Quantitative Evaluation of Disease Severity in Connective Tissue Disease-associated Interstitial Lung Disease by Dual-energy Computed Tomography

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Research

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Abstract

BACKGROUND: High-resolution computed tomography (HRCT) is recommended for diagnosing and monitoring connective tissue disease-associated interstitial lung disease (CTD-ILD). Quantitative computed tomography has the potential to precisely assess the radiological severity of CTD-ILD, but has still been under study.

OBJECTIVE: To investigate whether dual-energy computed tomography (DECT), a novel quantitative technique, can be used in the quantitative severity assessment in CTD-ILD.

METHODS: This cross-section study recruited adult CTD-ILD patients who underwent a DECT scan from the ICE study between October 2019 and April 2021. DECT parameters, including effective atomic number (Z_{eff}), volume, and monochromatic CT number (MCTN) of each lung lobe, were evaluated. CTD-ILD was classified into extensive CTD-ILD and limited CTD-ILD by staging algorithm combined pulmonary function test (PFT) and total extent of ILD (TEI) score based on the chest CT. Dyspnea, cough, and life quality were scored by Borg dyspnea score, Leicester cough questionnaire (LCQ), and short-form 36 health survey questionnaire (SF-36), respectively.

RESULTS: There was a total of 121 CTD-ILD patients enrolled. Higher Z_{eff} value (3.11 vs 2.26, $p < 0.001$), higher MCTN (-721.31 vs -801.44, $p < 0.001$), and lower lung volume (2481.13cm³ vs 3525.52cm³, $p < 0.001$) were found in extensive CTD-ILD compared with limited CTD-ILD. DECT parameters had a moderate to high correlation with FVC%pre ($|r| = 0.647\text{--}0.750$, $p < 0.01$) and DLCO%pre ($|r| = 0.424\text{--}0.484$, $p < 0.01$), and moderate to high correlation with TEI ($|r| = 0.411\text{--}0.719$, $p < 0.01$). Receiver operating characteristic (ROC) analysis suggested MCTN had the best performance for extensive CTD-ILD discrimination in right middle lung lobe (AUC = 0.877, cut-off: -805, $p < 0.001$), with a sensitivity of 86.36% and a specificity of 77.42%. The Z_{eff} value was the independent risk factor for dyspnea and cough (OR = 3.716 for dyspnea, $p < 0.05$; OR = 2.294 for cough, $p < 0.05$), and lung volume significantly contributed to the mental component summary (MCS) in SF-36 ($\beta = 0.190$, $p < 0.05$).

CONCLUSIONS: DECT parameters can be applied to evaluate the severity of CTD-ILD.

Introduction

Connective tissue disease-associated interstitial lung disease (CTD-ILD) is a predominant type of ILD, as well as a common and serious pulmonary complication of CTD¹. It has been reported to be the leading cause of significant morbidity and mortality of CTD², constituting 31.76% mortality of this disease³. The survival time of CTD-ILD patients was 1.7 times shorter than CTD patients without ILD³. The severity of ILD is usually associated with poor outcome and life quality of CTD-ILD patients^{4,5}. Therefore, accurate evaluation of ILD severity may provide evidence for the appropriate clinical decision in the diagnosing and monitoring of CTD-ILD patients.

Pulmonary function test (PFT) and high-resolution computed tomography (HRCT) have been still the two major tools to diagnose and evaluate CTD-ILD in clinical practices, rather than lung biopsy⁶. Declines of PFTs, such as forced vital capacity (FVC), vital capacity, and diffusing capacity of the lungs for carbon monoxide (DLCO), are predictors for exacerbations and mortality of ILD⁷. But the results of PFTs weakly reflect the extent of ILD⁷ and could be confounded by the presence of comorbidities, such as pleural disease⁸, chronic airway diseases, pulmonary hypertension, or anemia^{9,10}. Furthermore, given that the measures of PFT heavily rely on the cooperation of patients¹¹, PFT is not applicable to some severe patients. HRCT can define different radiological patterns and distribution of ILD abnormalities, which is fundamental to the diagnosis and monitoring of ILDs. Increased extents of fibrosis abnormalities, including honeycombing, reticulation, and traction bronchiectasis, were the predictors of worse prognosis of ILD^{12,13}. However, most assessments in the above studies were visual or semi-quantitative analysis, which was subjective evaluation, and relied on experienced radiologists or pulmonologists¹⁴. Recently, there have been several quantitative assessment methods under investigation, like quantitative lung fibrosis (QLF) score¹⁵, and computer-aided lung informatics for pathology evaluation and ratings (CLIPER)¹⁶, but these methods require additional professional software and lesion identification by senior radiologists or pulmonologists. Therefore, it is worth exploring a more precise and convenient quantitative evaluation technology.

Dual-energy computed tomography (DECT) was demonstrated to simultaneously provide the lung function information, as well as the anatomic information in pulmonary diseases¹⁷. This novel quantitative technique refers to the near-simultaneous acquisition of CT images at two X-ray energy levels without additional dose or compromised image quality¹⁸. It provides additional quantitative information than the conventional CT by generating material decomposition and monochromatic images according to effective atomic number (Z_{eff}) in each image voxel^{19,20}. The post-processing inherent software of DECT can overlay Z_{eff} images on the original CT images which allow qualitative and quantitative evaluation of regional pulmonary involvement. Up to now, DECT has shown its clinical applications value in malignant lung lesions, chronic airway diseases, pulmonary embolism, and pulmonary ventilation abnormalities^{21–24}. However, its value in interstitial lung abnormality is still unknown.

Considering the ability of DECT to structurally and functionally image lung lesions, we hypothesized that DECT could be applied in CTD-ILD severity assessment. To test this hypothesis, DECT parameters in different severity of CTD-ILD patients were evaluated, and the correlations of DECT parameters with the manifestation of respiratory symptoms (dyspnea and cough), life quality level, PFTs, and the extent of ILD were investigated, respectively.

Material And Methods

Study design and subjects

This cross-sectional study was designed to explore whether DECT parameters could reflect the severity of CTD-ILDs evaluated by CT, PFTs (FVC% predicted and DLCO% predicted), symptoms scales (dyspnea scored by Borg dyspnea score, cough scored by Leicester Cough Questionnaire (LCQ)), and life quality scale (36 items Short Form Health Survey (SF-36)). This study was approved by Ethics Committee on Biomedical Research (2020-216) at West China Hospital, and all the patients had written informed consent.

A total of 121 adult stable CTD-ILD patients, followed up in ICE study (Interstitial lung disease in West China Hospital: a 24-month prospective Cohort on the real world) between October 2019 and April 2021, were included. The diagnosis of CTD-ILD was determined by the multidisciplinary group with expert radiology, pathology, rheumatology, and pulmonology based on the diagnosis criteria of ILD and CTDs according to 2008 British Thoracic Society ILD guideline²⁵, and recommendations by American Rheumatism and the American College of Rheumatology¹, respectively. The diagnosis of undifferentiated CTD-ILD (UCTD-ILD) in this study was made according to the official statement of the European Respiratory Society/American Thoracic Society for interstitial pneumonia with autoimmune features (IPAF)²⁶. Exclusion criteria included idiopathic ILD, ILD for other causes (such as sarcoidosis, drug, toxicity, or PAP), acute exacerbations of interstitial lung disease, pulmonary infection, heart failure to avoid its influence on the DECT parameters, refused consent, or missing DECT scan data. Figure 1 showed the process of patients screening. The normal lung images data of healthy people from a physical examination program was also included in the stratification analysis.

Data collection

The demographics and clinical characteristics were reviewed by the well-trained researchers, including basic information (age, sex, body mass index, smoking history), symptoms (dyspnea scaled by Borg dyspnea score, cough scaled by LCQ), quality of life (SF-36, consisting of physical component summary (PCS) subscale for a physical health evaluation, and mental component summary (MCS) subscale for a mental health evaluation, with higher scores indicating better quality of life), common comorbid conditions (chronic obstructive pulmonary disease, coronary artery disease, diabetes mellitus, hypothyroidism, anemia, etc). Dyspnea was classified into no dyspnea (Borg dyspnea score = 0), mild dyspnea ($0 < \text{Borg dyspnea score} \leq 2$) and moderate to severe dyspnea (Borg dyspnea score ≥ 3). Cough was classified into no cough (LCQ = 0), mild dyspnea ($\text{LCQ} \geq 17$) and severe cough ($0 < \text{LCQ} < 17$)²⁷.

Pulmonary function test was conducted according to the recommendations of the American Thoracic Society/European Respiratory Society. FVC% predicted and DLCO% predicted were classified into mild (FVC% predicted $\geq 80\%$ and DLCO% predicted $\geq 80\%$), moderate (FVC% predicted $\geq 50\%$ and DLCO% predicted $\geq 50\%$ and not the mild cases), and severe (FVC% predicted $\leq 50\%$ or DLCO% predicted $\leq 50\%$).

Image Acquisition with DECT

All patients were scanned on a 256-slice CT scanner (Revolution CT, GE Healthcare, Milwaukee WI, USA) without contrast injection according to standards set. The DECT was obtained with the following parameters: fast switching between tube voltages of 80 and 140 kV, automatic mA selection for obtaining a noise index (NI) of 15, the spiral pitch of 0.984, tube rotation time of 0.5s, detector width of 80mm (128×0.625mm). Images were reconstructed using a “detail” kernel with a slice thickness of 1.25mm and a reconstruction interval of 0.625 mm.

The DECT images were transferred to an advanced workstation (ADW4.7) equipped with the GSI for post-processing. The data processing step included lung extraction and segmentation with identification and extraction of central airways and manual segmentation of the anatomical lobes in the thoracic analysis software. The segmentation of the lungs was achieved into the right upper lobe (RU), right middle lobe (RM), right lower lobe (RL), left upper lobe (LU), left lower lobe (LL) using an adaptive density-based morphological approach²⁸. The corresponding DECT parameters of each lung lobe were achieved according to the extracted histogram, such as lung lobe volume, the mean, minimum, maximum values of the effective atomic number (Z_{eff}), and the monochromatic CT number (MCTN) at the 70keV energy level²⁷ (Figure.2).

The Extent of ILD

The extent of ILD was visually scored at five levels (origin of great vessels, the main carina, the pulmonary venous confluence, halfway between the third and fifth sections, and immediately above the right hemidiaphragm), and the total extent of ILD (TEI) on DECT was calculated as the mean of the five scores, according to the previous ILD staging system²⁹. The extent of the abnormality was estimated to be the nearest 5% in each section. 20% was selected to be the TEI threshold as it was proved to be the powerful predictor of mortality²⁹. All semi-quantitative image evaluations of ILD were performed by two independent chest radiologists (LC with 7 years, TY with 12 years of experience in thoracic CT diagnosis). Discordances were settled by consensus.

Severity assessment of CTD-ILD

Limited/extensive staging system combined TEI and PFTs was recommended to assess the severity of CTD-ILD, with greater prognostic value compared with the variable alone²⁹. According to the limited/extensive staging system, the CTD-ILD was staged as limited disease (TEI < 10%, or in indeterminate cases FVC% pre $\geq$ 70%), or extensive disease (TEI > 30%, or in indeterminate cases FVC% pre < 70%), which represented the mild, or severe CTD-ILD, respectively.

Statistical analysis

Continuous variables were presented as means $\pm$ SD or median (range). Count variables were presented as frequency or percentage. Differences were analyzed using the student's t-test or ANOVA for continuous variables (LSD test was used for multiple comparisons), or chi-square test for count variables. Pearson correlation coefficients (r values) or Spearman correlation coefficients was used to quantify the correlation. Binary logistic regression was performed to study the association between DECT parameters and onset of dyspnea or cough symptom. Linear regression analysis was performed to determine the prediction of DECT parameters to the SF-36 in CTD-ILD patients. Receiver operating characteristics (ROC) analysis was performed to determine the area under the curve (AUC) for the diagnostic performance of DECT to differentiate the extensive from limited CTD-ILD. All data were presented for statistical analysis using SPSS 20.0 (IBM, Armonk, NY, USA). Differences corresponding to $p < 0.05$ were considered significant.

Results

Demographic and clinical characteristics

121 stable CTD-ILD patients were enrolled (Figure.1), with 86 specific CTD (SCTD)-ILD, 23 UCTD-ILD, and 12 mixed CTD (MCTD)-ILD (Table.1). They were female predominant (84.3%), with a mean age of 49.22 ± 9.94 years old, a mean body mass index of 23.26 ± 3.34 kg/m², and a 16.5% smoking history. Common comorbid conditions occurred in 63 (54.3%) patients. Mild physiological impairment occurred in included patients with mean FVC% predicted 83.23 ± 23.95 , and median DLCO% predicted

64.60 (ranged from 53.40 to 80.18). Combined with semi-quantitative chest CT assessment and FVC%pre, 62 (51.2%) CTD-ILD patients were segregated into 62 (51.2%) limited CTD-ILD, and 44 (36.4%) extensive CTD-ILD, 14 (12.4%) missed data. In available Borg dyspnea score and LCQ scores, 58 (46.2%) patients had dyspnea, 55 (52.4%) had cough, 32 (30.5%) had both dyspnea and cough symptoms, 39 (37.1%) had dyspnea or cough, and 34 (32.4%) had no respiratory symptoms (Table 3). The median PCS score of SF-36 was 52.03, ranging from 45.50 to 55.84, and the MCS score of SF-36 was 51.98, ranging from 45.05 to 56.88.

DECT parameters in different severity of CTD-ILDs

Differences of DECT parameters in different severity of CTD-ILDs were analyzed. According to the limited/extensive staging system combined TEI and PFTs, the extensive CTD-ILD patients (TEI > 30%, or in indeterminate cases FVC% pre < 70%) were shown to have significantly lower volume (2481.13 cm³ vs 3525.52 cm³, $p < 0.001$), higher Z_{eff} value (3.11 vs 2.26, $p < 0.001$), and higher MCTN (-721.31 HU vs -801.44 HU, $p < 0.001$) in the whole lung, as well as each lung lobe (Table 2), when compared with limited CTD-ILDs (TEI < 10%, or in indeterminate cases FVC% pre $\geq$ 70%). According to the TEI or PFT findings, the severe CTD-ILD patients (TEI > 20% for extent; FVC% pre $\leq$ 50% or DLCO % pre $\leq$ 50% for PFT) also had significantly lower volume, higher Z_{eff} value, and higher MCTN compared with moderate and mild patients (TEI $\leq$ 20% for extent; FVC% pre > 50% and DLCO % pre > 50% for PFT) (online supplement Table S1 and S2). When compared with normal lung images, lobe volume and MCTN of bilateral lower lung lobe were significantly corresponding different according to the gradient severity, which was reported in the online supplement Table S3.

The correlations of DECT parameters in whole lung and each lung lobar with PFT and semi-quantitative chest CT assessment were summarized in online supplement Table S4. Figure 3 showed the LV positively correlated with VC ($r = 0.9119$, $p < 0.0001$), TLC ($r = 0.8730$, $p < 0.0001$), FVC ($r = 0.9097$, $p < 0.0001$) and DLCO ($r = 0.6950$, $p < 0.0001$), while Z_{eff} value and MCTN negatively correlated with FVC% pre ($r = -0.6466$, $p < 0.0001$ for Z_{eff} value; $r = -0.6728$, $p < 0.0001$ for MCTN), VC ($r = 0.615$, $p < 0.01$ for Z_{eff} value; $r = -0.617$, $p < 0.01$ for MCTN), TLC% pre ($r = 0.626$, $p < 0.01$ for Z_{eff} value; $r = -0.633$, $p < 0.01$ for MCTN), and DLCO% pre ($r = -0.459$, $p < 0.01$ for Z_{eff} value; $r = -0.484$, $p < 0.01$ for MCTN) shown in the online supplement Table S4. The Z_{eff} value and MCTN showed a significantly high positive correlation with TEI ($r = 0.7039$, $p < 0.01$ for Z_{eff} value; $r = 0.7191$, $p < 0.001$ for MCTN).

Among DECT parameters significantly differentiate extensive from limited CTD-ILDs, the Z_{eff} value and MCTN of middle lobe and lower lobes had the higher AUCs (range from 0.832 to 0.877, $p < 0.001$) than those for lung (lobe) volume or upper lobes, shown in Figure 4 and online supplement Table S5. And the MCTN of the right middle lung lobe (cutoff value = -805) achieved the highest AUC (0.877, 95%CI: 0.810-0.944), with a sensitivity of 86.36% and a specificity of 77.42%, to detect extensive CTD-ILD (Figure 4 and online supplement Table S5).

DECT parameters' performance in different symptoms of CTD-ILDs

The CTD-ILD patients with both dyspnea and cough had smaller total lung volume, significantly higher Z_{eff} value, and significantly higher MCTN when compared to no respiratory symptom and one symptom ($p = 0.226$, 0.002, and 0.001, respectively), showed in Table 3. The similar trends were also shown in patients with more severe dyspnea (online supplement Table S6) and with more severe cough (Table S7). Univariate analysis suggested that Z_{eff} value and MCTN were the risk factors for dyspnea and cough, meanwhile lung volume was the risk factor for dyspnea. Due to the collinearity of Z_{eff} value and MCTN, multivariate analysis excluding MCTN suggested that Z_{eff} value was the independent risk factor for dyspnea and cough (OR = 3.716 for dyspnea, 95% CI: 1.773- 7.786, $p = 0.001$; OR = 2.294 for cough, 95% CI: 1.165- 4.516, $p = 0.016$), and the same to MCTN (online supplement Table S10 and S11).

DECT parameters contribute to the life quality of CTD-ILDs

Life quality is impaired in CTD-ILD patients, influencing clinical prognosis³⁰. The SF-36 health survey is an approach to measure life quality, and recommended for CTD-ILD patients³¹. It was shown in our study that DECT parameters (LV, average Z_{eff} value, and average MCTN) significantly correlated with PCS and MCS scores of SF-36 ($p < 0.05$, Table S4), with $|r|$ ranged from 0.207 to 0.325. The linear regression models showed that LV ($\beta = 0.190$, $p = 0.045$) significantly contributed to the mental component summary (MCS) adjusted for age, gender, BMI, smoke, type of CTD and respiratory symptoms (Table S9).

Discussion

To our knowledge, this is the first research to evaluate the application of DECT with Gemstone Spectral Imaging (GSI) in CTD-ILD patients. In this study, we showed that DECT parameters could be used to reflect the clinical severity of CTD-ILD patients: increased severity of CTD-ILD assessed by symptoms, CT, and PFT was significantly associated with reduced LV, elevated Z_{eff} value, and increased MCTN. MCTN and Z_{eff} value had robust differentiate value to detect the presence of extensive CTD-ILD from limited CTD-ILD. Additionally, higher Z_{eff} value was the independent risk factor for dyspnea and cough in CTD-ILD patients. Lung volume reduction can reflect the CTD-ILD patients' life quality.

In terms of interstitial lung abnormality assessment, the DECT is superior to texture analysis or machine learning methods. As shown in several studies, the correlation coefficients of fibrosis quantitative score based on the texture metrics^{15 32} with FVC% pre ranged from -0.41 to -0.60 (-0.6), and with DLCO% pre ranged from -0.37 to -0.49 (-0.68). Combined with ILD patterns, the coefficients of radiologists' assessment with CALIPER could achieve 0.73¹⁶, similar to our study. However, all of them need additional software development and long supervised or non-supervised learning. As a novel quantitative technique, DECT with the inherent software is convenient for quantitative analysis in a shorter time. Besides, the DECT quantitative analysis doesn't need an experienced specialist to define the interstitial patterns. Therefore, DECT seems to have more advantages in evaluating CTD-ILD patients.

Z_{eff} and MCTN represent the characteristics of the composite atom for the mixture of various materials or a compound²². The pathological basis of interstitial lung abnormality was pulmonary alveolar unit inflammation or interstitial fibrosis, leading to the mixture of various cells and tissues increased³³. This might be the reason why Z_{eff} value and MCTN could evaluate in severe CTD-ILD patients. Our study showed that lung volume highly correlated with VC, TLC and FVC: the lung volume reduced, with the reduction of VC, TLC and FVC in severe CTD-ILD patients, consistent with previous studies³⁴, which might due to the fibrotic tissue shape lungs contracture, and harder to expand. In our study, Z_{eff} value was shown to be more contributed to cough than MCTN, meanwhile, MCTN and LV performed better than Z_{eff} value in dyspnea and mental health evaluation.

Therefore, DECT parameters exhibited complementary evaluation capacity of CTD-ILD. As reported³⁵, the CT numbers of the virtual monochromatic images at approximately 70keV were equal to those of the conventional 120-kVp CT images. Thus, the MCTN at 70keV could be considered as the CT numbers at conventional CT images which is the only quantitative parameter. DECT could provide not only more quantitative parameters, but also lower image noise and higher contrast-to-noise³⁵, this is one of the advantages of DECT over the conventional CT scan.

Right middle lung lobe involvement might be the unexpected and ignorant risk factor for the severity of CTD-ILD. There was a case reported that the right middle lung lobe was diagnosed with acute interstitial pneumonitis after contralateral lung tumor resection³⁶. Although bilateral lower lung lobe and subpleural distribution are the characteristics of CTD-ILD with usual interstitial pneumonitis or non-special interstitial pneumonia pattern, our study showed that middle lung lobe lesions could predict severe CTD-ILD patients. The result reminds us middle lung lobe in CTD-ILD deserved more attention. The value of the middle lung lobe in CTD-ILD, and its correlation with the severity of CTD-ILD need further investigation.

The DECT parameters (LV, Z_{eff} value, or MCTN) were associated with the symptoms or life quality of CTD-ILD patients in our study. One of the management goals of CTD-ILD is to improve the health-related quality of life. The SF-36 health survey was a good outcome measurement, and it was recommended to be applied in CTD-ILD patients³¹. However, SF-36 was rarely applied in quantitative computed tomography assessment research. In our study, it was indicated that LV contributed to the health-related quality of life in CTD-ILD patients. The Z_{eff} value and MCTN were the significant markers for cough and dyspnea, respectively. Therefore, DECT could complement pulmonary physiology function, at the same time, provide information regarding clinical features in CTD-ILD.

While our results were valuable, we recognized several limitations in our study. Firstly, given that there was a significant imbalance in the radiological patterns (usual interstitial pneumonitis and non-special interstitial pneumonia) among the included patients, radiological patterns analysis was not conducted. Secondly, this was a cross-sectional study without information on the outcome

or progression. Further researches with the available events of outcome or progression would be conducted. Thirdly, the data set was from a single center with a small sample size, so it could not be readily generalized. Further studies with additional populations and large samples are needed. Since our population was ILD patients with CTDs, caution should be exercised in extrapolating our findings to other causes of ILD. We recognized these limitations and believed that further validation of our preliminary results was warranted to predict the progression, acute exacerbation, or death.

Conclusion

In conclusion, our results suggested that DECT parameters were able to discriminate severe ILD abnormality from mild one in patients with CTD-ILD, and correlated with physical function and extent of ILD involvement. DECT parameters (LV, Z_{eff} value, or MCTN) independently associated with symptoms or life quality of CTD-ILD patients, and complement to PFT and CT in evaluating CTD-ILD. We believed that DECT could represent an accurate and convenient alternative tool in evaluating of CTD-ILD.

Abbreviations

CTD-ILD Connective tissue disease-associated interstitial lung disease, GSI Gemstone spectral imaging, CT Computed tomography, DECT Dual-energy computed tomography, HRCT High-resolution computed tomography, LV Lung volume, Z_{eff} Effective atomic number; Effective-z, MCTN Monochromatic CT number at 70 keV, HU Hounsfield units, keV Kilo electron volt, RA Rheumatoid arthritis, SSc Systemic sclerosis/scleroderma, PM/DM Polymyositis/dermatomyositis, SLE Systemic lupus erythematosus, SjS Sjögren syndrome, UCTD Undifferentiated connective tissue disease, SCTD Specific connective tissue disease, MCTD mixed connective tissue disease, RL Right lower lung lobe, LL Left lower lung lobe, RM Right middle lung lobe, RU Right upper lung lobe, LU Left upper lung lobe, AUC Area under the curve, ROC Receiver operating characteristic, CI Confidence interval, PCS Physical Component Summary, MCS Mental Component Summary.

Declarations

Ethics approval and consent to participate

This study was approved by Ethics Committee on Biomedical Research (2020-216) at West China Hospital. Subject consent was waived.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

Not applicable.

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Authors' contributions

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Tables

Table.1 Connective tissue disease associated interstitial lung disease (CTD-ILD) cohort demographic and clinical characteristics.

Demographic and Clinical characteristics	Mean±SD or N(%) or Median(range)
Age (y)	49.22 ±9.94
Female-No. (%)	102(84.3)
BMI (kg/m ²)	23.26 ±3.34
Ethnicity (Han nationality)-No. (%) §	107 (88.4)
Ever/current smoker-No. (%) §	20(16.5)
Comorbid conditions-No. (%) £	63(54.3)
Type of CTD	
Specific CTD(SCTD)	86(79.1)
Systemic sclerosis/scleroderma (SSc)	24(19.8)
Polymyositis/dermatomyositis (PM/DM)	35(28.9)
Sjögren Syndrome (SjS)	9(7.4)
Rheumatoid Arthritis (RA)	11(9.1)
Systemic lupus erythematosus (SLE)	7(5.8)
Undifferentiated CTD(UCTD)	23(19.0)
Mixed CTD(MCTD)	12(9.9)
Dyspnea ^λ (Borg dyspnea score)	
No dyspnea	56(53.8)
Mild dyspnea	37(35.6)
Moderate to Severe dyspnea	21(10.6)
Cough ⁺⁺ (LCQ)	
No cough	50(47.6)
Mild cough	30(28.6)
Severe cough	25(23.8)
Pulmonary Function Test ¶	
FVC % predicted ¶	83.23 ±23.95
FEV ₁ %predicted ¶	81.67 ±21.44
TLC %predicted ¶	80.84±20.85
DLCO % predicted ⁺	64.60(53.40,80.18)
Severity of CTD-ILD ^f	
Limited CTD-ILD	62(51.2)
Extensive CTD-ILD	44(36.4)
NA	15(12.4)
SF-36 ^λ (range 0-100)	

Physical Component Summary (PCS) score 52.03(45.50, 55.84)

Mental Component Summary (MCS) score 51.98(45.05, 56.88)

Data are presented as mean± SD or n (%) or Median(range).

#: N=121, unless otherwise stated; £: N=120; §: N=118; f: N=106; ++: N=105; λ: N=104; ¶: N=99; +: N=96.

BMI body mass index, CTD connective tissue disease, ILD interstitial lung disease, LCQ Leicester Cough Questionnaire, FVC forced vital capacity, FEV1 forced expiratory volume in one second, TLC total lung capacity, DLCO diffusion capacity of the lung for carbon monoxide, SF-36 36 item Short Form Health Survey, NA not available.

Table 2 Comparison the chest DECT parameters among limited CTD-ILD and extensive CTD-ILD.

	Limited ILD	Extensive ILD	t / χ^2	p
Total-No.	62	44		
Age (y)	48.61±9.08	52.09±12.09	-1.691	.094
BMI (kg/m ²)	23.29±3.00	22.59±3.93 §	0.988	.327
Female-No. (%)	52(83.8%)	38(86.4%)	0.125	.724
Han nationality-No. (%)	59 (95.2%)	37(84.1%) §	1.761	.264
Ever/current smoker-No. (%)	12(19.4%)	5(11.9%) §	1.016	.185
Comorbid conditions-No. (%)	28(45.2%) £	27(61.4%) f	2.750	.251
Lung volume (cm ³)	3525.52±1071.79	2481.13±1050.08	4.985	.000
V_RL	609.98±309.28	338.29±234.94	5.137	.000
V_RM	387.52±166.57	280.58±145.70	3.428	.001
V_RU	914.88±256.44	782.39±308.19	2.409	.018
V_LL	542.17±278.56	324.05±260.08	4.082	.000
V_LU	1070.97±301.06	755.81±358.76	4.902	.000
Average Z _{eff} value	2.26±0.44	3.11±0.68	-7.257	.000
Z_RL	2.73±0.72	3.80±0.90	-6.808	.000
Z_RM	2.01±0.37	2.90±0.81	-6.805	.000
Z_RU	1.89±0.31	2.53±0.70	-5.682	.000
Z_LL	2.72±0.68	3.71±0.80	-6.864	.000
Z_LU	1.93±0.30	2.61±0.69	-6.075	.000
Average MCTN (HU)	-801.44±41.56	-721.31±65.49	-7.157	.000
MCTN_RL	-755.16±69.66	-656.34±85.25	-6.554	.000
MCTN_RM	-825.73±34.98	-741.73±75.92	-6.841	.000
MCTN_RU	-837.11±28.99	-777.14±67.93	-5.511	.000
MCTN_LL	-755.55±64.85	-661.45±79.20	-6.710	.000
MCTN_LU	-833.63±26.14	-769.89±66.80	-6.011	.000

#: N=106, unless otherwise stated; £: N=59; §: N=42; f: N=43.

DECT dual-energy computed tomography, CTD-ILD connective tissue disease-associated interstitial lung disease, BMI body mass index, V_RL volume of right lower lung lobe, V_RM volume of right middle lung lobe, V_RU volume of right upper lung lobe, V_LL volume of left lower lung lobe, V_LU volume of left upper lung lobe, Z_RL Zeff value of right lower lung lobe, Z_RM Zeff value of right middle lung lobe, Z_RU Zeff value of right upper lung lobe, Z_LL Zeff value of left lower lung lobe, Z_LU Zeff value of left upper lung lobe, MCTN Monochromatic CT Number at 70 keV, MCTN_RL monochromatic CT number of right lower lung lobe, MCTN_RM monochromatic CT number of right middle lung lobe, MCTN_RU monochromatic CT number of right upper lung lobe, MCTN_LL monochromatic CT number of left lower lung lobe, MCTN_LU monochromatic CT number of left upper lung lobe.

Table 3. Comparison the DECT parameters according to respiratory symptoms (dyspnea and cough based on Borg and LCQ).

	No symptom	Dyspnea or Cough	Dyspnea & Cough	F/ χ^2	P value	P value		
						0 VS 1	0 VS 2	1 VS 2
Total-No.	34	39	32					
Age (y)	50.21±9.21	47.92±10.72	52.19±12.58	1.363	.260			
BMI (kg/m ²)	22.58±2.83 ^f	23.15±4.02	22.83±3.49	0.236	.790			
Female (%)	31(91.2)	32(82.1)	25(78.1)	2.211	.331			
Han nationality (%)	29(87.9) ^f	37(94.9)	29(90.6)	1.229	.570			
Ever/current smoker (%)	2(6.1) ^f	8(20.5)	8(25)	4.520	.104			
Comorbidity (%)	17(50.0)	23(62.2) [£]	16(51.6) [§]	1.253	.534			
Lung Volume (cm ³)	3243.92±1034.21	3105.39±989.78	2781.80±1299.56	1.511	.226			
V_RL	534.27±284.46	512.24±292.25	415.89±305.51	1.515	.225			
V_RM	341.84±154.42	350.34±151.63	335.67±176.65	0.075	.928			
V_RU	889.24±300.72	819.37±232.42	826.65±303.46	0.665	.517			
V_LL	487.99±222.42	467.08±275.63	365.50±327.08	1.846	.163			
V_LU	990.58±345.36	956.36±305.25	838.09±384.21	1.786	.173			
Average Z _{eff} value	2.43±0.58	2.51±0.64	2.97±0.74	6.728	.002	.588	.001	.004
Z_RL	2.92±0.81	3.07±0.96	3.60±0.94	5.170	.007	.472	.003	.016
Z_RM	2.21±0.61	2.28±0.73	2.63±0.74	3.284	.041	.671	.019	.043
Z_RU	2.02±0.45	2.11±0.54	2.39±0.73	3.538	.034	.482	.011	.049
Z_LL	2.91±0.78	2.96±0.74	3.71±0.89	10.461	.000	.780	.000	.000
Z_LU	2.07±0.44	2.11±0.46	2.53±0.76	6.269	.003	.745	.001	.003
Average MCTN (HU)	-787.12±56.47	-777.67±59.14	-732.41±69.01	7.468	.001	.514	.000	.003
MCTN_RL	-739.03±80.69	-723.90±92.78	-671.16±83.78	5.620	.005	.457	.002	.012
MCTN_RM	-807.41±61.40	-799.64±68.40	-766.88±66.45	3.549	.032	.615	.014	.039
MCTN_RU	-827.09±44.17	-816.13±49.73	-789.50±70.95	3.858	.025	.402	.007	.047
MCTN_LL	-740.32±73.68	-732.46±68.61	-658.56±87.76	11.532	.000	.662	.000	.000
MCTN_LU	-821.76±42.63	-816.23±41.98	-775.97±73.42	6.802	.002	.661	.001	.002

0=no respiratory symptom, 1=with dyspnea or cough, 2=with dyspnea and cough.

Total-No.=104, unless otherwise stated; f: N=33, £: N=37; §: N=31.

DECT dual-energy computed tomography, LCQ Leicester Cough Questionnaire, CTD-ILD connective tissue disease-associated interstitial lung disease, BMI body mass index, V_RL volume of right lower lung lobe, V_RM volume of right middle lung lobe, V_RU volume of right upper lung lobe, V_LL volume of left lower lung lobe, V_LU volume of left upper lung lobe, Z_RL Zeff value of right lower lung lobe, Z_RM Zeff value of right middle lung lobe, Z_RU Zeff value of right upper lung lobe, Z_LL Zeff value of left lower lung lobe, Z_LU Zeff value of left upper lung lobe, MCTN Monochromatic CT Number at 70 keV, MCTN_RL monochromatic CT

number of right lower lung lobe, MCTN_RM monochromatic CT number of right middle lung lobe, MCTN_RU monochromatic CT number of right upper lung lobe, MCTN_LL monochromatic CT number of left lower lung lobe, MCTN_LU monochromatic CT number of left upper lung lobe.

TABLE 4. Binary Logistic Regression Analysis of Univariate Analysis and Multivariate Analysis with Dyspnea of CTD-ILD patient.

	Univariate Analysis					Multivariate Analysis				
	β value	SE	Wals	OR (95%CI)	<i>P</i> value	β value	SE	Wals	OR (95%CI)	<i>P</i> value
Age (y)	0.017	0.018	0.876	1.017(0.981-1.055)	<i>.349</i>					
Gender (male/female)	-0.043	0.531	0.007	0.957(0.338-2.713)	<i>.935</i>					
Han nationality	-0.076	0.702	0.012	0.927(0.234-3.668)	<i>.914</i>					
BMI (kg/m ²)	-0.007	0.057	0.014	0.993(0.889-1.110)	<i>.907</i>					
Ever/current smoke	-0.457	0.522	0.767	0.633(0.228-1.761)	<i>.381</i>					
Comorbidity	-0.315	0.403	0.611	0.730(0.331-1.608)	<i>.434</i>					
Lung volume (L)	-0.459	0.204	5.073	0.632(0.424-0.942)	.024					
Average Z _{eff} value	1.209	0.357	11.480	3.350(1.665-6.741)	.001	1.313	.377	12.095	3.716 (1.773-7.786)	.001
Average MCTN (HU)	0.014	0.004	12.517	1.014(1.006-1.022)	.000					
Type of CTD										
CTD (SCTD vs UCTD)	-0.217	0.505	0.185	0.805(0.299-2.164)	<i>.667</i>					
CTD (MCTD vs UCTD)	0.000	0.775	0.000	1.000(0.219-4.564)	<i>1.000</i>					

Note: N=104, significance with p<0.05

CTD-ILD connective tissue disease associated interstitial lung disease, BMI body mass index, MCTN monochromatic CT number at 70 keV, CTD connective tissue disease, UCTD Undifferentiated connective tissue disease, MCTD mixed connective tissue disease.

TABLE 5. Binary Logistic Regression Analysis of Univariate Analysis and Multivariate Analysis with Cough of CTD-ILD patient.

Figures

	Univariate Analysis					Multivariate Analysis				
	β value	SE	Wals	OR (95%CI)	<i>P</i> value	β value	SE	Wals	OR (95%CI)	<i>P</i> value
Age (y)	0.006	0.018	0.102	1.006(0.971-1.042)	<i>.749</i>					
Gender (male/female)	-1.270	0.610	4.328	0.281(0.085-0.929)	.037					
Han nationality	-0.348	0.701	0.247	0.706(0.179-2.791)	<i>.619</i>					
BMI (kg/m ²)	0.031	0.057	0.296	1.031(0.923-1.153)	<i>.586</i>					
Ever/current smoke	-1.368	0.606	5.090	0.255(0.078-0.836)	.024	1.658	0.634	6.841	5.251(1.515-18.194)	.009
Comorbidity	0.174	0.399	0.191	1.190(0.545-2.601)	<i>.662</i>					
Lung volume (L)	-.118	0.180	0.430	0.889(0.625-1.264)	<i>.512</i>					
Average Z _{eff} value	0.686	0.320	4.584	1.985(1.060-3.719)	.032	0.830	0.346	5.770	2.294(1.165-4.516)	.016
Average MCTN (HU)	0.008	0.003	5.273	1.008(1.001-1.015)	.022					
Type of CTD										
CTD (SCTD vs UCTD)	-0.272	0.512	0.282	0.762(0.279-2.077)	<i>.595</i>					
CTD (MCTD vs UCTD)	-1.253	0.827	2.293	0.286(0.056-0.056)	<i>.130</i>					

Note: N=102, significance with p<0.05

CTD-ILD connective tissue disease associated interstitial lung disease, BMI body mass index, MCTN monochromatic CT Number at 70 keV, CTD connective tissue disease, UCTD Undifferentiated connective tissue disease, MCTD mixed connective tissue disease.

Figure 1

The component distribution histograms of DECT parameter in 66-year-old man, diagnosed of interstitial lung disease associated with MCTD (PM/DM and Sjögren syndrome).

Figure 2

DECT parameters correlation with PFT findings and TEI.

Figure 3

Receiver operating characteristic curve to demonstrate optimal cutoff value of DECT parameters to detect presence of extensive disease of CTD-ILD.

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