European Journal of Radiology 112 (2019) 200–206

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Automated CT quantification methods for the assessment of interstitial lung disease in collagen vascular diseases: A systematic review

Florien S. van Royen[a,*], Sofia A. Moll[b], Jacob M. van Laar[c], Joris M. van Montfrans[b], Pim A. de Jong[a], Firdaus A.A. Mohamed Hoesein[a]

[a] Department of Radiology, Division of Imaging, University Medical Centre Utrecht and Utrecht University, Utrecht, the Netherlands
[b] Department of Paediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital Utrecht, Utrecht, the Netherlands
[c] Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht and Utrecht University, Utrecht, the Netherlands

ARTICLE INFO

Keywords:
Systematic review
Lung diseases, Interstitial
Connective tissue diseases
Computed tomography, X ray

ABSTRACT

Interstitial lung disease (ILD) is highly prevalent in collagen vascular diseases and reduction of ILD is an important therapeutic target. To that end, reliable quantification of pulmonary disease severity is of great significance. This study systematically reviewed the literature on automated computed tomography (CT) quantification methods for assessing ILD in collagen vascular diseases. PRISMA-DTA guidelines for systematic reviews were used and 19 original research articles up to January 2018 were included based on a MEDLINE/Pubmed and Embase search. Quantitative CT methods were categorized as histogram assessment (12 studies) or pattern/texture recognition (7 studies). R^2 for correlation with visual ILD scoring ranged from 0.143 ($p < 0.01$) to 0.687 ($p < 0.0001$), for FVC from 0.048 ($p < 0.0001$) to 0.504 ($p < 0.0001$) and for DLCO from 0.015 ($p = 0.61$) to 0.449 ($p < 0.0001$). Automated CT methods are independent of reader's expertise and are a promising tool in the quantification of ILD in collagen vascular disease patients.

1. Introduction

Patients with collagen vascular disease are commonly affected by disease-related interstitial lung disease (ILD). ILD is a shared name for several types of diffuse parenchymal abnormalities of lung tissue and is characterized by inflammation and/or progressive scarring and fibrosis of lung parenchyma [1]. Collagen vascular diseases are a group of autoimmune diseases, sometimes also referred to as connective tissue diseases. This group consists of systemic sclerosis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren Syndrome, inflammatory myositis (including polymyositis, dermatomyositis and antisynthetase syndrome) and mixed connective tissue diseases [1]. The most common ILDs in this population are organizing pneumonia (OP), nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), lymphoid interstitial pneumonia (LIP) and acute interstitial pneumonia (AIP) [2,3]. ILD is associated with severe morbidity and early mortality [4]. Early diagnosis and quantification of the severity of ILD is important for treatment initiation, monitoring, and prognostication.

Thoracic computed tomography (CT), next to clinical assessment and physiological measures, plays an important role in diagnosing ILD, assessing disease severity and progression of disease, and assessing efficacy of treatment. Interstitial abnormalities visible on pulmonary CT include reticulation, consolidation, traction bronchiectasis, ground glass opacity, architectural distortion, volume loss and honeycombing [5]. To date, evaluation of interstitial lung involvement on CT is performed by reader-based visual assessment and/or by subjective semi-quantitative scoring methods [6]. However, these assessments are subjective and time-consuming and, even in a research setting, substantial inter- and intra- observer variability have been reported, which may affect disease management in ILD [7]. Several attempts have been made in developing standardized computer-aided diagnosis systems to quantify ILD on pulmonary CT imaging.

Our aim was to systematically review the literature on automated computed tomography quantification methods for ILD severity assessment in collagen vascular disease patients and the correlation of these quantification methods to visual CT assessment, pulmonary function tests or other clinical outcome measures.

2. Methods

PRISMA guidelines for conducting a systematic review of diagnostic test accuracy (PRISMA-DTA) were applied for this review [8]. A systematic search using MEDLINE/Pubmed and Embase databases was conducted. The terms 'computed tomography', 'interstitial lung

* Corresponding author at: Heidelberglaan 100, 3584 CX Utrecht, the Netherlands.
E-mail address: florienvanroyen@gmail.com (F.S. van Royen).

https://doi.org/10.1016/j.ejrad.2019.01.024
Received 17 August 2018; Received in revised form 17 December 2018; Accepted 21 January 2019

Table 1
Included studies divided in histogram-based method versus pattern-/texture-based method.

Histogram method		Pattern/texture method
HU cut-off/ percentile method	Parameters: kurtosis, skewness, MLA etc.	
Ninaber et al. [10] (S)	Ariani et al. [21] (C)	Tashkin et al. [19] (C)
Salaffi et al. [23] (S)	Camiciottoli et al. [25] (C)	Kazantzi et al. [12] (C)
Salaffi et al. [24] (S)	Ariani et al. [20] (C)	Khanna et al. [18] (S)
Çetinçakmak et al. [16] (S)	Koyama et al. [28] (C)	Kim et al. [13] (S)
Marten et al. [27] (S)		Kim et al. [15] (S)
Marten et al. [26] (S)		Rosas et al. [22] (C)
Yabuuchi et al. [11] (S)		Kim et al. [14] (C)
		Jacob et al. [17] (C)

S = Simple one step/one threshold method.
C = Complex method including multiple parameters.

disease', 'quantification' and several synonyms were used for English-language sources from 1991 through January 23 2018. The MEDLINE/Pubmed and Embase search strings are listed in supplementary Table 1.

Articles were independently screened for eligibility based on title and abstract by two of the investigators (FvR and SM) and in case of uncertainty this was discussed with another investigator (PdJ). Inclusion criteria were: (1) original research articles (2) that used any type of automated quantification method (3) on CT (4) in a patient population consisting of one type or multiple types of collagen vascular diseases in all disease stages (5) with or without previously found ILD and (6) that included a comparison with visual ILD assessment, and/or pulmonary function tests and/or clinical disease outcome measures.

Exclusion criteria were: studies reporting (1) only semi-quantitative CT scoring or visual assessment of ILD, (2) non-CT imaging methods for quantification of ILD, (3) ILD not specifically related to collagen vascular diseases, (4) animal studies, (5) studies written in a language other than English and (6) all article forms other than original research articles such as: case reports, editorials, reviews, conference papers, letters and short communications.

Full-text articles that met all criteria were included for comparison. Studies were compared based on (1) quantification method, (2) study design, (3) correlation of quantitative CT to visual CT assessment and (4) correlation of quantitative CT to physiology (pulmonary function tests) or clinical outcome.

Risk of bias and assessment of applicability was evaluated using the QUADAS-2 tool for diagnostic studies [9]. The QUADAS-2 tool consists of 4 domains: patient selection, index test, reference standard and flow and timing. It addresses the risk of bias in the methodology applied in the included studies as well as the applicability for the current review.

The studies were categorized in two categories of automated CT methods: histogram based methods and pattern or texture recognition methods. A histogram-based method was defined as a method using density or volume thresholds or histogram parameters for CT quantification of ILD. An example of a histogram-based method is shown in Fig. 1. A pattern or texture based method was defined as a method using the recognition of specific ILD patterns or textures for CT quantification of ILD. Histogram methods were further split in three subgroups. One subgroup consists of threshold or percentile methods that identified ILD either above or below a user-defined cut-off value (Fig. 1). Another subgroup consists of methods using histogram parameters such as mean lung attenuation, skewness (asymmetry of the histogram) and kurtosis (the sharpness of the peak of the histogram) to calculate ILD. A third subgroup consists of volume methods that used pixel distribution or a density mask to identify ILD on CT. In addition, quantification methods were also dichotomized in simple (S) and complex (C) methods. Simple methods were defined as methods that used one threshold or a simple methodology in the quantification of ILD. Complex methods were defined as methods that used multiple parameters in the quantification of ILD.

To compare correlation between quantitative CT, visual CT assessment, pulmonary function tests and clinical outcome measures, correlation coefficients were retrieved from each study. When a quantitative CT method consisted of multiple parameters, for clarity reasons only one parameter (the parameter for total disease extent or, if no such parameter was used, the best correlating parameter) was chosen for comparison in this review. R^2 was calculated from reported correlation coefficients.

3. Results

3.1. Literature search

The literature search yielded a total of 486 references. The literature screening process is described in Fig. 2. After removing duplicates, 431 references remained that were screened for title/abstract. Twenty-six articles were assessed full-text of which 8 did not meet our inclusion. One article was added through searching of the reference lists, leaving 19 studies for the qualitative analysis and data extraction.

The included studies for the systematic review are summarized for comparison in supplementary Table 2 based on study sample, quantification method, design, correlation of quantitative CT to visual CT assessment, correlation of quantitative CT to physiology/pulmonary function tests or clinical outcome, comments and limitations.

3.2. Critical appraisal

Critical appraisal was performed using the QUADAS-2 tool [9]. One question was not scored (domain 2: index test question 1) as this question involved blinding of the results of the index tests, which is not applicable for automatic measurements. For some papers, a second question was not scored as well (domain 3: reference standard question 2), for the same reason: if only pulmonary function tests were used as reference standard no blinding was needed as these are automatic as well. Results of the critical appraisal are shown in supplementary Table 3. For risk of bias assessment, all studies scored 'good' on patient selection. Two studies defined threshold for quantitative CT after analysis, which could induce bias [10,11]. In five studies it was unclear whether the reference test (visual assessment) was interpreted without knowledge of the index test (quantitative CT) outcome [10,12–15]. Five studies scored low on 'flow and timing' because not all patients were included in the analysis [14,16–19]. For instance, if not all patients received pulmonary function test, this could induce bias. In four studies the time interval between CT and PFT was not specified, this resulted in 'unclear' bias score [13,20–22]. For applicability assessment for this review, one study scored 'high risk' on patient selection: this study included only rheumatoid arthritis patients and excluded other collagen vascular diseases [22]. Three index tests were of applicability concern: one study used lower lobe volume as an outcome and not ILD directly [16], one study reported outcomes of two more visual index tests not applicable for this study [18] and one study only quantified ground

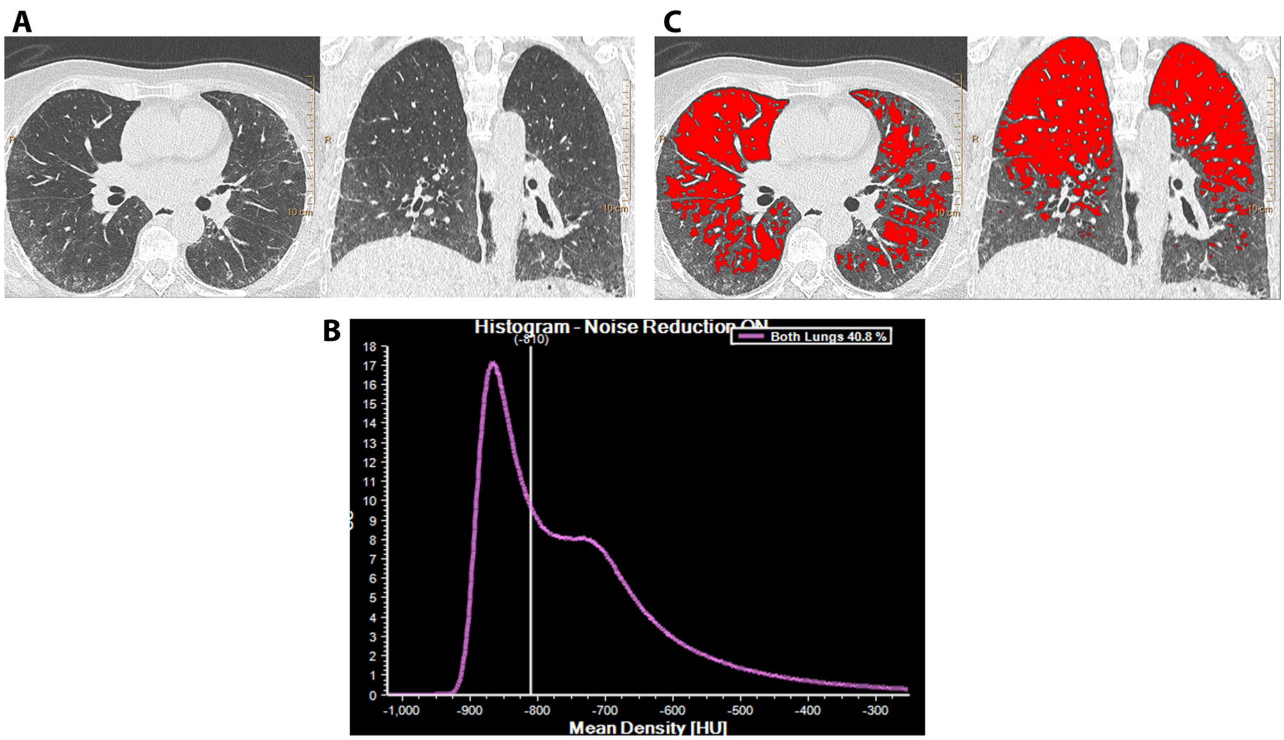

Fig. 1. A, B, C: Interstitial lung disease on CT in a systemic sclerosis patient (A) and accompanying histogram with a threshold set at -810 HU (Hounsfield units) (B). Red colour represents all non-ILD affected lung tissue below a threshold of -810 HU; diseased lung is not marked and shows the CT ILD patterns (C).

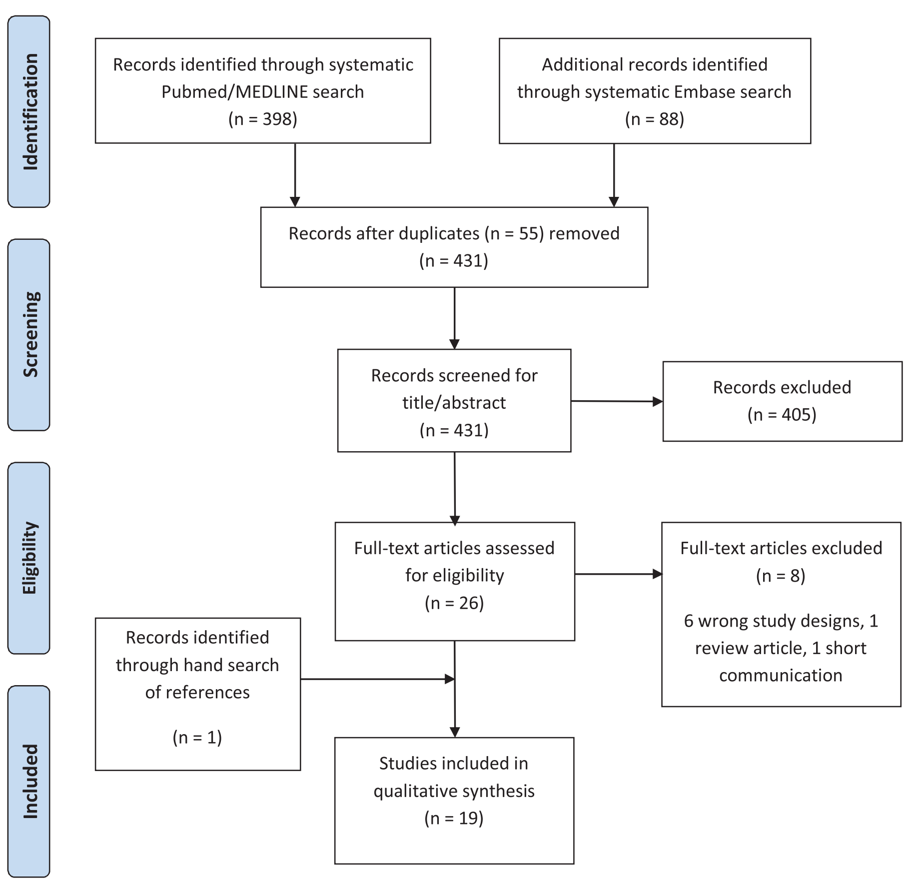

Fig. 2. Literature screening process.

Table 2
Reported correlations of quantitative ILD scores with visual scoring, FVC and DLCO.

Study	Type of method	Simple/complex	Correlation to visual scoring, R^2 (p value)	Correlation to FVC, R^2 (p value)	Correlation to DLCO, R^2 (p value)
Ariani et al. [21]	Histogram	Complex	0.143 (0.0023)[a]	–	–
Ariani et al. [20]	Histogram	Complex	0.360 (< 0.0001)[b]	0.292 (< 0.0001)[c]	0.176 (0.0001)[d]
Camiciottoli et al. [25]	Histogram	Complex	–	0.504 (< 0.0001)[e]	0.384 (< 0.0001)[f]
Çetinçakmak et al. [16]	Histogram	Simple		0.291 (0.012)[g]	0.015 (0.61)[g]
Jacob et al. [17]	Pattern/texture	Complex	0.39 (< 0.0001)[h]	–	–
Kazantzi et al. [12]	Pattern/texture	Complex	ICC = 0.809 (CI = 0.599-0.895)[i]	0.069 (0.116)[j]	0.112 (0.043)[j]
Khanna et al. [18]	Pattern/texture	Simple	–	0.144 (0.008)[k]	0.123 (0.01)[k]
Kim et al. [15]	Pattern/texture	Simple	0.384 (< 0.0001)[l]	0.096 (< 0.001)[m]	0.123 (< 0.001)[m]
Kim et al. [13]	Pattern/texture	Simple	–	0.109 (0.003)[n]	–
Kim et al. [14]	Pattern/texture	Complex	–	0.152 (0.0003)[o]	0.203 (0.0001)[o]
Koyama et al. [28]	Histogram	Complex	–	0.336 (< 0.01)[p]	0.372 (< 0.01)[p]
Marten et al. [26]	Histogram	Simple	0.423 (0.002)[q]	0.343 (0.007)[q]	0.340 (0.007)[q]
Marten et al. [27]	Histogram	Simple	0.513 (< 0.0001)[r]	0.233 (0.0008)[r]	0.282 (< 0.0001)[r]
Ninaber et al. [10]	Histogram	Simple	0.314 (< 0.01)[s]	0.410 (< 0.001)[s]	0.240 (0.001)[s]
Rosas et al. [22]	Pattern/texture	Complex	p < 0.001[t]	0.233[u]	0.283[u]
Salaffi et al. [23]	Histogram	Simple	0.687 (< 0.0001)[v]	0.240 (< 0.0001)[v]	0.426 (< 0.0001)[v]
Salaffi et al. [24]	Histogram	Simple	0.516 (< 0.0001)[v]	0.309 (< 0.0001)[v]	0.449 (< 0.0001)[v]
Tashkin et al. [19]	Pattern/texture	Complex	–	0.048 (< 0.0001)[w]	0.185 (< 0.0001)[w]
Yabuuchi et al. [11]	Histogram	Simple	–	–	0.230 (0.04)[x]

[a] Histogram parameter skewness.
[b] Histogram parameter pKurt.
[c] Histogram parameter tMLA.
[d] Histogram parameter pKurt.
[e] Histogram parameter kurtosis.
[f] Histogram parameter skewness.
[g] Total percentage of lower lobe volume (PLLV).
[h] Correlation between pulmonary vessel volume (PVV) and visual ILD extent.
[i] Confidence interval between CAD-based disease extent quantification and visual scoring.
[j] CAD-based disease extent quantification.
[k] Quantitative assessment of total extent of interstitial lung disease in whole lung, placebo group at baseline.
[l] Average correlation of all zones between quantitative lung fibrosis (QLF) and semi-quantitative lung fibrosis score.
[m] Whole lung CAD quantitative lung fibrosis (QLF).
[n] Correlation between 12-month changes in QLF and in FVC in whole lung.
[o] Correlation with QILD in whole lung at baseline.
[p] Correlation with histogram parameter kurtosis from reconstruction algorithm A.
[q] Correlation with mean extent of ILD at a threshold of -800 HU.
[r] Correlation with CAD high attenuation values (HAV).
[s] Correlation with 85th percentile density (Perc85).
[t] Correlation with CAD ILD score in rheumatoid arthritis.
[u] Correlation with CAD ILD in a mixed population of rheumatoid arthritis and familial pulmonary fibrosis.
[v] Correlation with ILD computerized-aided method (CaM).
[w] Correlation QILD in whole lung (WL).
[x] Correlation with quantitative extent of ground-glass opacities.

glass opacities and no other CT ILD findings [11]. All studies scored well on applicability of reference standard.

3.3. Study populations

Thirteen studies [10,11,13–16,18–21,23–25] used a study population consisting of systemic sclerosis patients including limited and diffuse disease, two articles used a study population of rheumatoid arthritis patients [22,26] and four articles used a mixed study population of collagen vascular disease patients [12,17,27,28]. A total of 1718 collagen vascular disease patients were analysed: 1444 with systemic sclerosis, 197 with rheumatoid arthritis, 34 with inflammatory myositis (polymyositis and dermatomyositis), 6 with SLE, 13 with Sjögren syndrome and 14 with mixed connective tissue disease. There is a possible overestimation in systemic sclerosis and rheumatoid arthritis patients as some studies might have used the same study population [13–15,18–21,23,24,26,27].

3.4. Study designs

Ten studies were prospective in design: nine used a cross-sectional setup [10,12,15,19,20,22–24,28], and one study used a longitudinal setup [14]. Nine studies were retrospective in design: six used a cross-sectional setup [16,17,21,25–27], and three studies used a longitudinal setup [11,13,18]. One study compared quantitative CT before and after autologous stem cell transplantation [11]. Two studies compared quantitative CT in a 1-year clinical trial [14,18]. One article compared a cohort of familial pulmonary fibrosis patients with a cohort of rheumatoid arthritis patients [22].

3.5. Computed tomography quantification methods

Quantification methods were divided in two categories (Table 1): (1) histogram based methods (including threshold and more complex histogram parameters based methods), and (2) pattern or texture recognition methods. Eleven studies were conducted via a histogram method [10,11,16,20,21,23–28] and eight studies were conducted via a pattern or texture recognition method [12–15,17–19,22]. Ten studies used a simple (one step/one threshold) quantification method [10,11,13,15,16,18,23,24,26,27], and nine studies used a more complex method including multiple parameters or quantitative CT indexes (Table 1) [12,14,17,19–22,25,28]. Freely or commercially available software were used in the studies. Six studies defined a histogram threshold for ILD, two set the threshold for ILD at -800 Hounsfield Unit

Table 3
Reported correlations of quantitative ILD scores with clinical outcome measures.

Study	Type of method	Simple/complex	Type of clinical outcome measurement	Correlation with quantitative CT, R^2 (p value)
Camiciottoli et al. [25]	Histogram	Complex	Walking	0.152[a]
			Hygiene	0.102[a]
			Lung scale	0.137[a]
			Disease scale	0.160[a]
			BDI magnitude of task	0.194[a]
			Borg score at rest	0.102[a]
			Spo_2 at rest	0.168[a]
			Spo_2 at 6 min	0.372[a]
Kim et al. [15]	Pattern/texture	Simple	Severity of cough	0.048 (0.0017)[b]
			Frequency of cough	0.036 (0.02)[b]
			Dyspnoea magnitude of task	0.026 (0.02)[b]
			Dyspnoea magnitude of effort	0.029 (0.01)[b]
Kim et al. [13]	Pattern/texture	Simple	Skin-thickness score	0.017 (0.25)[c]
			HAQ-DI	0.012 (0.34)[c]
Kim et al. [14]	Pattern/texture	Complex	Skin score	0.058 (0.027)[d]
			Dyspnoea	0.032 (0.10)[d]
Salaffi et al. [24]	Histogram	Simple	HAQ-DI	0.356 (< 0.0001)[e]

[a] Histogram parameter MLA.
[b] Correlation with severity of QLF score.
[c] Whole lung CAD quantitative lung fibrosis (QLF).
[d] Correlation with QILD in whole lung at baseline.
[e] Correlation with ILD computerized-aided method (CaM).

(HU) [26,27], one used a threshold of -800 HU for ground glass opacity [11], two used an ILD threshold of -700 HU [23,24], and one used an optimal percentile density of 85% (Perc85) for ILD [10].

3.6. Comparison of quantitative CT to reader-based ILD scoring

In 11 studies the correlation between visual CT assessment and quantitative CT assessment was reported (Table 2). For visual assessment, four different scores were used. Visual scores as proposed by Goh and Wells [6] were used in three studies [20,21,26]. Kazerooni scores [29] were used in two studies [10,15]. Warrick [30] scoring was used in two studies [23,24]. Scores from Desai [31] was used in one article [12]. Three studies [17,22,27] did not reference the method used for visual assessment.

For comparison to quantitative CT method, ten studies used a Pearson or Spearman correlation and one study used an intraclass correlation coefficient. R^2 for correlation of quantitative CT with visual ILD scoring ranged from 0.143 ($p < 0.01$) to 0.687 ($p < 0.0001$), all reporting a significant correlation.

3.7. Comparison of quantitative CT to pulmonary function test (PFT)

Seventeen articles compared quantitative CT to pulmonary function test (PFT) [10–16,18–20,22–28]. For comparison to quantitative CT method, all seventeen used a Pearson or Spearman correlation. R^2 for correlation of quantitative CT with FVC ranged from 0.048 ($p < 0.0001$) to 0.504 ($p < 0.0001$) and for diffusing capacity for carbon monoxide (DLCO) from 0.015 ($p = 0.61$) to 0.449 ($p < 0.0001$). Results are depicted in Table 2. For the PFT parameters only FVC and DLCO are reported in this review because these parameters were studied more often than other pulmonary function parameters such as FEV1 and TLC. Fifteen studies reported a statistically significant correlation with FVC and fifteen studies reported a statistically significant correlation with DLCO.

3.8. Comparison of quantitative CT to clinical outcome measures

Five studies used health assessment and/or dyspnoea/breathing questionnaires to measure disease outcome [13–15,24,25]. One study used 6 min walking test [25]. Reported Pearson or Spearman correlation coefficients between quantitative CT and clinical outcome measures are depicted in Table 3. R^2 ranged from 0.012 ($p = 0.34$) to 0.372.

4. Discussion

We systematically searched, appraised and summarized the literature on two different automated computed tomography quantification methods for interstitial lung disease in collagen vascular disease patients. Both histogram and texture based methods associate significantly with visual scores, pulmonary function tests and clinical parameters such as 6 min walking test. We anticipate that these types of automated quantitative CT methodology will increasingly play a role in research and subsequently in medical decision-making. However, the clinical value remains to be determined, as well as reproducibility across hospitals and between CT scans from different vendors, and other potential confounders.

Based on our review both histogram and texture methods show equal promise, precluding a conclusion that one automated CT quantification technique is preferable over the other. Pattern or texture recognition methods featured a tendency to report weaker correlations with visual assessment and pulmonary function tests than the histogram methods. However, not all included studies reported correlation and therefore unreported insignificant correlations could distort these results. The present analysis showed that the correlation of quantitative CT with reader-based visual ILD assessment on CT for all studies had a wide range and a direct comparison is lacking. Some studies, both from histogram and textures, provide more intuitive results such as percentage diseased lung and this may eventually play a role in the acceptance of quantitative CT. Also, texture based methods can provide more specific phenotypic information (fibrotic versus non-fibrotic) compared to histogram based methods.

Pulmonary function tests are relatively easy to perform and recommended for evaluating the pulmonary condition in CVD patients. Therefore, ideally, a diagnostic quantification technique corresponds to pulmonary function test outcomes. The pulmonary function tests parameters DLCO and FVC were most often reported to correlate with CT ILD quantification. This could implicate that gas transfer is more affected than lung compliance in interstitial lung disease [19]. In literature, lung function parameter DLCO is considered to correlate the most with extent of lung involvement on CT. However, DLCO is not a specific biomarker in predicting severity of ILD. Other disease manifestations such as pulmonary hypertension or anaemia could also be the cause of aberrant DLCO measurements. Considerable measurement errors of DLCO have also been reported [18,24]. Moreover, Khanna et al. reported that the change in DLCO over 1 year did not correlate to quantitative CT [18], indicating conflicting results in the reliability of DLCO outcome values. The same applies for FVC. Conflicting results have been reported on the prognostic ability of FVC in ILD related to systemic sclerosis [32]. FVC values in collagen vascular disease patients might be influenced by other confounders, such as muscle weakness and extra thoracic restriction from skin disease in systemic sclerosis, and therefore severity of ILD might not always be associated with FVC values [32].

Interstitial lung disease, amongst other disease related complications, may affect quality of life of collagen vascular disease patients. In general, low correlations were reported to quality of life assessment methods in the few studies that reported quality of life. The low correlation between quantitative CT and disease severity questionnaires (such as the health assessment questionnaire disability index HAQ-DI) might be caused by other disease-related factors such as arthritis and myopathy [19]. Salaffi et al. however, reported that HAQ-DI correlated strongly to HRCT and should be included as an outcome measure for severity of fibrosis in systemic sclerosis [24]. The value of combining quantitative CT, pulmonary function and health assessment or quality of life questionnaires remains to be further determined as a composite endpoint.

Some challenges in quantitative CT have also been reported. One of them is the misclassification of structures. Some studies reported the possibility of an overestimation because of identification of pulmonary vasculature as interstitial lung disease [26,27]. Other studies reported the possibility of underestimation of ILD because of missed structures or incomplete lung segmentation. For instance, Salaffi et al. reported that their density mask was not able to discriminate honeycombing from normal lung density and thereby possibly underestimating disease severity [23]. Kim et al. reported an underestimation of ILD in the visual assessment in comparison to quantitative CT [15].

Furthermore, there is no clear cut-off value defined for ILD in the CT histogram in the literature. Marten et al. tried to set a threshold for ILD using quantitative CT imaging and reported a Hounsfield Unit (HU) threshold of -800 most ideal for ILD [26], Salaffi et al. preferred -700 to quantify lung disease [23]. Yabuuchi et al. found a threshold of -800 for ground glass opacity quantification most suitable [11]. Ninaber et al. reported an optimal percentile density of 85% (Perc85) that correlated the best with pulmonary function test [10]. Possibly, cut-offs vary also for different scanners. Other challenges and potential confounders include radiation dose and reconstruction algorithm, scanner calibration, vendor, resolution, inspiration level and progressive volume loss in fibrotic areas, which could lead to lower abnormal lung percentages with progressive disease.

Among the included studies were some medication studies and longitudinal follow-up studies that reported other interesting applications for quantitative CT. Jacob et al. demonstrated that automated quantitative CT is able to track prognosis of ILD and showed that pulmonary vessel volume is an independent predictor of mortality caused by ILD in collagen vascular diseases [17]. The group by Ariani published results on mortality prediction in a separate paper and demonstrated that quantitative CT is able to distinguish mortality risk categories in systemic sclerosis patients [33]. Kim et al. demonstrated that quantitative CT is able to track treatment efficacy in a 1-year clinical trial with oral cyclophosphamide [13,14]. Yabuuchi et al. showed pulmonary improvement with automated quantitative CT in systemic sclerosis patients after autologous stem cell transplantation [11]. However, more research is needed to further investigate optimal CT biomarkers for tracking prognosis and treatment efficacy.

Recently, deep learning methods have been introduced for quantifying ILD on CT [34–36]. These methods use machine-learning algorithms to automatically recognize patterns based on the identification of significant features. Deep learning methods have not yet been tested in collagen vascular disease patients but would be interesting to evaluate in future research on quantitative CT in this patient population.

Besides ILD, emphysema has been associated with usual interstitial pneumonia in never-smokers rheumatoid arthritis patients and with worsened disease outcome [37]. None of the included articles quantify emphysema in collagen vascular disease patients. Including quantitative CT methods for emphysema besides ILD would therefore be a desirable direction for future research.

This overview has the following limitations. First of all, we comprehensively searched and included articles mentioning quantitative CT and a study population of collagen vascular disease patients in title or abstract; we thus may have missed studies. Secondly, the included studies differed greatly in study design and methodology, which complicated comparison and meta-analytic approach. Thirdly, most studies used a small study population and some used the same study population as other investigator groups, which may complicate generalizability. Moreover, the heterogeneity of collagen vascular diseases and associated ILD is a limitation, although most research was done in systemic sclerosis patients. Lastly, one of the PRISMA-DTA checklist points, drafting a 2 × 2 data could not be met for the reported studies, as this did not fit the study design of the included studies.

To our best knowledge a study reviewing all literature on automated quantitative CT of ILD assessment in collagen vascular diseases had not been performed previously. Our appraisal and comprehensive summary showed the great promise of quantitative CT, challenges and future directions.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declarations of interest

None.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.ejrad.2019.01.024.

References

[1] A. Fischer, R. du Bois, Interstitial lung disease in connective tissue disorders, Lancet 380 (2012) 689–698, https://doi.org/10.1016/S0140-6736(12)61079-4.

[2] C. Jokerst, H. Purdy, S. Bhalla, An overview of collagen vascular disease–associated interstitial lung disease, Semin. Roentgenol. 50 (2015) 31–39, https://doi.org/10.1053/j.ro.2014.04.006.

[3] T.J. Doyle, P.F. Dellaripa, Lung manifestations in the rheumatic diseases, Chest 152 (2017) 1283–1295, https://doi.org/10.1016/J.CHEST.2017.05.015.

[4] D. Khanna, S. Mittoo, R. Aggarwal, S.M. Proudman, N. Dalbeth, E.L. Matteson, K. Brown, K. Flaherty, A.U. Wells, J.R. Seibold, V. Strand, Connective tissue disease-associated interstitial lung diseases (CTD-ILD) - report from OMERACT CTD-ILD working group, J. Rheumatol. 42 (2015) 2168–2171, https://doi.org/10.3899/jrheum.141182.

[5] J. Ahuja, D. Arora, J.P. Kanne, T.S. Henry, J.D. Godwin, Imaging of pulmonary manifestations of connective tissue diseases, Radiol. Clin. North Am. 54 (2016) 1015–1031, https://doi.org/10.1016/j.rcl.2016.05.005.

[6] N.S.L. Goh, S.R. Desai, S. Veeraraghavan, D.M. Hansell, S.J. Copley, T.M. Maher, T.J. Corte, C.R. Sander, J. Ratoff, A. Devaraj, G. Bozovic, C.P. Denton, C.M. Black, R.M. du Bois, A.U. Wells, Interstitial lung disease in systemic sclerosis, Am. J. Respir. Crit. Care Med. 177 (2008) 1248–1254, https://doi.org/10.1164/rccm.200706-877OC.

[7] Z.A. Aziz, HRCT diagnosis of diffuse parenchymal lung disease: inter-observer variation, Thorax 59 (2004) 506–511, https://doi.org/10.1136/thx.2003.020396.

[8] M.D.F. McInnes, D. Moher, B.D. Thombs, T.A. McGrath, P.M. Bossuyt, T. Clifford,

J.F. Cohen, J.J. Deeks, C. Gatsonis, L. Hooft, H.A. Hunt, C.J. Hyde, D.A. Korevaar, M.M.G. Leeflang, P. Macaskill, J.B. Reitsma, R. Rodin, A.W.S. Rutjes, J.-P. Salameh, A. Stevens, Y. Takwoingi, M. Tonelli, L. Weeks, P. Whiting, B.H. Willis, Preferred reporting items for a systematic review and meta-analysis of diagnostic test accuracy studies, JAMA 319 (2018) 388, https://doi.org/10.1001/jama.2017.19163.

[9] P.F. Whiting, A.W.S. Rutjes, M.E. Westwood, S. Mallet, J.J. Deeks, J.B. Reitsma, M.M.G. Leeflang, J.A.C. Sterne, P.M.M. Bossuyt, QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies, Ann. Intern. Med. 155 (2011) 529–536.

[10] M.K. Ninaber, J. Stolk, J. Smit, E.J. Le Roy, L.J.M. Kroft, M. Els Bakker, J.K. De Vries Bouwstra, A.A. Schouffoer, M. Staring, B.C. Stoel, Lung structure and function relation in systemic sclerosis: application of lung densitometry, Eur. J. Radiol. 84 (2015) 975–979, https://doi.org/10.1016/j.ejrad.2015.01.012.

[11] H. Yabuuchi, Y. Matsuo, H. Tsukamoto, T. Horiuchi, S. Sunami, T. Kamitani, M. Jinnouchi, M. Nagao, K. Akashi, H. Honda, Evaluation of the extent of ground-glass opacity on high-resolution CT in patients with interstitial pneumonia associated with systemic sclerosis: comparison between quantitative and qualitative analysis, Clin. Radiol. 69 (2014) 758–764, https://doi.org/10.1016/j.crad.2014.03.008.

[12] A. Kazantzi, L. Costaridou, S. Skiadopoulos, P. Korfiatis, A. Karahaliou, D. Daoussis, A. Andonopoulos, C. Kalogeropoulou, Automated 3D interstitial lung disease extent quantification: performance evaluation and correlation to PFTs, J. Digit. Imaging 27 (2014) 380–391, https://doi.org/10.1007/s10278-013-9670-z.

[13] H.J. Kim, M.S. Brown, R. Elashoff, G. Li, D.W. Gjertson, D.A. Lynch, D.C. Strollo, E. Kleerup, D. Chong, S.K. Shah, S. Ahmad, F. Abtin, D.P. Tashkin, J.G. Goldin, Quantitative texture-based assessment of one-year changes in fibrotic reticular patterns on HRCT in scleroderma lung disease treated with oral cyclophosphamide, Eur. Radiol. 21 (2011) 2455–2465, https://doi.org/10.1007/s00330-011-2223-2.

[14] H.J. Kim, D.P. Tashkin, D.W. Gjertson, M.S. Brown, E. Kleerup, S. Chong, J.A. Belperio, M.D. Roth, F. Abtin, R. Elashoff, C.H. Tseng, D. Khanna, J.G. Goldin, Transitions to different patterns of interstitial lung disease in scleroderma with and without treatment, Ann. Rheum. Dis. 75 (2016) 1367–1371, https://doi.org/10.1136/annrheumdis-2015-208929.

[15] H.J. Kim, D.P. Tashkin, P. Clements, G. Li, M.S. Brown, R. Elashoff, D.W. Gjertson, F. Abtin, D.A. Lynch, D.C. Strollo, J.G. Goldin, A computer-aided diagnosis system for quantitative scoring of extent of lung fibrosis in scleroderma patients, Clin. Exp. Rheumatol. 28 (2010), https://doi.org/10.1016/j.surg.2006.10.010.Use.

[16] M.G. Çetinçakmak, C. Göya, C. Hamidi, G. Tekbaş, Ö. Abakay, İ. Batmaz, S. Hattapoğlu, A. Yavuz, A. Bilici, Quantitative volumetric assessment of pulmonary involvement in patients with systemic sclerosis, Quant. Imaging Med. Surg. 6 (2016) 50–56 (Accessed 7 June 2017), http://qims.amegroups.com/article/view/9289/9860.

[17] J. Jacob, B.J. Bartholmai, S. Rajagopalan, A.L. Brun, R. Egashira, R. Karwoski, M. Kokosi, A.U. Wells, D.M. Hansell, Evaluation of computer-based computer tomography stratification against outcome models in connective tissue disease-related interstitial lung disease: a patient outcome study, BMC Med. 14 (2016) 190, https://doi.org/10.1186/s12916-016-0739-7.

[18] D. Khanna, V. Nagaraja, C. hong Tseng, F. Abtin, R. Suh, G. Kim, A. Wells, D.E. Furst, P.J. Clements, M.D. Roth, D.P. Tashkin, J. Goldin, Predictors of lung function decline in scleroderma-related interstitial lung disease based on high-resolution computed tomography: implications for cohort enrichment in systemic sclerosis-associated interstitial lung disease trials, Arthritis Res. Ther. 17 (2015) 372, https://doi.org/10.1186/s13075-015-0872-2.

[19] D.P. Tashkin, E.R. Volkmann, C.-H. Tseng, H.J. Kim, J. Goldin, P. Clements, D. Furst, D. Khanna, E. Kleerup, M.D. Roth, R. Elashoff, Relationship between quantitative radiographic assessments of interstitial lung disease and physiological and clinical features of systemic sclerosis, Ann. Rheum. Dis. 75 (2016) 374–381, https://doi.org/10.1136/annrheumdis-2014-206076.

[20] A. Ariani, M. Silva, E. Bravi, M. Saracco, S. Parisi, F. De Gennaro, F. Lumetti, L. Idolazzi, V. Seletti, P. Caramaschi, C. Benini, F.C. Bodini, C.A. Scirè, G. Lucchini, D. Santilli, F. Mozzani, D. Imberti, E. Arrigoni, G. Delsante, R. Pellerito, E. Fusaro, N. Sverzellati, Operator-independent quantitative chest computed tomography versus standard assessment of interstitial lung disease related to systemic sclerosis: a multi-centric study, Mod. Rheumatol. 25 (2015) 724–730, https://doi.org/10.3109/14397595.2015.1016200.

[21] A. Ariani, F. Lumetti, M. Silva, D. Santilli, F. Mozzani, G. Lucchini, G. Delsante, N. Sverzellati, Systemic sclerosis interstitial lung disease evaluation: comparison between semiquantitative and quantitative computed tomography assessments, J. Biol. Regul. Homeost. Agents 28 (2014) 507–513 (Accessed 7 June 2017), http://www.ncbi.nlm.nih.gov/pubmed/25316138.

[22] I.O. Rosas, J. Yao, N.A. Avila, C.K. Chow, W.A. Gahl, B.R. Gochuico, Automated quantification of high-resolution CT scan findings in individuals at risk for pulmonary fibrosis, Chest. 140 (2011) 1590–1597, https://doi.org/10.1378/chest.10-2545.

[23] F. Salaffi, M. Carotti, S. Bosello, A. Ciapetti, M. Gutierrez, E. Bichisecchi, G. Giuseppetti, G. Ferraccioli, Computer-aided quantification of interstitial lung disease from high resolution computed tomography images in systemic sclerosis: Correlation with visual reader-based score and physiologic tests, Biomed Res. Int. (2015) 1–8, https://doi.org/10.1155/2015/834262.

[24] F. Salaffi, M. Carotti, E. Di Donato, M. Di Carlo, L. Ceccarelli, G. Giuseppetti, Computer-aided tomographic analysis of interstitial lung disease (ILD) in patients with systemic sclerosis (SSc). Correlation with pulmonary physiologic tests and patient-centred measures of perceived dyspnea and functional disability, PLoS One 11 (2016), https://doi.org/10.1371/journal.pone.0149240.

[25] G. Camiciottoli, I. Orlandi, M. Bartolucci, E. Meoni, F. Nacci, S. Diciotti, C. Barcaroli, M.L. Conforti, M. Pistolesi, M. Matucci-Cerinic, M. Mascalchi, Lung CT densitometry in systemic sclerosis: correlation with lung function, exercise testing, and quality of life, Chest 131 (2007) 672–681, https://doi.org/10.1378/chest.06-1401.

[26] K. Marten, V. Dicken, C. Kneitz, M. Hoehmann, W. Kenn, D. Hahn, C. Engelke, Computer-assisted quantification of interstitial lung disease associated with rheumatoid arthritis: preliminary technical validation, Eur. J. Radiol. 72 (2009) 278–283, https://doi.org/10.1016/j.ejrad.2008.07.008.

[27] K. Marten, V. Dicken, C. Kneitz, M. Höhmann, W. Kenn, D. Hahn, C. Engelke, Interstitial lung disease associated with collagen vascular disorders: disease quantification using a computer-aided diagnosis tool, Eur. Radiol. 19 (2009) 324–332, https://doi.org/10.1007/s00330-008-1152-1.

[28] H. Koyama, Y. Ohno, Y. Yamazaki, M. Nogami, A. Kusaka, K. Murase, K. Sugimura, Quantitatively assessed CT imaging measures of pulmonary interstitial pneumonia: effects of reconstruction algorithms on histogram parameters, Eur. J. Radiol. 74 (2010) 142–146, https://doi.org/10.1016/j.ejrad.2009.02.006.

[29] E.A. Kazerooni, F.J. Martinez, A. Flint, D.A. Jamadar, B.H. Gross, D.L. Spizarny, P.N. Cascade, R.I. Whyte, J.P. Lynch, G. Toews, Thin-section CT obtained at 10-mm increments versus limited three-level thin-section CT for idiopathic pulmonary fibrosis: correlation with pathologic scoring, AJR Am. J. Roentgenol. 169 (1997) 977–983, https://doi.org/10.2214/ajr.169.4.9308447.

[30] J.H. Warrick, M. Bhalla, S.I. Schabel, R.M. Silver, High resolution computed tomography in early scleroderma lung disease, J. Rheumatol. 18 (1991) 1520–1528 (Accessed 1 July 2017), http://www.ncbi.nlm.nih.gov/pubmed/1765976.

[31] S.R. Desai, S. Veeraraghavan, D.M. Hansell, A. Nikolakopolou, N.S.L. Goh, A.G. Nicholson, T.V. Colby, C.P. Denton, C.M. Black, R.M. du Bois, A.U. Wells, CT features of lung disease in patients with systemic sclerosis: comparison with idiopathic pulmonary fibrosis and nonspecific interstitial pneumonia, Radiology 232 (2004) 560–567, https://doi.org/10.1148/radiol.2322031223.

[32] T.A. Winstone, D. Assayag, P.G. Wilcox, J.V. Dunne, C.J. Hague, J. Leipsic, H.R. Collard, C.J. Ryerson, Predictors of mortality and progression in scleroderma-associated interstitial lung disease: a systematic review, Chest 146 (2014) 422–436, https://doi.org/10.1378/chest.13-2626.

[33] A. Ariani, M. Silva, V. Seletti, E. Bravi, M. Saracco, S. Parisi, F. De Gennaro, L. Idolazzi, P. Caramaschi, C. Benini, F.C. Bodini, C.A. Scirè, G. Carrara, F. Lumetti, V. Alfieri, E. Bonati, G. Lucchini, M. Aiello, D. Santilli, F. Mozzani, D. Imberti, E. Michieletti, E. Arrigoni, G. Delsante, R. Pellerito, E. Fusaro, A. Chetta, N. Sverzellati, Quantitative Chest Computed Tomography Is Associated With Two Prediction Models of Mortality in Interstitial Lung Disease Related to Systemic Sclerosis, (2019), https://doi.org/10.1093/rheumatology/kew480 (n.d.).

[34] G.B. Kim, K.-H. Jung, Y. Lee, H.-J. Kim, N. Kim, S. Jun, J.B. Seo, D.A. Lynch, Comparison of shallow and deep learning methods on classifying the regional pattern of diffuse lung disease, J. Digit. Imaging 31 (2018) 415–424, https://doi.org/10.1007/s10278-017-0028-9.

[35] M. Anthimopoulos, S. Christodoulidis, L. Ebner, A. Christe, S. Mougiakakou, Lung pattern classification for interstitial lung diseases using a deep convolutional neural network, IEEE Trans. Med. Imaging 35 (2016) 1207–1216, https://doi.org/10.1109/TMI.2016.2535865.

[36] S.L.F. Walsh, L. Calandriello, M. Silva, N. Sverzellati, Deep learning for classifying fibrotic lung disease on high-resolution computed tomography: a case-cohort study, Lancet Respir. Med. 6 (2018) 837–845, https://doi.org/10.1016/S2213-2600(18)30286-8.

[37] J. Jacob, J.W. Song, H.-Y. Yoon, G. Cross, J. Barnett, W.L. Woo, F. Adams, M. Kokosi, A. Devaraj, E. Renzoni, T.M. Maher, D.S. Kim, A.U. Wells, Prevalence and effects of emphysema in Never-Smokers with rheumatoid arthritis interstitial lung disease, EBioMedicine 28 (2018) 303–310, https://doi.org/10.1016/J.EBIOM.2018.01.038.