Quantitative chest tomography indexes are related to disease activity in systemic sclerosis: results from a cross-sectional study

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Abstract

Objective

The aim of this study is to verify if there are correlations between quantitative chest tomography (QCT) indexes and disease activity (DA) in a cohort of patients with systemic sclerosis (SSc).

Methods

SSc patients were assessed for DA and underwent high resolution chest tomography (CT). CT images were analysed with an operator-independent algorithm extracting the QCT indexes. DA assessment was conducted according to the EUSTAR index, where a score ≥2.5 indicates high DA (hDA). Correlations between clinical data and QCT indexes were investigated with the Spearman's test. The Mann-Whitney test assessed the distribution of the QCT indexes among the groups. Receiver operating characteristics (ROC) curve and linear regression analysis were conducted in order to identify the best cut-off value and contribution for each QCT index in assessing hDA in SSc patients.

Results

Sixty patients (52 females, mean age 53.2 years, mean disease duration 5.3 years) were enrolled. A significant difference was found in QCT indexes distribution between patients with hDA and those with low DA. A mild strength correlation between QCT indexes and DA was observed. Once performed ROC curves and linear regression, Skewness on parenchymal lung <1.85 gave a significant contribution to the model in identifying subjects with hDA ($p<0.001$), showing sensitivity 79.5%, specificity 68.7%, and accuracy 76.6%.

Conclusion

QCT indexes correlate with SSc DA. These data introduce new possibilities for QCT application in clinical practice, especially in patient's follow-up. Moreover, QCT could be implemented in a new SSc DA score based on operator-independent parameters.

Key words

systemic sclerosis, high resolution chest tomography, quantitative chest tomography, disease activity, quantitative evaluation

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Introduction

Systemic sclerosis (SSc) is a connective tissue disease where the principal hallmark is the progressive fibrotic involvement of skin and internal organs (1). SSc is associated with a high risk of disability and high mortality (2). Over time, studies on what is recognised as the "vascular hypothesis" have indicated the importance of the early stages of the disease in which the mechanisms that will result in organ damage are established (3). Early diagnosis can allow prompt treatment slowing down the progression of disease damage (4-5). This is supported by the association between Disease Activity (DA), mainly present during the early stages of the disease, and disease damage (6). Therefore, the definition of DA has an inevitable impact on clinical practice, especially on therapeutic choices. Over the years, there has been a progressive refinement of the details that contribute to the definition of DA, and this is especially observed in pathologies characterised by a systemic involvement and an intricate pathophysiological system, such as SSc.

Nowadays, interstitial lung disease (ILD) is the leading cause of death in SSc (7-8). ILD affects up to 80% of patients with a 10-year mortality near to 40% (5,9). High-resolution chest tomography (HRCT) has a pivotal role in recognising ILD and it is considered the "gold standard" to evaluate extension of ILD (10). Several attempts have recently been made to standardise CT evaluation. Semi-quantitative scores have a good correlation with DA (11). These scores are burdened by relevant variability, even among expert observers (12-13). Quantitative CT (QCT) is standing out as an operator independent tool scoring in the assessment of ILD involvement thanks to the application of automatic post-processing software. QCT divides the lung into voxel (*i.e.* 3D pixels) and returns a densitometric value of the x-ray attenuation of each one. QCT has shown promising results when used to define disease extent and severity and, therefore, in the definition of the already established organ damage (5, 14-15).

Over the years, several scoring scales have been created to evaluate DA in SSc in order to obtain the best performance (16). Due to the complexity of the disease pathogenesis and its heterogeneous clinical manifestations that can be expressed in different areas of DA, subdivision into domains of various scores is commonly proposed. The study of the pulmonary domain revealed some difficulties. The 2001 score investigated pulmonary DA through Diffusion Lung Capacity of carbon monoxide (DLCO) <80% of predicted and the patient-reported worsening of the pulmonary symptoms (17). Subsequent studies showed that these parameters were not sufficiently able to demonstrate pulmonary involvement. Therefore, others were proposed, mainly involving Pulmonary Function Tests (PFT) (18), which are strongly effort-dependent and the patient collaboration has a pivotal role in the obtaining acceptable results (19). During PFT, poor patient cooperation is a common occurrence and this supports the need to find alternative methods capable of identify DA in the pulmonary domain that can easily be performed by patients.

To our knowledge, there is no study on QCT correlation with DA in SSc. The aim of this study is to evaluate the ability of QCT to identify SSc patients with high disease activity score (hDA), which is when effective treatment could stop or slow the disease progression.

Material and methods

Patients and clinical evaluation

Adult SSc patients who met the ACR/EULAR classification criteria were consecutively enrolled from rheumatological outpatient' clinic (20). All enrolled patients underwent a clinical visit to assess DA according to the EUSTAR index (21). Low DA (lDA) was defined for a total score <2.5; a score ≥2.5 was considered indicative of hDA. Pulmonary function tests and chest CT were also performed within 2 weeks from the visit. Both examinations were performed as a routine assessment for disease staging or in patients with high risk for progression of pulmonary involvement. This included patients with Forced Vital Capacity or DLCO less than 80% of predicted, suspected lung involvement from lung physical exami-

Table I. Definition of the QCT indexes considered in this study.

Index	Definition
Mean lung attenuation	Mean of the x-ray attenuation values for each voxel.
Standard deviation	It is a measure of the dispersion of the value resulting from the square root of the variance. The lower the values, the closer their distribution is to the mean, and vice versa.
Skewness	It is an index of the absence of asymmetry in a distribution. The value 0 is observed in a symmetrical curve (*e.g.* Gaussian curve), negative values indicate left asymmetry and vice versa.
Kurtosis	It considers the hump and the tails of the curve, where the value of 3 is observed in a Gaussian curve. Values >3 indicates greater frequency in the middle and extreme classes, <3 in intermediate classes.
Gini coefficient	It is a measure of the inequality dispersion of the values. The value 0 indicates perfect equality of the values, the values of 100 maximum inequality.

nation or patients reported episodes of dyspnea. Age below 18 and pregnancy were considered exclusion criteria.

QCT assessment

Each chest CT underwent an operator-independent quantitative assessment as previously described (22-24). Horos (www.horosproject.org, Ninble Co LLC d/b/a Purview, Annapolis, Maryland, USA, last access August 31, 2021), an open-source freeware software, provided the following QCT indexes: Mean Lung Attenuation (MLA), Standard Deviation, Skewness, Kurtosis, and Gini coefficient both for the parenchymal and total lung (briefly defined in Table I). Areas with voxels between -950 and -400 HU were considered lung parenchyma. In this way, we obtained indexes regarding lung parenchyma (pQCT indexes, *e.g.* pMLA, pStandard Deviation, pSkewness, pKurtosis, pGini Coefficient) and total lung (tQCT indexes, *e.g.* tMLA, tStandard Deviation, tSkewness, etc). Figure 1 shows an example of lung segmentation.

Ethics

The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of Parma (protocol code 34379, date of approval: October 17, 2013). Informed consent was obtained from all subjects involved in the study.

Statistical analysis

Statistical analysis was conducted with IBM SPSS ® Statistics 20.0 (Armonk, New York, USA). Once the non-normal distribution was ascertained, non-parametric tests were used. The Spearman's test with Bonferroni's correction was used for correlations and the Mann-Whitney test to compare the values between the groups. Receiver Operating Characteristic (ROC) curve defined the cut-off values of the significant QCT parameters, and linear regression with collinearity test explored their role. A p-value <0.05 was considered statistically significant.

Results

Sixty patients with SSc-ILD were enrolled; 16 patients had hDA. No differences in sex prevalence, age, nor disease duration between hDA and lDA patients were found. Complete characteristics of the SSc population enrolled are summarised in Table II.

Significant correlations were found between DA index, modified Rodnan Skin Score (mRSS), data from pulmonary function tests (PFT), DLCO and most QCT indexes. No correlations were observed between QCT indexes and age, disease duration, and C-reactive protein (Table III).

The QCT index distribution was different between lDA and had patients. Notably, pMLA (mean rank 27.1 *vs*. 39.8, p=0.01), pStandard Deviation (mean rank 27.6 *vs*. 38.2, p=0.03), pSkewness (mean rank 34.3 *vs*. 19.9, p=0.005), pKurtosis (mean rank 34.1 *vs*. 20.4, p=0.007), pGini Coefficient (mean rank 27.3 *vs*. 39.2, p=0.02), tMLA (mean rank 27.5 *vs*. 38.5, p=0.03) and tSkewness (mean rank 33.7 *vs*. 21.5, p=0.01) were statistically different (Table IV and Fig. 2).

All these QCT indexes had a good performance in distinguishing lDA from hDA patients. Data from ROC curves are summarised in Table V. When QCTi were analysed together in linear regression, only pSkewness ≤1.85 gave a significant contribution to the model (p<0.001).

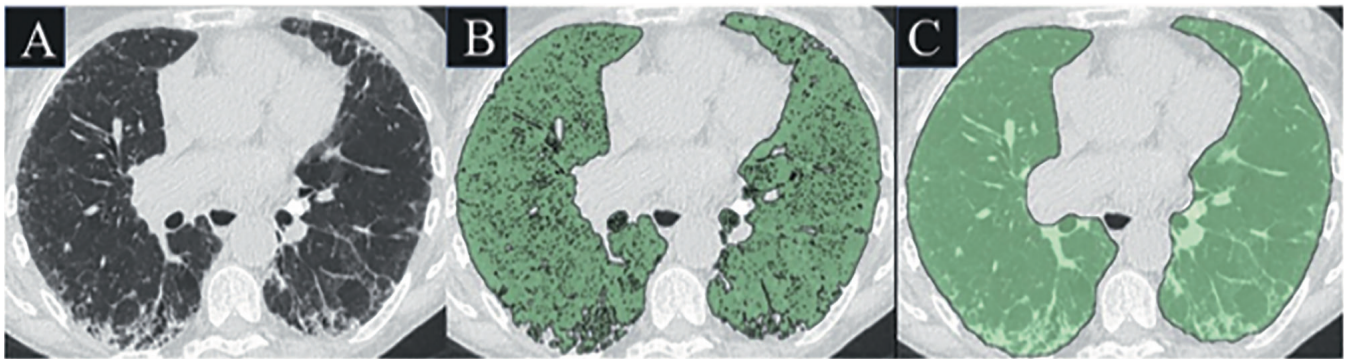

Fig. 1. Examples of QCT lung segmentation in a patient with SSc-ILD (**A**). The Region of Interest (ROI) of parenchymal lung (**B**) embeds only the lung voxels in an interval of attenuation (*i.e.,* between -950 HU and -400 HU). The ROI of the total lung (**C**) includes all voxel within the lung regardless of the attenuation values.

Table II. Characteristics of the enrolled patients.

Item	Whole cohort	hDA	lDA	p-value
Gender	Female 52 (86.7%); Male 8 (13.3%)	Female 12 (75%); Male 4 (25%)	Female 40 (90.9%); Male 4 (9.1%)	0.79
Age	Mean 53.2 years (SD 15.6)	Mean 53.6 years (SD 13.6)	Mean 53.5 years (SD 16.1)	0.3
Disease duration	Mean 5.3 years (SD 4.2)	Mean 6.1 years (SD 4.9)	Mean 5 years (SD 3.9)	0.2
Diffuse / Limited cutaneous Systemic sclerosis	27 / 33	7 (43.7%) / 9 (56.2%)	26 (59.9%) / 18 (40.1%)	0.58
First symptom excluded Raynaud's phenomenon				
Sclerodactyly	15 (25%)	6 (37.5%)	9 (20.4%)	0.18
Dyspnea	14 (23.3%)	4 (25%)	10 (22.7%)	0.85
Digital ulcers	11 (18.3%)	3 (18.7%)	8 (18.1%)	0.96
Dysphagia	10 (16.7%)	2 (12.5%)	8 (18.1%)	0.6
Dyspepsia	4 (6.7%)	1 (6.2%)	3 (6.8%)	0.93
Not known	6 (10%)	0	6 (13.6%)	0.12
Antinuclear antibodies titre	54 (90%)	14 (87.5%)	40 (90.9%)	0.7
1/2560	5 (8.3%)	2 (12.5%)	3 (6.8%)	0.48
1/1280	5 (8.3%)	2 (12.5%)	3 (6.8%)	0.48
1/640	29 (48.3%)	6 (37.5%)	23 (52.2%)	0.31
1/320	8 (13.3%)	3 (18.7%)	5 (11.3%)	0.46
1/160	4 (6.6%)	0	4 (9%)	0.21
1/80	3 (5%)	1 (6.2%)	2 (4.5%)	0.79
Not known	6 (10%)	2 (12.5%)	4 (9%)	0.7

hDA: high disease activity; lDA: low disease activity; SD: standard deviation; NS: not significant.

Table III. Correlation between clinical data and QCT indexes.

Item	**pMLA**	**pSDev**	**pSkew**	**pKur**	**pGc**	**tMLA**	**tSDev**	**tSkew**	**tKur**	**tGc**
Age	R= -0.02 *p*=0.87	R=0.16 *p*=0.21	R=-0,2 *p*=0.86	R= -0.04 *p*=0.71	R=0.11 *p*=0.37	R= -0.3 *p*=0.78	R= -0.22 *p*=0.08	R= -0.01 *p*=0.9	R= -0.01 *p*=0.91	R= -0.1 *p*=0.44
Disease duration	R=0.11 *p*=0.36	R= -0.09 *p*=0.46	R =0.008 *p*=0.95	R=0.01 *p*=0.93	R= -0.07 *p*=0.56	R =0.1 *p*=0.42	R=0.004 *p*=0.97	R=0.1 *p*=0.41	R=0.13 *p*=0.31	R= -0.05 *p*=0.65
EUSTAR activity index	R=0.19 *p*=0.12	**R=0.36 *p*=0.005**	**R= -0.36 *p*=0.005**	R= -0.33 *p*=0.008	**R=0.36 *p*=0.004**	R =0.16 *p*=0.19	R =0.32 *p*=0.01	R= -0.3 *p*=0.009	R= -0.3 *p*=0.01	**R=0.36 *p*=0.004**
mRSS	**R=0.41 *p*=0.001**	R =0.19 *p*=0.13	**R= -0.39 *p*=0.002**	**R= -0.38 *p*=0.002**	R =0.3 *p*=0.01	**R=0.37 *p*=0.003**	R =0.05 *p*=0.67	**R=-0.35 *p*=0.005**	R= -0.3 *p*=0.01	R=0.19 *p*=0.13
FVC	R=-0.37 *p*=0.007	R= -0.28 *p*=0.02	**R=0.36 *p*=0.004**	**R=0.35 *p*=0.005**	R= -0.31 *p*=0.01	R= -0.27 *p*=0.03	R= -0.21 *p*=0.09	R=0.32 *p*=0.01	R=0.26 *p*=0.04	R= -0.3 *p*=0.01
FEV1	R= -0.28 *p*=0.02	R= -0.33 *p*=0.009	R= 0.34 *p*=0.007	R=0.35 *p*=0.006	R= -0.32 *p*=0.01	R= -0.15 *p*=0.24	R= -0.23 *p*=0.06	R=0.28 *p*=0.02	R=0.2 *p*=0.11	R= -0.3 *p*=0.01
FEV1/FVC ratio	R=0.15 *p*=0.24	R= -0.3 *p*=0.78	R= -0.09 *p*=0.49	R= -0.07 *p*=0.58	R=0.03 *p*=0.79	R=0.22 *p*=0.08	R= -0.04 *p*=0.76	R= -0.16 *p*=0.31	R= -0.18 *p*=0.16	R=0.017 v0.89
TLC	R= -0.23 *p*=0.08	R =-0.36 *p*=0.006	R=0.33 *p*=0.01	R=0.33 *p*=0.01	R= -0.33 *p*=0.01	R= -0.25 *p*=0.05	**R= -0.42 *p*=0.001**	**R=0.37 *p*=0.005**	R=0.34 p =0.01	**R= -0.4 *p*=0.002**
DLCO	R= -0.33 *p*=0.009	**R= -0.4 *p*=0.001**	**R=0.44 *p*<0.001**	**R=0.44 *p*<0.001**	**R= -0.41 *p*=0.001**	R= -0.29 *p*=0.02	R= -0.28 *p*=0.02	R=0.32 *p*=0.007	R=0.26 *p*=0.03	**R= -0.35 *p*=0.005**
DLCO/VA	R= -0.13 *p*=0.31	R= -0.15 *p*=0.24	R=0.2 *p*=0.12	R=0.19 *p*=0.14	R= -0.17 *p*=0.18	R= -0.1 *p*=0.42	R= -0.14 *p*=0.26	R=0.09 *p*=0.46	R=0.05 *p*=0.66	R= -0.14 *p*=0.27
CRP	R= -0.09 *p*=0.46	R= -0.18 *p*=0.16	R=0.16 *p*=0.2	R=0.17 *p*=0.17	R= -0.2 v0.12	R= -0.05 *p*=0.66	R= -0.16 *p*=0.2	R=0.11 *p*=0.39	R=0.06 *p*=0.61	R= -0.17 *p*=0.17

p: parenchymal; t: total lung; MLA: mean lung attenuation; SDev: standard deviation; Skew: skewness; Kurt: surtosis; Gc: Gini coefficient; mRSS: modified Rd lung capacity for carbon monoxide; DLCO/VA: DLCO/alveolar volume; CPR: C-reactive protein; R: coefficient of correlation; *p*: *p*-value.
Using Bonferroni's correction, a *p*-value equal to or lower than 0.005 was considered statistically significant (highlighted in bold in the table).

Discussion

In SSc, DA arouses great interest and identifying the "window of opportunity" allows prompt treatment thus reducing the risk for irreversible damage. This is particularly challenging for a disease with systemic involvement such as SSc. The new EUSTAR criteria is one of the most commonly used methods for defining DA in SSc and was developed to overcome some limitations observed with the previous criteria (21, 25). Moreover, other critical issues may be raised using other DA parameters in clinical practice. First, lung involvement is investigated only with DLCO <70%, which could also be an expression both of vascular and fibrotic disease damage. This test, difficult to perform for some patients, is burdened by a significant variability because it considers only functional loss, and it is not specific for ILD (26). Secondly, there is the patient's subjective assessment of cutaneous involvement. However, this is less impacting compared to the previous DA criteria. Finally, the evaluation of modified Rodnan Skin Score is bound to a wide variability among the observers and it requires specific training. For these reasons, chest HRCT assessment could represent an additional criterion to implement into DA assessment, regarding the investigation of the lung impairment. It is well known that the presence of ground glass opacities precedes the establishment of fibrotic lesions and it can be reversible with treatment (27). In SSc, a correlation between DA and the presence of frequent cough was observed. This was significantly reduced during treatment of SSc-ILD, but returned one year after its suspension (28). However, cough cannot be considered as a satisfactory parameter to investigate the pulmonary domain as it is possibly caused by other factors (*e.g.* gastroesophageal reflux disease, commonly observed in SSc). The data observed by HRCT clearly provides direct evidence of lung involvement. In a previous study, a correlation was observed between ground glass opacities

Table IV. Median values of QTC index in subjects with low and high disease activity.

Item	Low Disease Activity	High Disease Activity	*p*-value
Parenchymal Mean lung attenuation	-842.4 (29.6)	-814.1 (36.8)	**0.01**
Parenchymal Standard deviation	93.6 (8.3)	102.4 (9.6)	**0.03**
Parenchymal Skewness	2.3 (0.5)	1.6 (0.59)	**0.005**
Parenchymal Kurtosis	5.9 (2.4)	2.8 (2.6)	**0.007**
Parenchymal Gini coefficient	84.9 (14.4)	103.3 (16.6)	**0.02**
Total Mean lung attenuation	-821 (34.7)	-789.6 (44.1)	**0.03**
Total Standard deviation	176 (23.9)	179.7 (30.9)	0.58
Total Skewness	3.19 (0.4)	2.7 (0.4)	**0.02**
Total Kurtosis	10.9 (2.5)	9.3 (3.2)	0.11
Total Gini coefficient	140 (29.3)	158.9 (37.1)	0.12

In parentheses, standard deviation; *p*-values <0.05 are given in bold.

Table V. Data from ROC curve analysis.

Index	AUC	95%IC	*p*-value	Cut-off	Sensitivity	Specificity	Accuracy
pMLA	0.71	0.55-0.86	0.01	*-826.1*	75%	63.6%	68.3%
pSDev	0.67	0.59-0.83	0.03	*97.3*	75%	63.6%	66.6%
pSkew	0.74	0.59-0.89	0.005	*1.85*	79.5%	68.7%	76.6%
pKurt	0.72	0.57-0.87	0.007	*3.4*	79.5%	68.7%	76.6%
pGc	0.69	0.54-0.85	0.02	*90.2*	81.3%	63.6%	66.6%
tMLA	0.68	0.51-0.84	0.03	*-813.1*	75%	61.4%	65%
tSkew	0.7	0.54-0.85	0.01	*2.85*	70%	62.5%	68.3%

p: parenchymal; t: total lung; MLA: mean lung attenuation; SDev: standard deviation; Skew: skewness; Kurt: kurtosis; Gc: Gini coefficient; AUC: area under the curve; 95%IC: 95% interval of confidence.

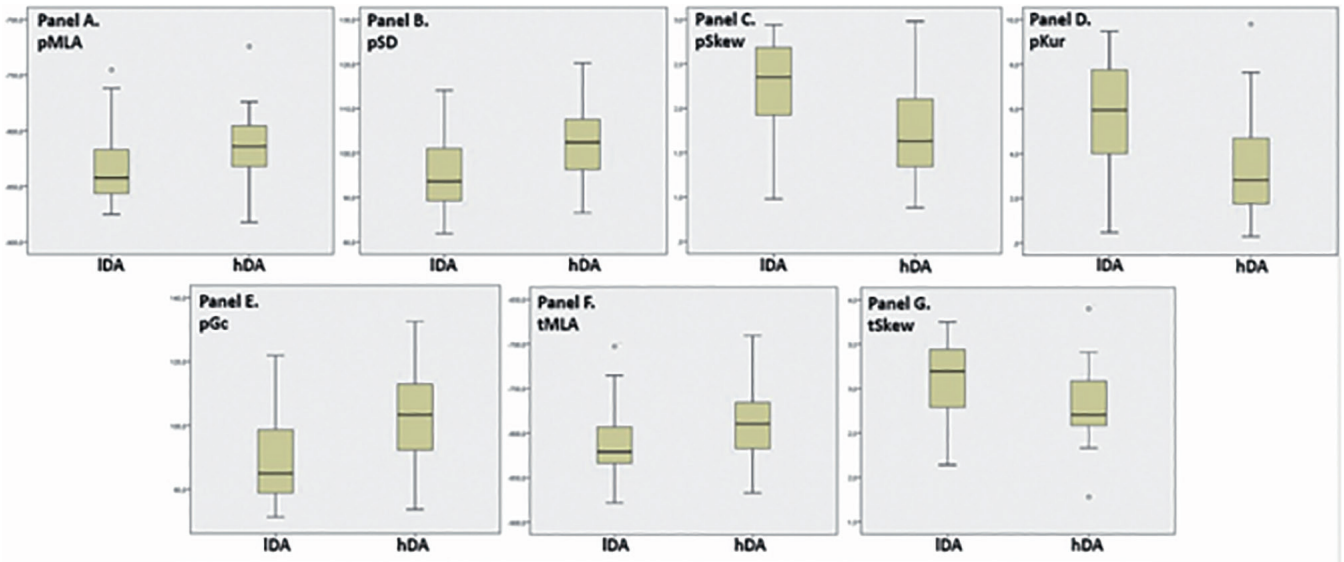

Fig. 2. Box-and-whiskers plots of QCT index values distribution in patient with low and high disease activity (lDA and hDA, respectively).
A: parenchymal mean lung attenuation; **B**: parenchymal standard deviation; **C**: parenchymal skewness; **D**: parenchymal Kurtosis; Panel **E**: parenchymal Gini coefficient; **F**: total mean lung attenuation; **G**: total skewness.

measured by semiquantitative methods and DA in the diffuse cutaneous variant of SSc, but the method is bound to variability among observers (11). The correlation between QCT indexes and DA supports the possibility to overcome this limitation.

In this study we confirm the correlation between QCT indexes and PFT. This is an expected observation as similar data were described in several studies evaluate with QCT, PFT and radiological standard assessment in SSc-ILD (24, 29). Therefore, we add our findings to the data supporting the reliability of QCT in assessing ILD in SSc. We also observed a correlation between QCT indexes and mRSS. As far as we know, this is the first report in literature. Other studies have observed a correlation between mRSS and PFT, proposing as a possible explanation for the similar pathophysiological pathway responsible for the involvement of skin and lungs in SSc (30). The absence of a correlation between QCT indexes and CRP could be explained by the fact that, while CRP provides information on a systemic state of inflammation, QCT returns data more specifically concerning pulmonary involvement of the disease. It is necessary to remember that CRP is the parameter which has the greatest weight in identifying DA in SSc, according to the current criteria (21). Therefore, QCT cannot replace DA criteria because it does not represent the complexity of the systemic involvement of SSc. On the contrary, the correlation that we have observed with DA and DLCO leads us to propose QCT as an alternative method to investigate pulmonary involvement as a criterion of DA and to be integrated with the other items of the score.

In our study, no correlations were observed between QCT indexes and age of the enrolled subjects or disease duration. A possible explanation for this could be that both are mainly related to disease progression towards irreversible damage and not to DA.

When we analysed QCT indexes, most of them had a different distribution between subjects with lDA and hDA and a correlation with DA. The data obtained from the linear regression showed that pSkewness contributed significantly to the model.

Regarding QCT indexes, and Skewness in particular, the literature is now showing evidence. Lower Skewness, together with lower Kurtosis and higher MLA, were associated with worse transplant free survival in patients with idiopathic pulmonary fibrosis (IPF) (31). More recently, a negative correlation between Skewness, presence of fibrosis in HRCT, and presence of diffuse pulmonary ossification in IPF was described (32). Moreover, Skewness was proposed as the best QCT index for prediction of mortality in IPF (33). Finally, another study used a composite index that incorporated MLA, Skewness and Kurtosis. This study observed a correlation between these indexes and the serum level of chemokine ligand 18, which has been proposed as a biomarker of lung inflammation and lung disease activity both in IPF and SSc-ILD (34-35). Our results propose Skewness as index able to identify DA in SSc and we hypothesise that this index could more accurately investigate the pulmonary domain of DA.

QCT can bring some significant advantages in DA assessment. It provides a reproducible evaluation of ILD severity in a few seconds. QCT assessment is operator-independent as shown by several studies which confirm QCT correlation with standard radiological evaluation and respiratory function tests in SSc-ILD. These advantages could have an immediate impact on the clinical evaluation as well as in the prospective evaluation. They could contribute to the definition of DA and in objectifying a progressive phenotype of ILD that could be susceptible to dedicated treatments (36). To date, relevant limitations for QCT use are the poor availability of software for processing images or the analysis costs and also the absence of validity studies with specific recommendations for QCT use from Scientific Societies (37).

In the present study, a free open-source software was used. However, our preliminary findings encourage the pursuit of improving the current methods of SSc DA assessment. In this respect, it should be considered that chest HRCT is recommended for every SSc patient at the time of diagnosis. Therefore, QCT may be performed for all patients without supplemental x-ray exposure. Furthermore, QCT can be performed using HRCT records. This can be done after the radiological exam and in absence of the radiologist, as long as it is used by trained personnel.

Some limitations of this study need to be stated. Primarily, it is important to clarify that this study has an exploratory purpose and, therefore, the number of the enrolled patients with hDA is relatively small. The cross-sectional design of the study does not allow to evaluate whether the indexes undergo variations over time if the disease were to change from an hDA to a lDA state, and *vice versa*. Furthermore, considering that DA should be evaluated on all patients regardless of specific or prevalent organ involvement and the previously mentioned exploratory nature of the study, we chose to analyse QCT data regardless of lung involvement. This could add interest to the data described which could be considered in all patients, regardless of organ involvement. Our future direction will be to enrol a larger number of patients in a multi-centre prospective study to confirm our preliminary findings and eventually to study differences between patients with and without ILD. In turn, it will be possible to better define the QCT parameters cut-offs and to evaluate the "sensitivity to change".

In conclusion, this is the first study evaluating the correlation between QCT parameters and SSc DA. We have observed that QCT can provide useful insights into recognising hDA SSc patients. This could introduce an opportunity of QCT implementation in a new DA score with higher sensitivity and specificity, in order to better stage SSc and tailor treatments for each patient.

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