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Concise report

Quantitative chest computed tomography is associated with two prediction models of mortality in interstitial lung disease related to systemic sclerosis

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Abstract

Objective. In this multicentre study, we aimed to evaluate the capacity of a computer-assisted automated QCT method to identify patients with SSc-associated interstitial lung disease (SSc-ILD) with high mortality risk according to validated composite clinical indexes (ILD-Gender, Age, Physiology index and du Bois index).

Methods. Chest CT, anamnestic data and pulmonary function tests of 146 patients with SSc were retrospectively collected, and the ILD-Gender, Age, Physiology score and DuBois index were calculated. Each chest CT underwent an operator-independent quantitative assessment performed with a free medical image viewer (Horos). The correlation between clinical prediction models and QCT parameters was tested. A value of $P < 0.05$ was considered statistically significant.

Results. Most QCT parameters had a statistically different distribution in patients with diverging mortality risk according to both clinical prediction models ($P < 0.01$). The cut-offs of QCT parameters were calculated by receiver operating characteristic curve analysis, and most of them could discriminate patients with different mortality risk according to clinical prediction models.

Conclusion. QCT assessment of SSc-ILD can discriminate between well-defined different mortality risk categories, supporting its prognostic value. These findings, together with the operator independence, strengthen the validity and clinical usefulness of QCT for assessment of SSc-ILD.

Key words: interstitial lung disease, pulmonary fibrosis, systemic sclerosis, Horos, OsiriX, quantitative chest CT, mortality risk model.

CLINICAL SCIENCE

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Rheumatology key messages

- QCT identifies SSc patients with the worst prognosis according to mortality prediction models.
- QCT can perform an interstitial lung disease-SSc assessment without any inter- or intra-variability.
- Horos and OsiriX, free medical image viewers, make interstitial lung disease assessment available to every rheumatologist.

Introduction

The interstitial lung disease (ILD) related to SSc is still an open challenge for rheumatologists. Most SSc patients have ILD, but only one in five will experience lung function impairment associated with an increased risk of death [1, 2]. The early identification of this group is mandatory in order to start appropriate treatment.

There is evidence of an association between prognosis and a number of demographic and clinical parameters (e.g. gender, age, antibody profile, lung function, extent of pulmonary fibrosis). Recently, Ryerson *et al.* [3] showed that risk models of idiopathic pulmonary fibrosis could be extended to SSc patients. In particular, the ILD-Gender, Age, Physiology (GAP) index and du Bois index (dBi) showed the best performance; both are based on age, gender and lung function [4, 5]. Notably, these models provide the ability to distinguish between SSc patients with different risk of death related to ILD and therefore select those subjects who will need early active surveillance and therapy for pulmonary disease.

Chest CT is the gold standard for detection of ILD because it provides a description of the extent and severity throughout the whole lung volume [6]. However, ILD rating by CT has low inter-observer agreement, even among experienced radiologists [7, 8]. Conversely, quantitative chest CT (QCT) allows this limit to be overcome by means of voxel-wise objective analysis of lung volume density, which is related to the extent and severity of ILD [9–11]. The development of free medical viewers (such as OsiriX or Horos) has made ILD assessment available to every rheumatologist. The objective ILD assessment obtained with OsiriX was correlated with the visual score of experienced radiologists and with lung function [12].

Therefore, it seems reasonable to wonder whether QCT might allow the identification of SSc-ILD patients with increased risk of death.

The first aim of this study was to assess the distribution of QCT in groups of SSc-ILD patients with different predicted mortality as determined by clinical risk models. Second, we compared the association between estimated risk of death and QCT or visual assessment of ILD, and calculated the cut-off with the best discriminatory performance.

Methods

This study was conducted according to the Declaration of Helsinki. All patients agreed to participate by signing informed consent forms approved by the local ethical committees (the ethical committees were as follows: Comitato Etico per Parma, Italy PROT N 34379; Comitato Etico per Piacenza, Italy REP. RIO N 1213/2014; Comitato Etico per Torino (Mauriziano), Italy PROT N CS/753; Comitato Etico per Torino, Italy DEL N 772/2014; and Comitato Etico per Cremona, Italy PROT N 9550/2014 ps).

Patients

One-hundred and forty-six consecutive SSc patients from six different Italian rheumatology units were enrolled. All the patients fulfilled the ACR/EULAR classification criteria for SSc [13]. Exclusion criteria were age $<$18 years and absence of ILD at the baseline chest CT. All examinations were performed as part of the routine and good clinical practice protocol.

Pulmonary function tests

Forced vital capacity (FVC) and diffusing capacity of CO of each patient were recorded at baseline and after 6–9 months. All centres performed pulmonary function testing according to the American Thoracic Society / European Respiratory Society standards [14].

Semi-quantitative assessments of CT

Three thoracic radiologists scored the CT images, by consensus, according to the semi-quantitative method proposed by Goh *et al*. [15]. Further details are available in the semi-quantitative assessments of CT (sQCT) assessment section of the supplementary data, available at *Rheumatology* online.

Mortality risk models

According to Ryerson *et al*. [3], the ILD-GAP index and the dBi are valid idiopathic pulmonary fibrosis risk models to predict mortality in SSc-ILD.

The ILD-GAP score takes into account the ILD subtype, gender, age, FVC and diffusing capacity of CO (if performable). We included only the subtype defined as 'ILD associated to connective tissue'. The ILD-GAP index classifies patients into four categories with an increasing risk of death at 1, 2 and 3 years [5].

The dBi combines age, history of respiratory hospitalization and FVC value and its change after 6 months. We included variation of FVC up to 9 months after baseline assessment. The total risk score of the dBi is related to the 1-year expected percentage of death events, with relative risk classes defined as $<$2, 2–5, 5–10, 10–20 and 20–30% [4].

Quantitative assessment

QCT was performed using an open-source medical image viewer, namely OsiriX (freely available online, http://www.osirix-viewer.com (7 December 2016, date last accessed)) [16], and its 64-bit open-source version, Horos (freely

available online, https://www.horosproject.org (7 December 2016, date last accessed)). Both software packages are extremely user friendly, with no need of radiological expertise to launch the automatic quantification of ILD on chest CTs. In this study, we chose Horos to perform the QCT with the same algorithm that we tested in a previous study [12]. The QCT parameters recorded were kurtosis (Kurt), skewness (Skew), mean lung attenuation, SD. and fibrosis ratio. For definitions of the QCT parameters, see the supplementary definitions section of the supplementary data, available at *Rheumatology* Online. The first four parameters were calculated both in parenchymal CT and in total CT lung as previously defined [17].

Statistical analysis

Statistical analysis was performed using R software (version 3.2.2, freely available online, https://www.r-project.org, (7 December 2016, date last accessed)). The ILD-GAP classes of predicted mortality were dichotomized as previously described [5]. The DuBois score was further collapsed into three clinically meaningful categories, in which the 1-year expectation of death was, respectively, $<$2, 5–10 and $>$10%. The difference between QCT parameters of patients with increasing mortality risk was sought by the Mann–Whitney *U*-test. The receiver operating characteristic curves analysis tested the performance of QCT parameters and sQCT assessment. The cut-offs were extracted by calculating the Youden index. A value of $P < 0.05$ was considered statistically significant.

Results

We enrolled 146 patients. Only 111 subjects had a second FVC assessment within 9 months from the baseline. All these patients were included in the first five dBi total risk score clusters. The other 35 patients received the second FVC assessment after 9 months, and their dBi was not calculated.

Mortality risk subgroups were similar in terms of years of disease, gender, smoking habit and prevalence of anti-Scl70 antibodies. Age was statistically higher in patient subgroups with the worst outcome; indeed, age is a parameter accounted in both risk prediction models. For more details, see supplementary Tables S1 and S2 available at *Rheumatology* Online.

Patients with high and low mortality risk predicted by ILD-GAP score had nearly all the QCT parameters being different one from another ($P < 0.005$). Likewise, subjects with increasing dBi had different QCT parameters ($P < 0.01$). The descriptive results of the distributions of QCT parameters by risk groups are reported in supplementary Tables S3 and S4, available at *Rheumatology* Online. Figure 1 shows examples of different distributions of QCT parameters.

Similar to QCT, the sQCT assessment was statistically different in patient subgroups determined by ILD-GAP index or dBi ($P < 0.05$).

Receiver operating characteristic curve analysis for high and low risk of mortality according to both prediction models was performed for each QCT parameter. For this purpose, dBi clusters were merged in order to create three couples of complementary subgroups with a mortality risk above or below the following 1-year expectations of death: 2, 5 and 10%. In general, the QCT parameter with the best discriminatory ability was the kurtosis of the parenchymal lung (pKurt). Table 1 lists the area under the curve of each QCT parameter and sQCT for each subgroup of mortality risk. Sensitivity analyses using three and five level outcomes for ILD-GAP or dBi supported the robustness of the results, and multivariate analyses confirmed the higher association for Kurt, Skew and mean lung attenuation compared with SD. and fibrosis ratio (please see the sensitivity analysis section of the supplementary data, supplementary Fig. S1 and supplementary Tables S5–S8, available at *Rheumatology* Online).

Discussion

This study shows that operator-independent quantification of ILD on chest CT is associated with risk of death as predicted by clinical scores. CT is considered with limited weight in death prediction models because of the lack of an operator-independent method to assess the extent and severity of ILD. Currently, the prevalent ILD pattern (i.e. ground glass or honeycombing) is the only chest CT characteristic taken into account in composite indexes to predict 1-year mortality. The main reason is that assessment of the extent of ILD is extremely variable among radiologists, even among experienced thoracic radiologists [7, 8].

Although there are many software packages able to make a quantitative ILD assessment, in clinical practice they are not used because they are complicated or expensive.

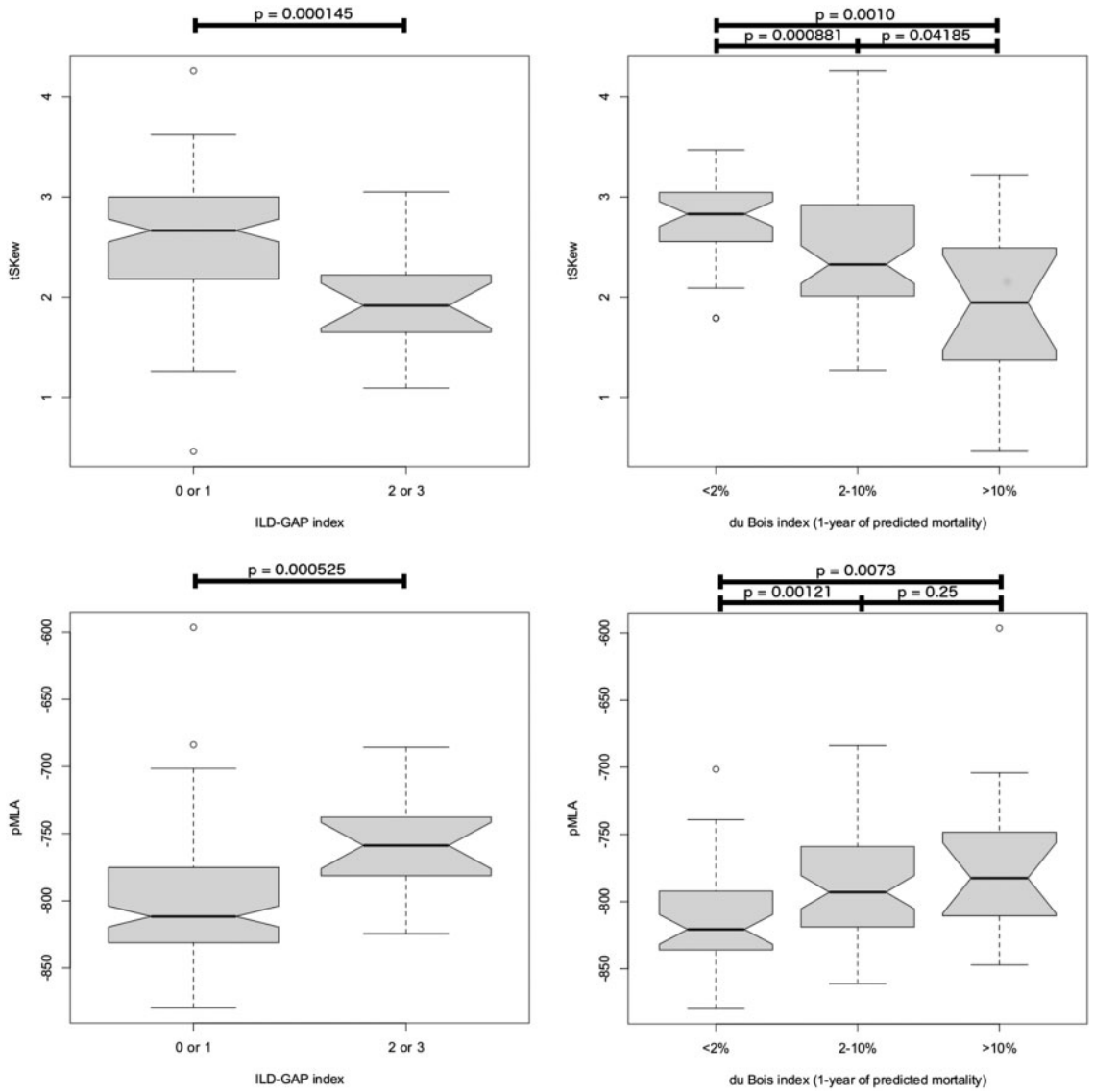
However, we have recently shown that free software, such as OsiriX (and its 64-bit version, Horos), can easily provide an SSc-ILD quantification that is consistent with assessment by the thoracic radiologist [12].

Goh *et al*. [15] identified a CT semi-quantitative ILD extent cut-off, which divides patients into groups with good or unfavourable prognosis. In our previous study, we demonstrated that QCT parameters are significantly different in these two groups. We also showed that the severity of lung impairment, as assessed according to the Medsger scale reflects different QCT values. [17], reflects different QCT values. However, this scale originated from a consensus conference; it is not validated in clinical practice, and its prognostic capacity has not yet been proved. In constrast, the mortality prediction models taken into account in the present study have been widely shown to provide reliable prognostic indications [3].

The present study supports the prognostic value of QCT. In fact, we compared QCT with two models of mortality prediction mainly based on history and functional data. Patients with a high risk of mortality according to these prediction models have significantly different QCT parameters compared with subjects who have only minor risk of death.

It is remarkable that the cut-offs identified in this study differ very little from those that emerged from previous

Fig. 1 Distribution of CT indexes in SSc patients with different mortality risk



Notched box-plots showing difference of tSkew and pMLA distribution between patients with different mortality risk according to both prediction models. tSkew: total lung skewness; pMLA: parenchymal mean lung attenuation.

studies [17, 18]. It is likely that the extent of ILD, impaired lung function and unchangeable risk factors (i.e. age and gender) are somehow encompassed by CT quantitative evaluation.

This study has several limits. The risk prediction models taken into account were developed mainly for idiopathic pulmonary fibrosis [4, 5]. These models tend to underestimate the mortality in SSc patients because they do not come from homogeneous and/or well-described patients. However, these models have recently been validated in an SSc cohort of patients [3]. In our study, we included patients with a long duration of disease even if these mortality prediction models were not investigated regarding the effect of other potentially severe SSc complications not related to ILD.

Many patients did not repeat the FVC within 6 months; therefore, we estimated the mortality risk according to the model of du Bois with an FVC variation in a longer time interval. Ryerson *et al.* [3] faced the same problem but, nevertheless, they validated the score in SSc subjects who did not have an FVC repeated within 6 months.

Chest CTs were retrieved retrospectively from different centres and, therefore, they were performed with different scanners as well as technical parameters. However, this possible heterogeneity did not prevent us from identifying patients with different mortality risk.

Table 1 Receiver operating characteristic curve analysis for 1-year risk of mortality as predicted by the interstitial lung disease-Gender, Age, Physiology index and du Bois index risk models

1-year predicted mortality	Variable	AUC (95% CI)	P-value	Cut-off	Sensibility (95% CI)	Specificity (95% CI)
ILD-GAP score >1(i.e. 1-year risk prediction of mortality >3.1%)	pKurt	0.806 (0.733,0.867)	<0.0001	1.48	88 (62, 98)	68 (60, 76)
	tKurt	0.768 (0.691,0.834)	<0.0001	4.89	69 (41, 89)	77 (69, 84)
	pSkew	0.790 (0.715,0.853)	<0.0001	1.20	69 (41, 89)	82 (74, 88)
	tSkew	0.792 (0.717,0.854)	<0.0001	2.25	81 (54, 96)	72 (64, 80)
	pSDev	0.748 (0.669,0.816)	0.0003	119.1	63 (35, 85)	83 (76, 89)
	tSDev	0.606 (0.522, 0.686)	0.22	–	–	–
	pMLA	0.766 (0.689, 0.832)	<0.0001	−788.9	81 (54, 96)	68 (60, 76)
	tMLA	0.768 (0.691, 0.833)	<0.0001	−769.3	88 (62, 98)	62 (53, 70)
	FR	0.600 (0.516, 0.680)	0.17	–	–	–
	sQCT score	0.750 (0.671, 0.817)	0.0002	23	69 (41, 89)	72 (64, 80)
dBi 1-year predicted mortality >2%	pKurt	0.727 (0.634,0.807)	<0.0001	1.49	53 (41, 65)	90 (76, 97)
	tKurt	0.711 (0.617,0.793)	<0.0001	6.76	67 (55, 77)	77 (61, 89)
	pSkew	0.733 (0.641,0.813)	<0.0001	1.43	61 (49, 72)	85 (70, 94)
	tSkew	0.719 (0.626,0.800)	<0.0001	2.49	69 (58, 80)	79 (64, 91)
	pSDev	0.715 (0.622,0.797)	<0.0001	111.8	56 (43, 67)	85 (70, 94)
	tSDev	0.627 (0.530, 0.717)	0.019	197.9	50 (38, 62)	82 (67, 93)
	pMLA	0.669 (0.573, 0.755)	0.0018	−820.2	78 (66, 87)	54 (37, 70)
	tMLA	0.675 (0.579, 0.761)	0.0010	−787.9	76 (65, 86)	59 (42, 74)
	FR	0.654 (0.557, 0.741)	0.0058	7.23	69 (58, 80)	69 (52, 83)
	sQCT score	0.670 (0.575, 0.757)	0.0009	25	38 (26, 50)	95 (83, 99)
dBi 1-year predicted mortality >5%	pKurt	0.640 (0.543,0.729)	0.023	1.40	55 (36, 74)	71 (60, 80)
	tKurt	0.642 (0.546,0.731)	0.036	4.58	48 (29, 68)	82 (72, 89)
	pSkew	0.651 (0.554,0.739)	0.012	1.42	66 (46, 82)	65 (53, 75)
	tSkew	0.642 (0.545,0.731)	0.032	2.16	52 (33, 71)	76 (65, 84)
	pSDev	0.665 (0.589,0.751)	0.0087	113.3	62 (42, 79)	72 (61, 81)
	tSDev	0.619 (0.522, 0.710)	0.044	191.5	72 (53, 87)	56 (45, 67)
	pMLA	0.619 (0.522, 0.710)	0.033	−824.0	93 (77, 99)	35 (25, 47)
	tMLA	0.617 (0.520, 0.707)	0.046	−782.8	76 (57, 90)	50 (39, 61)
	FR	0.600 (0.502, 0.691)	0.11	–	–	–
	sQCT score	0.610 (0.513, 0.701)	0.12	–	–	–
dBi 1-year predicted mortality >10%	pKurt	0.698 (0.604,0.782)	0.035	0.92	64 (35, 87)	79 (70, 87)
	tKurt	0.737 (0.645,0.816)	0.010	4.44	71 (42, 92)	84 (75, 90)
	pSkew	0.697 (0.603,0.781)	0.032	1.27	64 (35, 87)	76 (67, 84)
	tSkew	0.726 (0.633,0.806)	0.014	2.05	71 (42, 92)	77 (68, 85)
	pSDev	0.716 (0.623,0.798)	0.022	121.6	64 (35, 87)	88 (79, 93)
	tSDev	0.661 (0.565, 0.748)	0.044	182.3	93 (66,100)	40 (30, 51)
	pMLA	0.657 (0.561, 0.744)	0.042	−802.4	71 (42, 92)	58 (47, 68)
	tMLA	0.655 (0.558, 0.742)	0.059	–	–	–
	FR	0.635 (0.538, 0.724)	0.11	–	–	–
	sQCT score	0.705 (0.611, 0.788)	0.028	28	64 (35, 87)	84 (75, 90)

The 95% CI is the 95% CI of the main cut-offs. The P-values represent the probability that the observed AUC is found when the true AUC is 0.5 (null hypothesis). AUC: area under the curve; dBi: du Bois index; FR: fibrosis ratio; ILD-GAP index: interstitial lung disease-Gender, Age, Physiology index; nss: not statistically significant; pKurt: parenchymal kurtosis; pMLA: parenchymal mean lung attenuation; pSD: parenchymal standard deviation; pSkew: parenchymal skewness; sQCT semi-quantitative assessment; tKurt: total lung kurtosis; tMLA: total mean lung attenuation; tSD: total lung standard deviation; tSkew: total lung skewness.

We do not think that the operator experience in informatics is a limit, because the procedure is easy and takes <1 min per patient. Likewise, the fact that OsiriX or Horos works only on MacOSX is not a true limit given the generally wide availability and use of Apple computers.

Even if the software used (Horos) is very user friendly and makes the QCT assessment easy, the QCT itself has some limits. In general, these limits are related to the lack of standardization of CT protocols (e.g. there is not a reference standard of CT slice thickness). QCT is based on chest CTs, which expose patients to a minimal biohazard attributable to the radiation. To date, this risk has never been quantified; anyway, the new low-radiation dose CTs will reduce it further [19]. Experts recommend a chest CT as soon as the diagnosis of SSc is made in order to

identify the ILD [20]. We therefore believe that if this method were to be applied to the first chest CT, it would provide a tangible benefit to the clinician to establish the prognosis for SSc patients. Even if chest CT is not recommended in monitoring SSc-ILD, some authors have suggested a CT follow-up only for patients with a high risk of ILD worsening (i.e. patients with a significant extent of ILD) [2]. From this perspective, the QCT assessment might take on a crucial role in the evaluation of prognosis as well as the mortality risk prediction models.

The introduction of QCT, despite the predicted limits, will lead to remarkable advantages. The paramount advantage consists of its operator independence. The possibility of performing QCT in a few seconds and without specific radiological training makes this method available to everyone. Moreover, QCT is suitable for multicentre investigations. As a consequence, researchers should consider QCT as an additional tool in ILD evaluation both in clinical practice and in trials.

Supplementary data

Supplementary data are available at *Rheumatology* Online.

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