTEPH is important. However, the main symptoms of
6 CTEPH are non-specific, namely shortness of breath, lethargy, easy fatiguability, and
7 cough. It is difficult to distinguish these symptoms from those caused by asthma and
8 chronic bronchitis in the early stage, and they are easily overlooked.¹¹⁻¹⁴ Catheter
9 pulmonary angiography is still considered the gold standard for diagnosing CTEPH, but
10 this examination is invasive and is usually not performed unless the patient is suspected
11 of having CTEPH. Symptomatic patients usually undergo CT or contrast-enhanced CT
12 (CECT) for the first examination. CTA has good potential to detect thromboembolic
13 changes at the lobar (97%–100% and 95%–100%, respectively) and segmental
14 (86–100% and 93–99%, respectively) levels.¹⁵⁻¹⁷ If PTE is detected by CECT, we can
15 suspect pulmonary thrombosis, including CTEPH. However, if thromboembolic lesions are
16 located only in the distal pulmonary arteries, PTE may not be identified by CECT. In such
17 cases, it is difficult to suspect CTEPH. In contrast, lung iodine distribution mapping by
18 DECT may be more sensitive regarding pulmonary blood flow.¹⁸ However, this imaging is
19 affected by cardiac function and lung field condition.⁴ As a result, it is often difficult to

1 determine if pulmonary perfusion is decreased owing to PTE. For assessing quantitative
2 parameters from iodine maps, there was a significant difference in whole-lung relative
3 average enhancement between acute PTE and control groups in previous study.¹⁹ There
4 was also a significant difference in whole-lung relative average enhancement between
5 COPD and control groups in previous study.²⁰ DECT has a high sensitivity for perfusion
6 deficits in patients with CTEPH.²¹ However, there was no study about CTEPH for
7 assessing quantitative parameters from iodine maps.

8 In this study, we found a significant difference in lung relative average
9 enhancement and SD between the patients in the normal group and CTEPH (no PTE and
10 PTE) group. Moreover, ROC analyses demonstrated moderate discriminatory power for
11 using lung relative average enhancement and SD to differentiate between patients in the
12 normal group and CTEPH (no PTE and PTE) group. Lung relative average enhancement in
13 the CTEPH group was lower than that of the normal group, and SD in the CTEPH group
14 was higher than that of the normal group. We speculate that lung relative average
15 enhancement represents a greater decrease in whole-lung perfusion, and that SD
16 represents greater variability in lung perfusion in the CTEPH group compared with the
17 normal group. However, when lung relative average enhancement and SD were used to
18 distinguish between the normal group and CTEPH (no PTE and PTE) group, many
19 patients in the normal group and CTEPH group overlapped and were difficult to

1 distinguish. In contrast, ROC analyses demonstrated high discriminatory power for using
2 SD/lung relative average enhancement to differentiate between patients in the normal
3 group and CTEPH (no PTE and PTE) group. SD/lung relative average enhancement may
4 reflect both decreased perfusion and variability in whole-lung perfusion in patients with
5 CTEPH. As a result, patients in the normal group and CTEPH group do not overlap and
6 are easily distinguished. Additionally, automated quantification is rapid and simple to
7 use. In this DECT technique, lung iodine distribution map, quantitative evaluation (lung
8 relative average enhancement and SD), CT, and CTA images can be obtained in a single
9 CECT. This method is less invasive than catheter pulmonary angiography. We can
10 evaluate the anatomy in CT images with thinner slices more precisely than in SPECT
11 images and detect PTE in CTA images.

12 The results of this study should be clinically useful. Using this quantitative
13 evaluation (lung relative average enhancement and SD), we may be able to detect
14 patients with CTEPH in normal CTA image findings; CTA cannot detect PTE.

15 There was no significant difference in lung relative average enhancement, SD,
16 and SD/lung relative average enhancement ratio between the CTEPH with no PTE and
17 CTEPH with PTE groups. We consider that the cause of this lack of difference was that
18 whole-lung perfusion was similarly reduced and varied in patients with CTEPH with or
19 without PTE regardless of whether PTE could be identified by DECT.

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2 **Limitations**

3 The present study had several limitations. First, this study included a low number of
4 CTEPH patients and lacked an external validation cohort. Second, most patients in the
5 CTEPH group in this study had a WHO functional class of II or III (n = 37) because they
6 were referred to our hospital to undergo balloon pulmonary angioplasty and other
7 cardiac procedures. Third, many patients in this study underwent DECT because of
8 suspected PTE and were excluded owing to pleural effusion, pneumonia, emphysema, or
9 a history of lung surgery and PTE. Therefore, the results cannot be generalized to the
10 entire population because of this specially-selected population subset. Fourth, the lung
11 parenchymal changes and extent of pulmonary arterial stenosis were not considered in
12 this study. Therefore, this may have changed lung relative average enhancement.
13 Finally, some patients with CTEPH in this study were already being treated with
14 anticoagulant therapy with edoxaban or warfarin when they underwent DECT in our
15 hospital. Therefore, pulmonary perfusion could have been influenced by anticoagulation.

16

17 **Conclusion**

18 The SD/lung relative average enhancement ratio reflects the decrease and
19 variability in pulmonary perfusion in patients with CTEPH, and is useful to make a clearer

1 distinction between CTEPH and the normal group compared with using lung relative
2 average enhancement or SD alone. We found no difference in lung relative average
3 enhancement, SD, and SD/lung relative average enhancement ratio between CTEPH
4 patients with and without PTE.

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References

1. Soler X, Hoh CK, Test VJ, et al. Single photon emission computed tomography in chronic thromboembolic pulmonary hypertension. *Respirology*. 2011;16:131-137.
2. Dartevielle P, Fadel E, Mussot S, et al. Chronic thromboembolic pulmonary hypertension. *Eur Respir J*. 2004;23:637-648.
3. Hoey ET, Mirsadraee S, Pepke-Zaba J, et al. Dual-energy CT angiography for assessment of regional pulmonary perfusion in patients with chronic thromboembolic pulmonary hypertension: initial experience. *Am J Roentgenol*. 2011;196:524-532.
4. Ferda J, Ferdová E, Mírka H, et al. Pulmonary imaging using dual-energy CT, a role of the assessment of iodine and air distribution. *Eur J Radiol*. 2011;77:287-293.
5. Sueyoshi E, Tsutsui S, Hayashida T, et al. Quantification of lung perfusion blood volume (lung PBV) by dual-energy CT in patients with and without pulmonary embolism: preliminary results. *Eur J Radiol*. 2011;80:e505-e509.
6. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.
7. Wilkens H, Konstantinides S, Lang IM, et al. Chronic thromboembolic pulmonary hypertension (CTEPH): updated recommendations from the Cologne Consensus

- 1 Conference 2018. *Int J Cardiol.* 2018;272S:69-78.
- 2 8. Hasegawa I, Boiselle PM, Hatabu H. Bronchial artery dilatation on MDCT scans of
3 patients with acute pulmonary embolism: comparison with chronic or recurrent
4 pulmonary embolism. *AJR Am J Roentgenol.* 2004;182:67-72.
- 5 9. Fleiss JL, Levin B, Paik MC. *Statistical Methods for Rates and Proportions.* 2nd ed. New
6 York: Wiley; 1981.
- 7 10. Piazza G, Goldhaber SZ. Chronic thromboembolic pulmonary
8 hypertension. *N Engl J Med.* 2011;364:351-360.
- 9 11. Mayer E, Jenkins D, Lindner J, et al. Surgical management and outcome of patients
10 with chronic thromboembolic pulmonary hypertension: results from an international
11 prospective registry. *J Thorac Cardiovasc Surg.* 2011;141:702-710.
- 12 12. Held M, Grün M, Holl R, et al. [Chronic thromboembolic pulmonary hypertension:
13 time delay from onset of symptoms to diagnosis and clinical condition at diagnosis].
14 *Dtsch Med Wochenschr.* 2014;139:1647-1662. [Article in German]
- 15 13. Gopalan D, Delcroix M, Held M. Diagnosis of chronic thromboembolic pulmonary
16 hypertension. *Eur Respir Rev.* 2017;26:160108.
- 17 14. Fedullo P, Kerr KM, Kim NH, et al. Chronic thromboembolic pulmonary hypertension.
18 *Am J Respir Crit Care Med.* 2011;183:1605-1613.

- 1 15. Ley S, Ley-Zaporozhan J, Pitton MB, et al. Diagnostic performance of state-of-
2 the-art imaging techniques for morphological assessment of vascular
3 abnormalities in patients with chronic thromboembolic pulmonary hypertension
4 (CTEPH). *Eur Radiol.* 2012;22:607-616.
- 5 16. Reichelt A, Hoepfer MM, Galanski M, et al. Chronic thromboembolic
6 pulmonary hypertension: evaluation with 64-detector row CT versus
7 digital subtraction angiography. *Eur J Radiol.* 2009;71:49-54.
- 8 17. Sugiura T, Tanabe N, Matsuura Y, et al. Role of 320-slice CT imaging
9 in the diagnostic workup of patients with chronic thromboembolic pulmonary
10 hypertension. *Chest.* 2013;143:1070-1077.
- 11 18. Fuld MK, Halaweish AF, Haynes SE, et al. Pulmonary perfused blood volume with
12 dual-energy CT as surrogate for pulmonary perfusion assessed with dynamic
13 multidetector CT. *Radiology.* 2013;267:747-756.
- 14 19. Sakamoto A, Sakamoto I, Nagayama H, et al. Quantification of lung perfusion blood
15 volume with dual-energy CT: assessment of the severity of acute pulmonary
16 thromboembolism. *AJR Am J Roentgenol.* 2014;203:287-91
- 17 20. Koike H, Sueyoshi E, Sakamoto I et al. Quantification of lung perfusion blood volume
18 by dual-energy CT in patients with and without chronic obstructive pulmonary
19 disease. *J Belg Soc Radiol.* 2015;99:62-68

1 21. Dournes G, Verdier D, Montaudon M, et al. Dual-energy CT perfusion and
2 angiography in chronic thromboembolic pulmonary hypertension: diagnostic
3 accuracy and concordance with radionuclide scintigraphy. *Eur Radiol.* 2014
4 ;24:42-51

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12 **Figure captions**

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14 **FIGURE 1.** Flowchart showing the patient selection.

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16 **FIGURE 2.** Individual data.

17 (a) Individual data for lung relative average enhancement in the normal group and
18 chronic thromboembolic pulmonary hypertension (CTEPH) group ($P < 0.0001$).

1 (b) Individual data for standard deviation (SD) in the normal group and CTEPH group (P
2 < 0.0001).

3 (c) Individual data for SD/lung relative average enhancement ratio in the normal group
4 and CTEPH group ($P < 0.0001$).

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6 **Figure 3.** Individual data.

7 (a) Individual data for lung relative average enhancement in the chronic thromboembolic
8 pulmonary hypertension (CTEPH) no pulmonary thromboembolism (PTE) group and the
9 CTEPH PTE group ($P = 0.9582$).

10 (b) Individual data for SD in the CTEPH no PTE group and the CTEPH PTE group ($P =$
11 0.6668).

12 (c) Individual data for standard deviation (SD)/lung relative average enhancement ratio
13 in the CTEPH no PTE group and CTEPH PTE group ($P = 0.4012$).

14

15 **FIGURE 4.** Receiver operating characteristic (ROC) analysis.

16 (a) ROC analyses demonstrated moderate discriminatory power for using lung relative
17 average enhancement to differentiate between patients in the normal group and chronic
18 thromboembolic pulmonary hypertension (CTEPH) group. When an area under the curve
19 (AUC) value of < 31.5 was used as the threshold for diagnosis, the sensitivity, specificity,

1 positive predictive value, and negative predictive value were 80.5%, 68.4%, 30.5%, and
2 95.3%, respectively.

3 (b) ROC analyses demonstrated moderate discriminatory power for using standard
4 deviation (SD) to differentiate between patients in the normal group and CTEPH group.

5 When an AUC value < 12.5 was used as the threshold for diagnosis, the sensitivity,
6 specificity, positive predictive value, and negative predictive value were 68.3%, 75.1%,
7 32.1%, and 93.2%, respectively.

8 (c) ROC analyses demonstrated high discriminatory power for using the SD/lung relative
9 average enhancement ratio to differentiate between patients in the normal group and
10 CTEPH group. When an AUC value < 44.2 was used as the threshold for diagnosis, the
11 sensitivity, specificity, positive predictive value, and negative predictive value were
12 92.7%, 97.5%, 86.5%, and 98.7%, respectively.

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14 **FIGURE 5.** Images for a 56-year-old woman without chronic thromboembolic pulmonary
15 hypertension (CTEPH).

16 (a) Fusion image in computed tomography (CT) angiography and a color-coded map
17 shows a slight iodine-deficient area in the lung field (arrows).

1 (b) Lung relative average enhancement and SD were calculated automatically
2 (surrounded). Lung relative average enhancement was 31, SD was 10, and SD/lung
3 relative average enhancement ratio was 32.3.

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5 **FIGURE 6.** Images for a 78-year-old woman with CTEPH and no pulmonary
6 thromboembolism (PTE).

7 (a) Fusion image in CT angiography and a color-coded map shows an iodine-deficient
8 area in the lung field (arrows).

9 (b) Lung relative average enhancement and SD were calculated automatically
10 (surrounded). Lung relative average enhancement was 23, SD was 17, and SD/lung
11 relative average enhancement ratio was 73.9.

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Table 1. Patients' Demographic and Clinical Characteristics

Variable	Normal (n=237)	CTEPH no PTE (n=14)	CTEPH PTE (n=27)
Age, years	65.9±15.9	73.4±12.7	68.3±13.3
Male, n	92	6	4
WHO functional class			
II		7	11
III		5	14
IV		2	2
History of cancer, n	80	0	2
Previously treated with anticoagulation therapy with edoxaban or warfarin, n	0	9	13
Previously treated with PEA or BPA, n	0	0	0

Data expressed as n or mean ± standard deviation (range). CTEPH indicates

chronic thromboembolic pulmonary hypertension; PTE, pulmonary

thromboembolism; WHO, World Health Organization; PEA, pulmonary
endarterectomy; BPA, balloon pulmonary angioplasty.

Table 2. Lung Relative Average Enhancement, SD, and SD/Lung Relative Average Enhancement Ratio in the Normal Group and CTEPH Group

Variable	Normal (n=237)	CTEPH (n=41)	p
Lung relative average enhancement (HU)	34.9±6.3	26.9±6.3	<0.0001
SD (HU)	11.6±1.9	14.7±3.3	<0.0001
SD/lung relative average enhancement × 100 (%)	33.7±5.0	55.7±10.4	<0.0001

Data expressed as n or mean ± standard deviation (range). CTEPH indicates chronic thromboembolic pulmonary hypertension; PTE, pulmonary thromboembolism; SD, standard deviation.

Table 3. Lung Relative Average Enhancement, SD, and SD/Lung Relative Average

Enhancement Ratio in the CTEPH no PTE group and CTEPH PTE group

Variable	CTEPH no PTE (n=14)	CTEPH PTE (n=27)	p
Lung relative average enhancement (HU)	26.9±8.6	26.9±4.6	0.9582
SD (HU)	15.0±3.8	14.6±3.0	0.6668
SD/lung relative average enhancement × 100 (%)	57.6±10.7	54.7±10.1	0.4012

Data expressed as n or mean ± standard deviation (range). CTEPH indicates

chronic thromboembolic pulmonary hypertension; PTE, pulmonary

thromboembolism; SD, standard deviation.

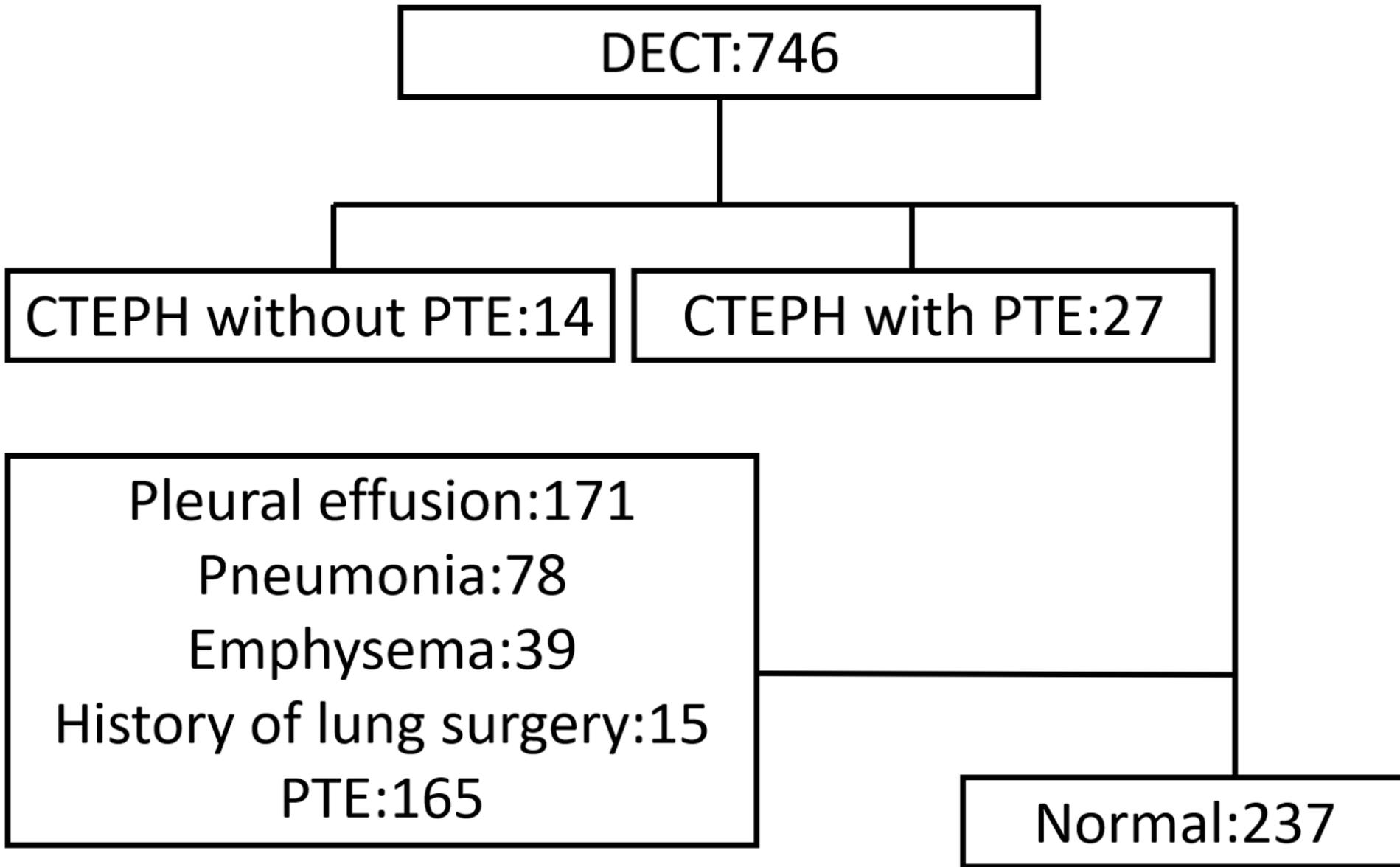


Figure 1

Normal vs CTEPH

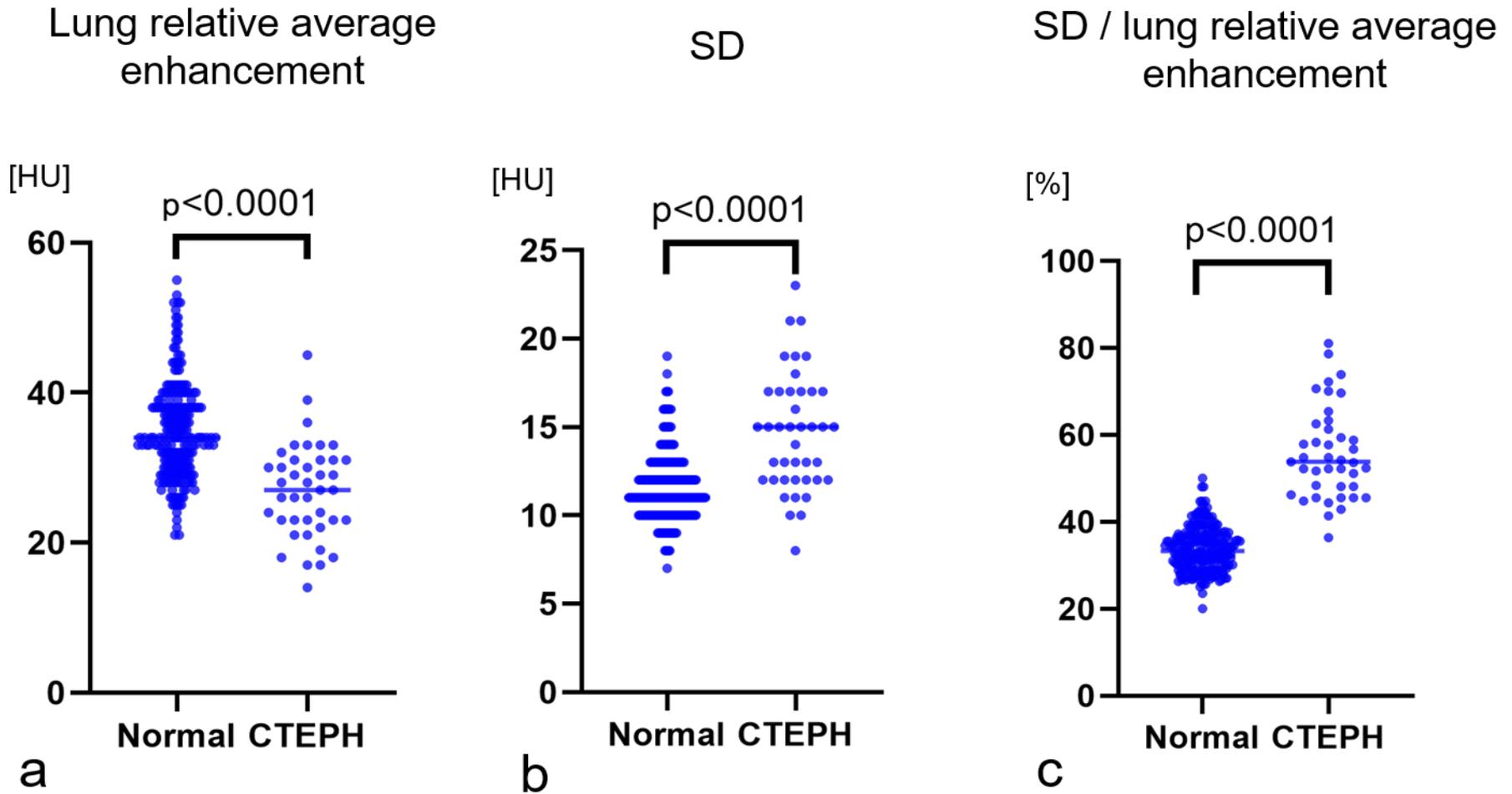
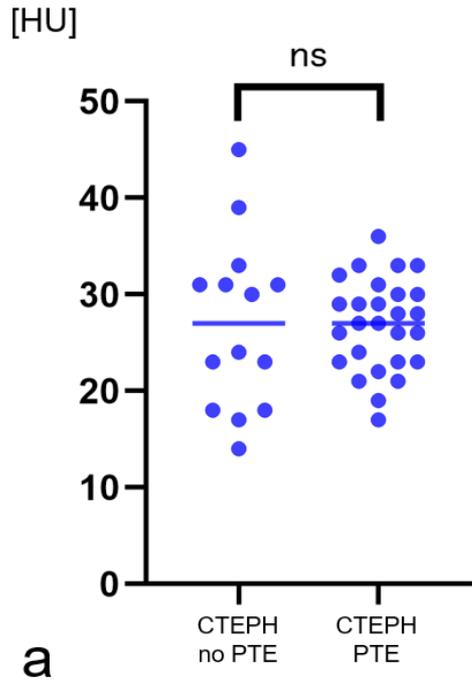


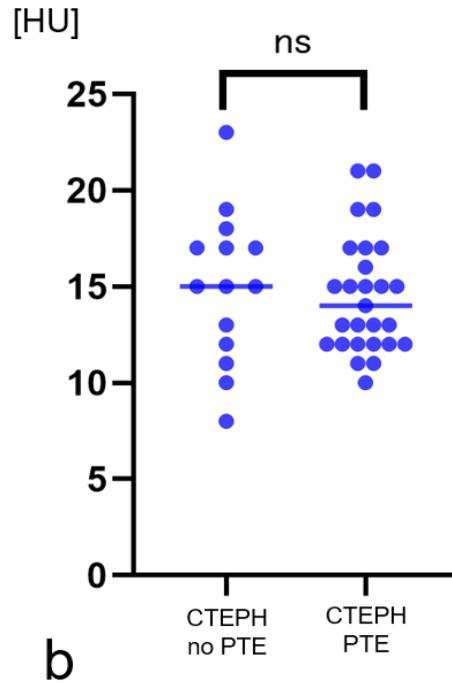
Figure 2

CTEPH no PTE vs CTEPH PTE

Lung relative average enhancement



SD



SD / lung relative average enhancement

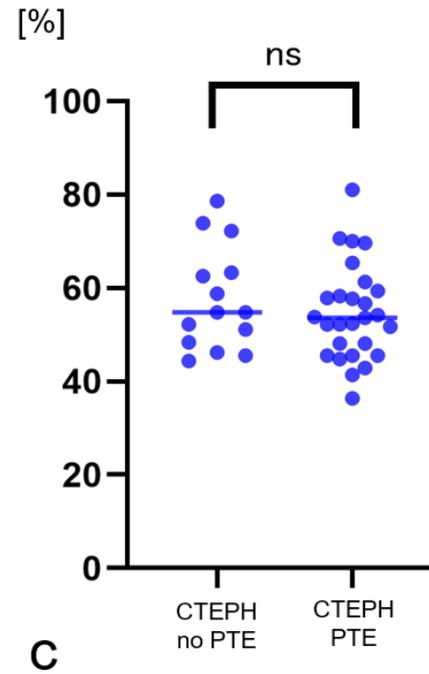
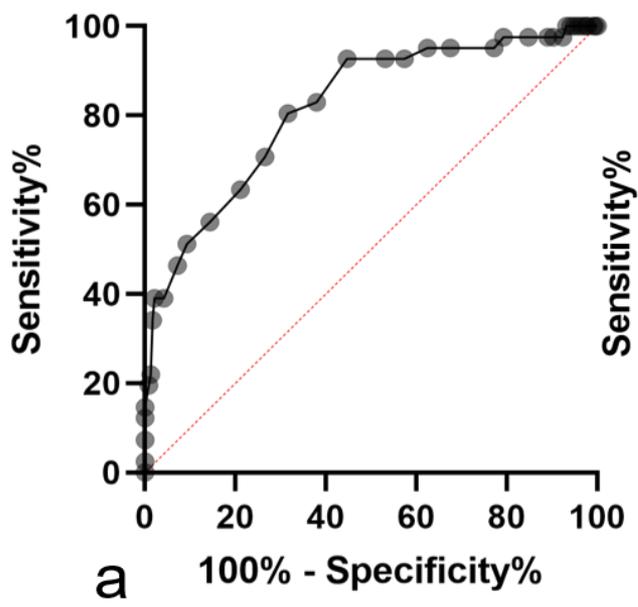
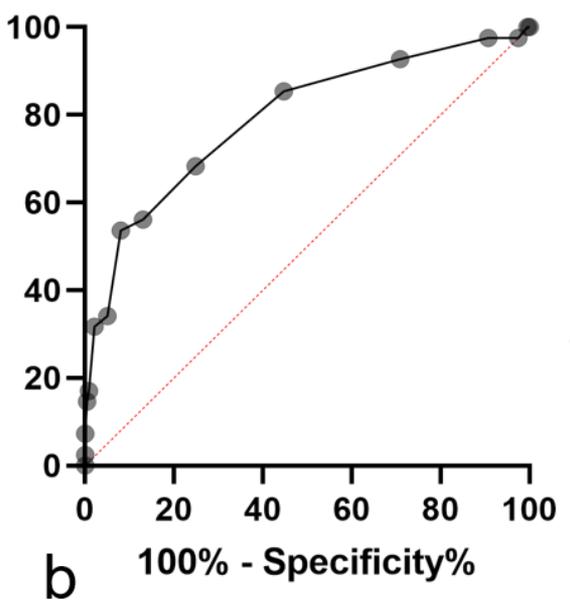


Figure 3

Lung relative average enhancement



SD



SD / lung relative average enhancement

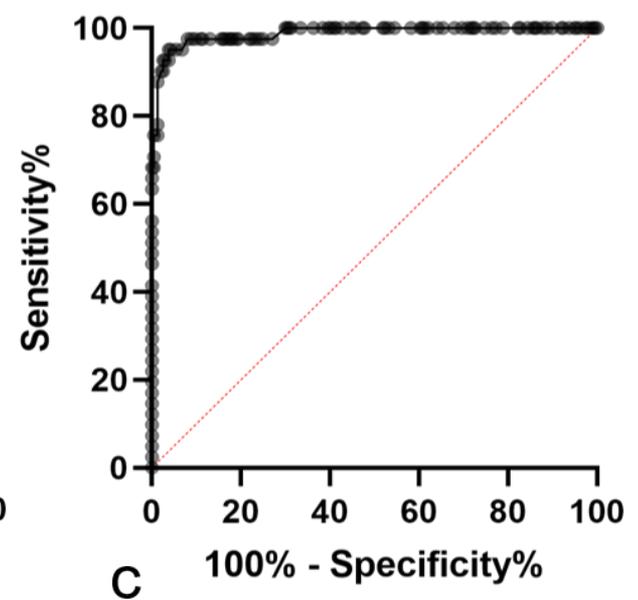
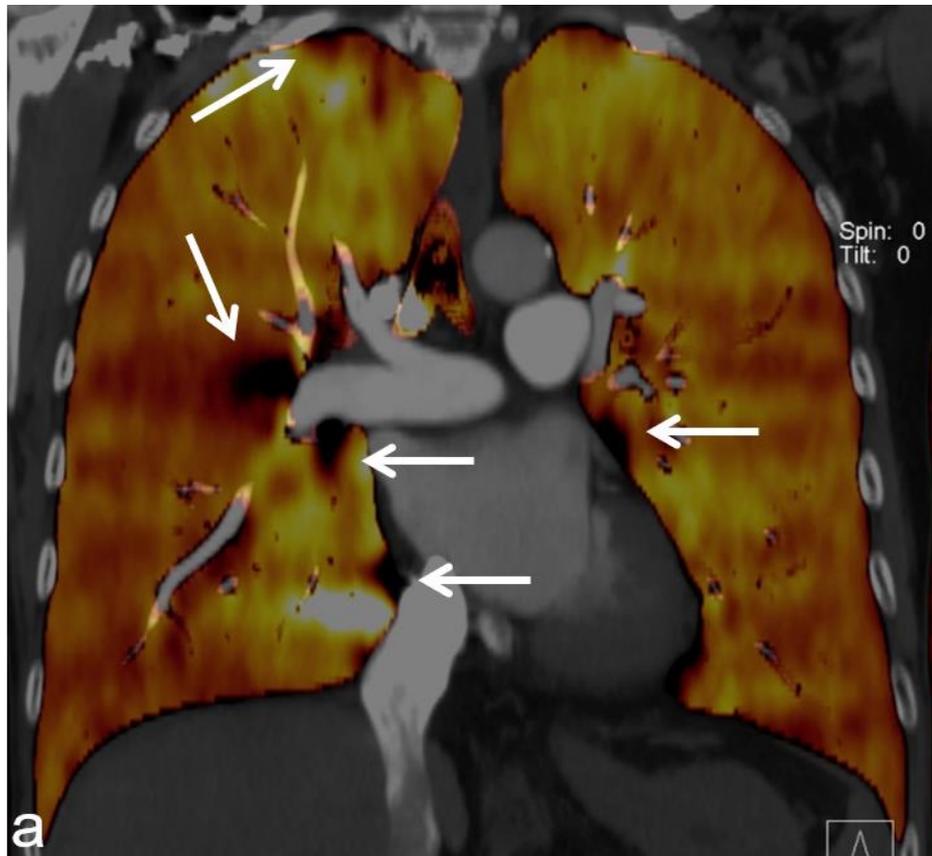
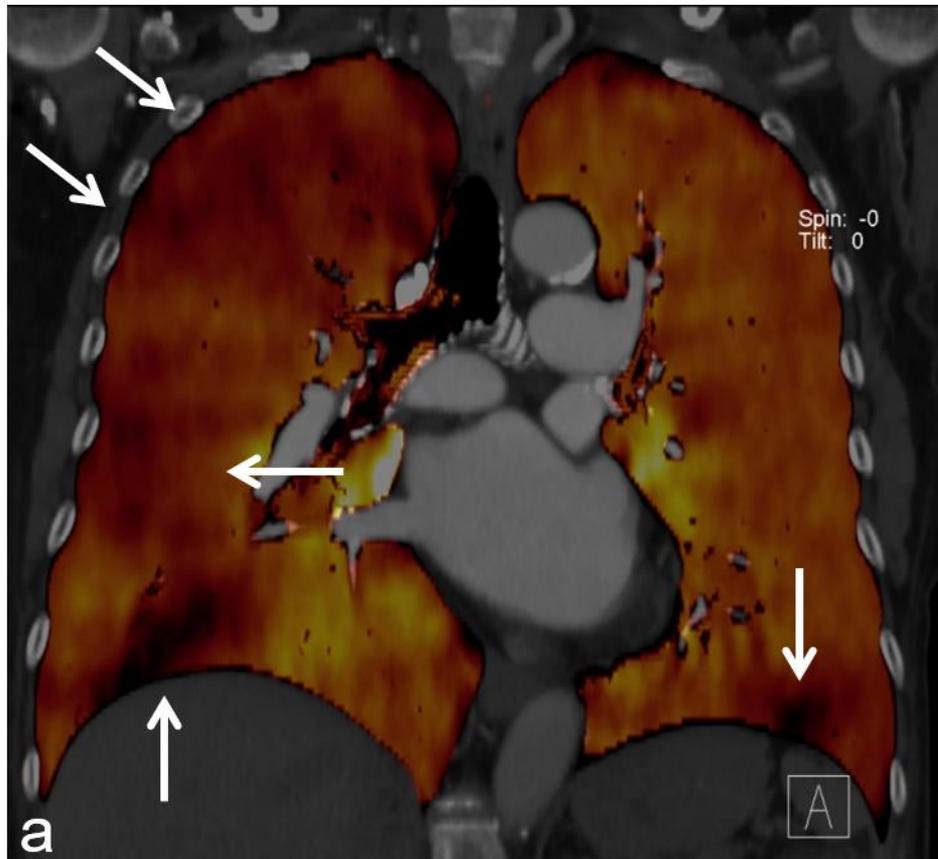


Figure 4



Analysis Region	Volume [cm ³]	Below Min. % of Voxels	Above Max. % of Voxels	Enhancement [HU]	Relative Enh. %
Total	3313	1	4	31 ± 10	79
Right	1850	1	4	32 ± 10	81
Left	1464	1	5	30 ± 9	77
Right - Lower	613	0	4	30 ± 8	79
Right - Middle	605	1	5	33 ± 11	84
R Right - Upper	632	1	3	32 ± 10	82
Left - Lower	485	0	6	29 ± 12	74
Left - Middle	475	1	5	30 ± 8	79
Left - Upper	503	1	3	30 ± 7	77

Figure 5



Analysis Region	Volume [cm ³]	Below Min. % of Voxels	Above Max. % of Voxels	Enhancement [HU]	Relative Enh. %
Total	2695	0	7	23 ± 17	14
Right	1642	0	6	19 ± 16	12
Left	1053	0	10	28 ± 18	17
Right - Lower	544	0	6	12 ± 15	7
Right - Middle	540	0	7	19 ± 14	12
Right - Upper	559	0	4	25 ± 17	15
Left - Lower	346	0	12	21 ± 22	13
Left - Middle	344	0	10	29 ± 16	18
Left - Upper	363	0	7	35 ± 9	21

b

Figure 6