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Evolving Role of Quantitative CT in Interstitial Lung Disease from Technical Challenges to Clinical Implementation

Anshu Kumari[1], Ashish Kumar Shukla[2], Shivanshu Chauhan[1], Ranjeet Singh[3], Jyoti Yadav[3], Bharat Bhushan Dagur[1], Rukamanee[1]

Institutional Addresses:

[1]PhD Scholar, Department of Radiodiagnosis, SMC, Santosh Deemed to be University, Ghaziabad Uttar Pradesh, India.

[2] Professor, Department of Radiodiagnosis, SMC, Santosh Deemed to be University, Ghaziabad Uttar Pradesh, India.

[3]Junior Resident, Department of Radiodiagnosis, Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India

Corresponding Author:

Dr. Ashish Kumar Shukla

Professor, Department of Radiodiagnosis

Santosh Deemed to be University, Ghaziabad, Uttar Pradesh, India

Running Head

Quantitative CT in Interstitial Lung Disease

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KEYWORDS

Automated analysis, Interstitial lung disease, Machine learning, quantitative CT, Radiomics

ABSTRACT:

Interstitial lung diseases (ILDs) comprise a heterogeneous group of more than 200 disorders affecting the lung parenchyma, marked by varying degrees of inflammation and fibrosis. High-resolution computed tomography (HRCT) remains central to ILD diagnosis and classification, yet visual interpretation is limited by subjectivity and substantial interobserver variability, reducing reliability for baseline assessment and longitudinal follow-up. Quantitative CT (qCT) has emerged as a powerful solution, offering objective, reproducible measurements of lung density, texture, vascular remodelling, and fibrosis extent. This systematic review evaluates the evolving role of qCT in ILD across diagnostic assessment, prognostication, disease monitoring, and emerging machine learning based applications. Following PRISMA guidelines, a comprehensive literature search identified 185 eligible studies. Across studies, qCT-derived biomarkers showed strong correlations with physiologic impairment, including forced vital capacity and diffusing capacity, and reliably

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predicted disease progression and mortality in idiopathic pulmonary fibrosis, connective tissue disease associated ILD, and hypersensitivity pneumonitis. Machine learning and deep learning approaches further improved segmentation accuracy, pattern recognition, and prediction of clinically meaningful outcomes, expanding the potential of qCT as a sensitive imaging biomarker. Despite these advances, several barriers limit routine clinical adoption. Variability in acquisition protocols, reconstruction methods, segmentation techniques, and feature extraction reduces reproducibility across scanners and institutions. Standardization efforts, combined with robust external validation and integration of explainable AI, are crucial for translating quantitative tools into practice. Overall, qCT represents a significant advancement in ILD imaging, with the potential to enhance diagnostic confidence, improve risk stratification, and enable more precise monitoring of therapeutic response.

1. Introduction

Interstitial lung diseases represent a broad and heterogeneous group of disorders defined by varying degrees of inflammation and fibrosis within the lung parenchyma (1). Their diverse etiologies, overlapping imaging features, and unpredictable clinical trajectories make diagnosis and long-term management particularly challenging. Early identification of disease activity and reliable prognostication are essential for optimizing treatment decisions, yet current diagnostic and monitoring strategies often fall short because they rely heavily on subjective interpretation and may fail to capture subtle changes over time (2).

High-resolution computed tomography (HRCT) remains the imaging cornerstone for ILD assessment, providing detailed visualization of parenchymal abnormalities. However, visual interpretation of HRCT is limited by reader experience and only modest interobserver agreement, especially in complex or borderline cases (3). These limitations have driven a growing interest in quantitative CT (qCT), which uses automated computational tools to extract objective measurements of lung density, texture and fibrotic change. By reducing observer dependency, qCT allows more consistent and reproducible assessment of disease extent and severity.

Recent innovations in machine learning and deep learning have further advanced qCT capabilities. Modern algorithms can perform highly accurate lung segmentation, classify ILD patterns, quantify fibrosis and even predict clinical outcomes. These developments have strengthened the role of qCT as a complementary tool to traditional imaging, supporting more precise diagnosis, risk stratification and longitudinal monitoring in patients with interstitial lung disease (4).

2. Methodology

This review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure a structured and transparent approach to literature synthesis.

Search Strategy

A comprehensive literature search was performed across the electronic databases PubMed/MEDLINE, Scopus, and Web of Science to identify relevant studies published between January 2010 and December 2024.

The search strategy incorporated a combination of Medical Subject Headings (MeSH) terms and free-text keywords, including: “quantitative CT,” “automated CT analysis,” “radiomics,” “machine learning,” “deep learning,” “interstitial lung disease,” and “interstitial lung abnormalities.”

Boolean operators (AND, OR) were used to refine the search. Reference lists of selected articles were also screened to identify additional relevant studies.

Study Selection

All retrieved records were imported into a reference management system, and duplicates were removed.

Study selection was performed independently by two reviewers in three sequential stages:

- Title screening
- Abstract screening
- Full-text review

Disagreements between reviewers were resolved through discussion and consensus.

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A total of 185 studies met the eligibility criteria and were included in the final analysis.

Inclusion Criteria

Studies were included if they met the following criteria:

- Original research articles or review articles
- Studies involving human subjects with interstitial lung disease (ILD) or interstitial lung abnormalities (ILAs)
- Use of quantitative CT (qCT), radiomics, or automated CT analysis
- Articles published in the English language

Exclusion Criteria

The following studies were excluded:

- Case reports and small case series
- Editorials, letters, and commentaries
- Studies not involving interstitial lung diseases
- Studies without quantitative or automated CT analysis

Data Extraction

Relevant data were systematically extracted from each included study, including:

- Study design and population characteristics
- Type of ILD or ILA evaluated
- Quantitative CT parameters (e.g., lung density, fibrosis extent, texture features)
- Machine learning or deep learning methods used
- Clinical and functional outcomes (e.g., forced vital capacity, diffusing capacity, mortality)

Quality Assessment

Due to heterogeneity in study designs and methodologies, a formal quantitative risk-of-bias tool was not consistently applicable. However, study quality was assessed qualitatively based on study design, sample size, and methodological rigor, and these factors were considered during data interpretation.

Data Synthesis

A qualitative synthesis of the included studies was performed. Findings were grouped into thematic categories, including technical aspects of qCT, quantitative biomarkers, machine learning applications, prognostic value, and clinical implementation.

3. Clinical Background And Unmet Needs

Why Quantification Matters in ILD

The clinical heterogeneity of ILD creates several diagnostic and prognostic challenges. Diagnostic uncertainty arises because many ILDs have overlapping imaging features, making pattern recognition difficult. Reader variability represents another major challenge, as visual assessment suffers from significant inter- and intra-observer variability. Disease monitoring poses difficulties because subtle changes in disease extent are difficult to detect visually, particularly for longitudinal studies (5). Treatment response assessment remains challenging when attempting to distinguish fibrotic progression from inflammatory stabilization. Additionally, current prognostic indices lack sensitivity for predicting individual patient outcomes.

Quantitative CT addresses these challenges by providing objective, reproducible measurements that overcome the inherent subjectivity of visual assessment (1). The development of automated tools enables quantification of patterns on HRCT with results that are objective, reproducible, sensitive to change, and predictive of disease progression (4).

4. Technical Aspects Of Quantitative Ct

Image Acquisition and Standardization

Standardized acquisition protocols form the foundation of reliable qCT analysis. Key parameters that influence quantitative measurements include tube voltage, slice thickness, reconstruction kernel, scan coverage, breathing protocol, and reconstruction method. Thin-section CT with slice thickness less than 1.25 mm is essential for accurate detection of fine structural details (6).

Standardization Challenges:

Variations in reconstruction parameters introduce significant measurement variability. A multicentre prospective study demonstrated that between two same-day CT scans, the absolute quantitative measurement variability of fibrosis extent in ILD was approximately 1%, with relative differences ranging from -14.8% to 16.1% (7). However, when different

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reconstruction parameters were used, these variabilities increased substantially to -11.3% to 3.9% for absolute differences and -123.1% to 18.4% for relative differences (7). This finding underscores the critical importance of protocol standardization.

Different scanner manufacturers and models produce different attenuation values, creating challenges for cross-institutional comparisons. The strong dependence of CT numbers on x-ray beam spectra limits quantitative applications and standardization from achieving robust widespread success (8).

Image Segmentation and Feature Extraction

Automated quantification requires accurate lung segmentation followed by pattern-specific classification. Modern approaches incorporate multiple categories of features extracted from CT images. Shape features provide information about disease extent measurement. First-order features characterize parenchymal density through mean intensity, skewness, and kurtosis. Second-order texture features assess heterogeneity using methods like gray-level co-occurrence matrices. Higher-order features analyse pattern complexity, while functional metrics evaluate vascular remodelling and small airway disease (9).

Deep learning-based segmentation has achieved superior performance compared to traditional threshold methods. A systematic review of automated segmentation methods demonstrated the rise of data-driven models, especially due to the deep learning trend, with increasing demand for high-quality data annotation (10), facilitating integrated quantitative analysis of lung parenchyma through density-based mapping, histogram-derived metrics, texture classification, and three-dimensional fibrosis visualization, as demonstrated in **Figure 1.**

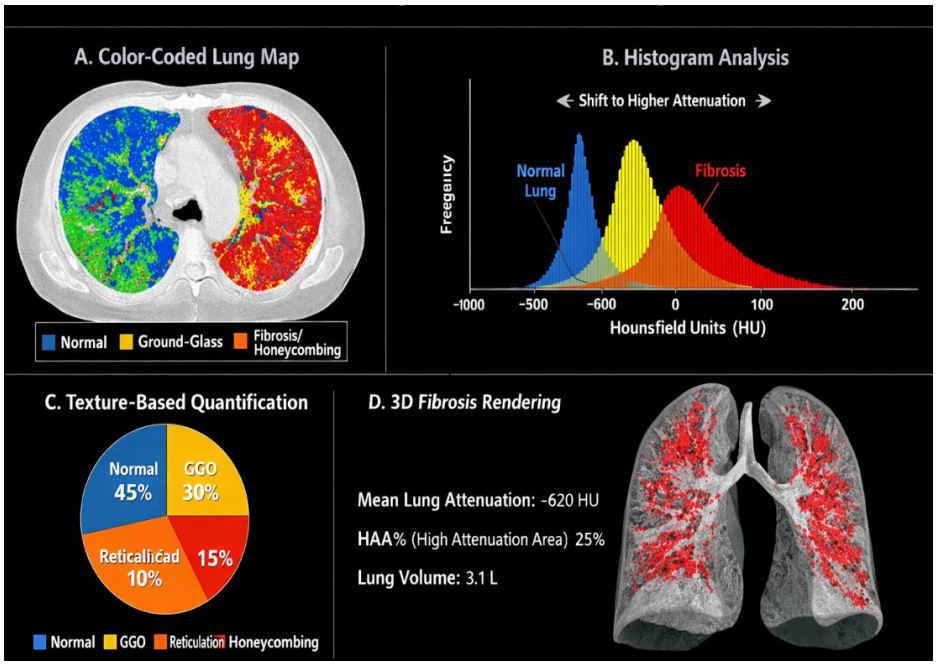

***Figure 1. Quantitative CT analysis workflow and representative outputs in interstitial lung* disease.**
(A) Color-coded lung map illustrating spatial distribution of normal lung (blue), ground-glass opacity (yellow), and fibrotic changes including reticulation and honeycombing (red).
(B) Histogram-based analysis of lung attenuation values demonstrating a rightward shift toward higher Hounsfield Units with increasing fibrotic burden.
(C) Texture-based quantification showing proportional distribution of normal lung, ground-glass opacity, reticulation, and honeycombing patterns.
(D) Three-dimensional rendering of fibrotic lung regions with quantitative metrics, including mean lung attenuation, high attenuation area (HAA%), and total lung volume.

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5. Quantitative Biomarkers In Ild

Quantification of ILD patterns and physiologic correlation

Automated quantitative CT (qCT) enables objective measurement of key interstitial lung disease (ILD) patterns on high-resolution computed tomography (HRCT), providing a standardized and reproducible assessment of disease extent and severity. Ground-glass opacity reflects inflammatory activity, reticulation indicates architectural remodeling, and honeycombing represents irreversible fibrosis associated with the usual interstitial pneumonia (UIP) pattern, which carries significant prognostic implications. Composite indices, such as the total fibrosis score, combine multiple imaging features and demonstrate improved reproducibility and stronger associations with pulmonary function and mortality compared with individual pattern metrics, as summarized in **Table 1.**

Representative HRCT patterns of fibrotic ILD, including reticulation, traction bronchiectasis, architectural distortion, and honeycombing, are illustrated in **Figure 2**. These imaging features form the basis of both visual assessment and quantitative analysis, highlighting the transition from early inflammatory changes to advanced fibrotic remodelling.

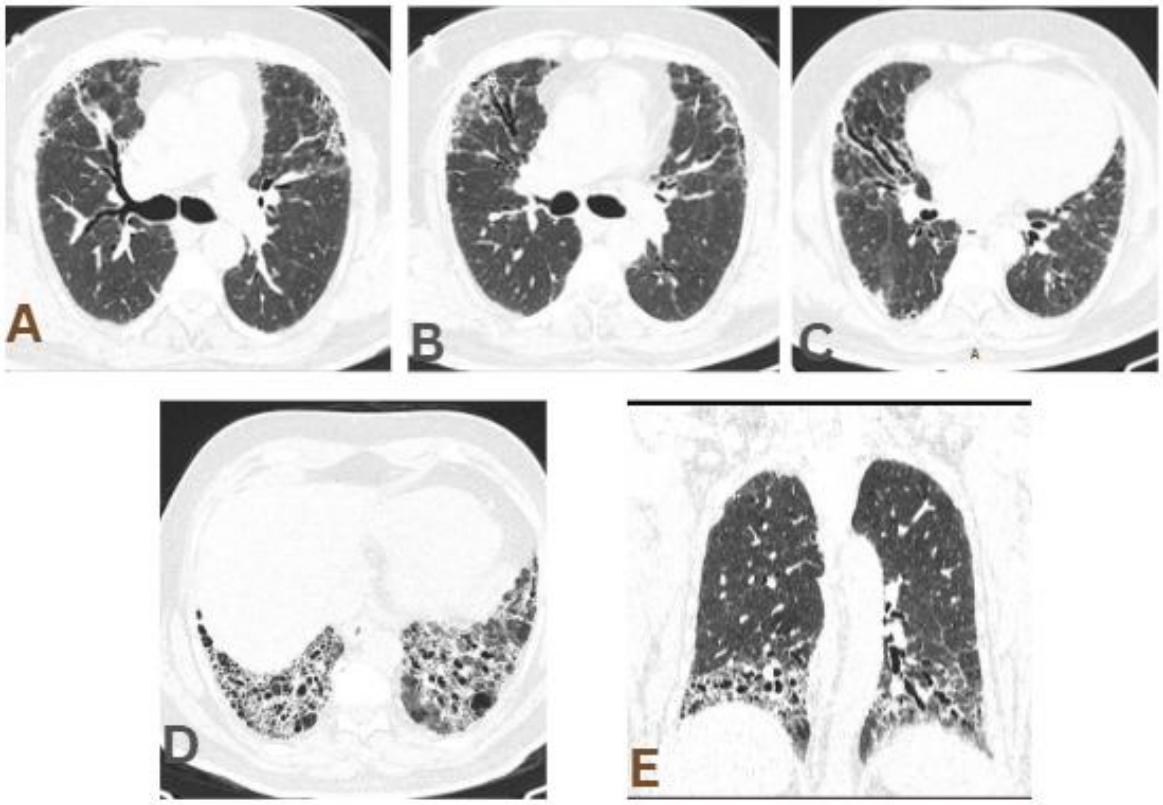

Figure 2. Representative HRCT features of fibrotic interstitial lung disease with annotated imaging findings
(A) *Axial high-resolution CT (HRCT) image demonstrating peripheral reticulation with early fibrotic changes,*
(B) *Bilateral reticular opacities with associated traction bronchiectasis,*
(C) *Subpleural fibrosis with architectural distortion and early honeycombing,*
(D) *Advanced basal-predominant honeycombing with clustered cystic airspace and surrounding fibrotic reticulation,*
(E) *Coronal HRCT image showing extensive bilateral subpleural fibrosis with honeycombing, consistent with a usual interstitial pneumonia (UIP) pattern*

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Table 1. Quantitative CT–derived ILD patterns and clinical significance

qCT pattern	Quantitative definition	Pathophysiologic correlate	Clinical significance
Ground-glass opacity	Percentage of lung volume with increased attenuation without distortion	Active inflammation	Disease activity, treatment response; correlates with KL-6
Reticulation	Volume fraction of linear opacities	Architectural remodelling	Disease extent and progression
Honeycombing	Volume of clustered cystic airspaces	Irreversible fibrosis, UIP pattern	Strong predictor of CPI, DLCO%, GAP stage, and mortality
Total fibrosis score	Composite of reticulation, honeycombing, traction bronchiectasis	Overall fibrotic burden	Improved reproducibility; correlates with FVC, DLCO, mortality

Quantitative CT metrics show consistent and clinically meaningful correlations with physiologic and clinical outcomes. Parameters such as normal lung volume and fibrotic lung volume differentiate survivors from non-survivors and serve as independent predictors of mortality. Fibrosis-related metrics, particularly honeycombing extent, demonstrate strong correlations with composite physiologic index (CPI) and diffusing capacity of the lung for carbon monoxide (DLCO). Additionally, CT-derived pattern extent correlates with serum biomarkers such as KL-6 and with hospitalization risk, supporting the role of qCT as a surrogate imaging biomarker of disease severity and progression, as shown in **Table 2**.

Overall, the integration of quantitative imaging biomarkers into clinical practice enhances the objectivity of ILD assessment, reduces interobserver variability, and enables more precise risk stratification and longitudinal disease monitoring.

Table 2. Relationship between quantitative CT metrics and physiologic and clinical outcomes

Outcome assessed	qCT parameter	Comparator	Key findings	Clinical implication
Survival	Normal lung volume (%)	Mortality	Lower in deceased vs survivors (p=0.001)	Independent predictor of 3-year mortality
Survival	Fibrotic lung volume (%)	Mortality	Higher in deceased vs survivors (p=0.011)	Risk stratification
Disease severity	Honeycombing extent	CPI, DLCO%	Highest correlation with CPI (r=0.612)	Best predictor of physiologic impairment
Disease activity	GGO, reticulation, honeycombing	Serum KL-6	Positive correlations	Imaging surrogate of inflammatory burden
Hospitalization risk	Reticulation + KL-6	Respiratory admission	AUC 0.810 (p<0.001)	Improved prediction of adverse outcomes

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6. Machine Learning And Deep Learning Approaches In Ild

Machine learning and deep learning techniques have substantially advanced quantitative CT analysis in ILD, enabling automated lung segmentation, pattern classification, fibrosis quantification, and outcome prediction. Convolutional neural network–based architectures such as U-Net variants, ResNet models, attention-based networks, and 3D convolutional models are most commonly used. These approaches improve detection accuracy, reduce observer variability, and support prognostic assessment and clinical trial endpoints. Several studies demonstrate strong diagnostic and prognostic performance of ML-based systems. Deep learning algorithms outperform visual assessment for non-invasive diagnosis of idiopathic pulmonary fibrosis, accurately identify UIP patterns in systemic sclerosis–ILD, and better distinguish patients with severe physiologic impairment in connective tissue disease associated ILD. These findings support the role of ML-driven qCT as a robust adjunct to expert interpretation as **Shown in Table 3**.

Table 3. Machine learning and deep learning applications in quantitative CT analysis of ILD

Study context	Algorithm / architecture	Task	Key performance results	Clinical relevance
IPF diagnosis	Deep learning CNN	ILD classification	AUC 0.87; sensitivity 0.67; specificity 0.90	Improves non-invasive IPF diagnosis
Systemic sclerosis–ILD	Deep learning HRCT model	UIP pattern detection	UIP probability associated with FVC decline (p=0.008) and reduced survival (p=0.001)	Prognostication and risk stratification
CTD-ILD	QZIP-ILD deep learning system	Fibrosis quantification	AUC 0.833 for FVC <70%, superior to visual scoring	Identifies severe physiologic impairment
General ILD	U-Net, ResNet, attention networks, 3D-CNN	Segmentation and pattern recognition	High accuracy and reproducibility	Standardized assessment and monitoring

7. Prognostic value, disease monitoring, and ILD subtype–specific insights

Quantitative CT offers objective and reproducible prognostic information across interstitial lung diseases by enabling standardized assessment of disease extent, progression, and survival risk. Baseline reductions in normal lung volume and increases in fibrotic lung volume are consistently associated with adverse outcomes, while longitudinal increases in ground-glass opacity and honeycombing reflect ongoing disease progression. Composite qCT metrics provide superior prognostic performance compared with individual parameters for predicting mortality and functional decline. Quantitative evaluation of pulmonary vascular parameters further enhances risk stratification, particularly in connective tissue disease–associated ILD, where vascular remodelling correlates with physiologic impairment. In idiopathic pulmonary fibrosis, quantification of the UIP pattern, especially honeycombing extent and pulmonary vessel volume, improves prognostic staging beyond conventional visual assessment. Subtype-specific applications extend to identifying high-risk phenotypes in rheumatoid arthritis–associated ILD and differentiating reversible from irreversible disease in hypersensitivity pneumonitis, underscoring the value of qCT in disease monitoring and prognostication as **Shown in Table 4.**

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Table 4. Prognostic value of quantitative CT metrics across ILD subtypes

ILD subtype	Key qCT metrics	Outcome predicted	Major findings	Clinical relevance
All ILD	Normal lung volume, fibrotic lung volume	Mortality	Lower normal lung volume and higher fibrosis predict worse survival	Baseline risk stratification
All ILD	GGO progression, honeycombing	Disease progression	Annual increases associated with FVC decline	Longitudinal monitoring
IPF	Honeycombing, pulmonary vessel volume (CALIPER)	Mortality	Independent predictors; improved staging systems	Prognostic staging, therapy monitoring
CTD-ILD	Disease extent, vascular parameters	Mortality, functional decline	Vascular remodeling correlates with GAP stage and PFTs	Enhanced prognostication
CTD-ILD	Deep learning qCT scores (QZIP-ILD)	Severe physiologic impairment	Higher AUC than visual scoring	Improved patient stratification
RA-ILD	Combined qCT and clinical staging	Survival	Identifies IPF-like phenotype with poor outcome	Risk stratification
HP	GGO, honeycombing	Reversibility vs fibrosis	GGO predicts reversibility; honeycombing irreversible	Treatment guidance

8. Interstitial Lung Abnormalities (Ilas): Emerging Applications

ILA Detection and Characterization

Interstitial lung abnormalities represent potential preclinical ILD, defined as abnormalities affecting greater than 5% of any lung zone (1). The challenge lies in accurate and consistent identification of ILA, given that its definition relies on a subjective threshold, making quantitative tools crucial for precise ILA evaluation.

Quantitative CT plays several important roles in ILA evaluation. Automated detection reduces visual subjectivity and enables quantification of minimal abnormalities. This capability predicts progression to clinical ILD and identifies at-risk populations for longitudinal monitoring. A study examining long-term follow-up of ILAs found that clinically significant ILD was subsequently diagnosed in approximately one-quarter of the screened population with ILAs (22). Emerging respiratory symptoms and progression of ILAs at follow-up chest CT were found to be predictors of clinically significant ILDs (odds ratio 5.56 for symptoms and 4.07 for progression) (22).

Subpleural fibrotic ILAs demonstrate higher progression risk. The combination of emerging respiratory symptoms plus ILA progression on imaging identifies patients at substantially increased risk for developing clinically significant interstitial lung disease requiring therapeutic intervention.

9. Technical standardization, measurement variability, and reproducibility

Quantitative CT is limited by challenges related to standardization of image acquisition, reconstruction, and analysis, which directly affect measurement reproducibility and inter-site comparability. Variability in reconstruction parameters, scanner vendors, and

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patient-related factors such as breathing effort and motion can substantially influence quantitative outputs. Although lung segmentation methods show generally high reliability, acquisition- and post-processing-related variability remains a key limitation, emphasizing the need for harmonized protocols.

Measurement precision has been evaluated in a multicentre same-day CT study of interstitial lung disease, in which identical protocols yielded narrow limits of agreement for absolute fibrosis extent (−0.9% to 1.0%). Quantitative CT improved readers' specificity for identifying fibrosis stability, supporting its clinical utility. For longitudinal monitoring, inadequate standardization can obscure true biological change and lead to misclassification of disease progression. Current evidence suggests that changes exceedingly approximately 5–10% in fibrosis extent are more likely to represent clinically meaningful progression, although thresholds may vary by disease subtype and technique.

Beyond technical factors, clinical implementation is constrained by governance issues, workflow integration, data management, and the need for transparent algorithms. Rigorous quality assurance strategies, including protocol harmonization, phantom validation, reproducibility testing, and explainable artificial intelligence, are essential to ensure reliable clinical adoption of quantitative CT **Shown in Table 5**.

Table 5. Technical standardization challenges and barriers to clinical implementation of quantitative CT in ILD

Domain	Key challenge	Impact on quantitative CT	Evidence / example	Recommended mitigation
Image acquisition	Variable reconstruction parameters	Increased measurement variability	Wider limits of agreement with protocol changes	Protocol harmonization
Scanner variability	Vendor and hardware differences	Reduced inter-site comparability	Attenuation differences across scanners	Harmonization algorithms, spectral CT
Patient-related factors	Breathing effort, motion, implants	Volume errors and segmentation artifacts	10–20% lung volume variability	Breath coaching, motion correction
Segmentation & features	Heterogeneous pipelines	Inconsistent feature reliability	Acquisition and post-processing effects	IBSI-compliant workflows
Clinical adoption	Governance and workflow barriers	Limited routine use	Lack of regulatory anchoring	Multicenter validation, workflow integration
Quality assurance	Insufficient validation	Reduced clinical confidence	Limited external testing	Phantom studies, reproducibility audits

10. Emerging Technologies And Future Directions

Photon-Counting Detector (PCD) CT

Latest CT technology promises enhanced quantification capabilities. A quantitative machine learning model analysed CT exams from patients who underwent same-day conventional and PCD-CT for suspected ILD (26). The study found that conventional and PCD-CT quantitative machine learning results had good to excellent concordance (concordance correlation coefficient greater than 0.8) for most features except total honeycombing, likely related to better PCD-CT honeycombing delineation.

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Overall, compared with conventional CT, PCD-CT had consistently more statistically significant correlation with pulmonary function test results for honeycombing features (26). The study concluded that even though most quantitative features were not impacted by the newer PCD-CT technology, model adjustment is necessary to optimize performance.

Photon-counting detector CT is inherently multi-energy, expands material decomposition capabilities, and improves spatial resolution and geometric quantification (8). The utility of virtual monoenergetic images to standardize CT numbers is particularly important, as virtual monoenergetic images can be the default image type in PCD-CT due to the full-time spectral nature of the technology.

Advanced Machine Learning Architectures

Emerging Capabilities:

Recent developments include transformer networks and vision transformers for improved pattern recognition, federated learning enabling multi-institutional model training without data sharing, and explainable AI techniques for clinical transparency (25). Self-supervised learning approaches reduce annotation burden, while transfer learning enables rapid deployment across institutions.

Clinical Translation:

Deep learning imaging biomarker research in ILD is currently undergoing accelerated development, driven by technological advances in image processing and analysis (27). Deep learning identifies patterns in high-dimensional data and maps them to segmentations or outcomes, which can be used to identify the imaging patterns that most accurately predict disease progression (4).

Machine-learning algorithms have demonstrated capability to identify ILD in at-risk populations, predict extent of fibrosis, correlate radiological abnormalities with lung function decline, and be used as endpoints in treatment trials (15). These advances exemplify how technology can improve care for people with ILD.

Multimodal Imaging Integration

PET/CT Radiomics:

Quantitative 18F-FDG PET-CT can assess presence and extent of interstitial lung disease in early severe diffuse cutaneous systemic sclerosis (28). A study found that 18F-FDG uptake was mainly increased in Dorso basal lung fields of patients with SSc-ILD compared to SSc without ILD and controls ($p=0.03$ and $p<0.001$, respectively). 18F-FDG uptake was higher in SSc patients with extensive ILD (greater than 20% versus less than 20%, $p=0.04$) and correlated with lower DLCO percentage (correlation -0.59, $p=0.02$) (28).

The results suggest the potential utility of 18F-FDG PET-CT in early detection of ILD progression and aiding in risk stratification by detecting metabolic activity in lungs of patients with early severe diffuse cutaneous SSc and ILD.

Novel Imaging Approaches:

Research into novel diagnostic techniques and targeted therapeutics in ILD is moving the field toward increased precision and improved patient outcomes (29). An array of molecular techniques, machine learning approaches, and other innovative methods are promising tools with potential to increase diagnostic accuracy.

11. Clinical Recommendations And Guidelines

Evidence-Based Recommendations

Based on current evidence, several recommendations emerge for clinical practice:

For Diagnostic Assessment:

Quantitative CT should complement but not replace visual expert assessment in diagnostic algorithms. Automated ILA detection is recommended for ILA-specific protocols. Pattern classification algorithms show strong accuracy when properly validated, though integration with multidisciplinary team discussion remains essential (30).

For Disease Monitoring:

Baseline qCT assessment is recommended for prognostication in IPF and CTD-ILD. Serial qCT monitoring at appropriate intervals for advanced disease provides objective tracking of disease evolution. Composite indices combining qCT with clinical parameters are superior to single parameters for comprehensive assessment (2).

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For Treatment Response:

Quantitative CT tracking of honeycombing, reticulation, and ground-glass opacity is recommended during antifibrotic trials. These metrics demonstrate greater sensitivity for detecting subtle changes compared to pulmonary function tests (5). Integration into clinical trial protocols enables more sensitive outcome detection and potentially smaller sample sizes.

For Research Applications:

Quantitative CT validation in prospective, multi-centre cohorts is mandatory before clinical adoption. Standardized protocols are essential for multi-institutional studies to ensure comparability of results. External validation on independent datasets is required to confirm algorithm generalizability (4).

Standardized Reporting Needs

The development of standardized reporting templates is essential for clinical implementation. Currently, heterogeneous and non-standardized reporting methods mean that direct comparison or meta-analysis of studies is not possible (2). Future efforts should focus on creating consensus-based reporting standards that include technical parameters, quantitative measurements, qualitative correlations, prognostic assessments, and comparison to prior studies when available.

12. Limitations Of Current Evidence

Study Design and Quality Issues

Identified Limitations:

The systematic review of quantitative CT in prognostication and disease monitoring of ILD identified that studies were limited by use of retrospective methodology without prospective validation and significant study attrition (2). Additionally, heterogeneous and non-standardized reporting methods meant that direct comparison or meta-analysis of studies was not possible.

Many investigations involve relatively small sample sizes, limiting statistical power. Male-predominant cohorts reduce generalizability to female populations. Follow-up duration varies widely across studies, making long-term prognostic assessments difficult to compare.

Methodological Issues

Algorithm variability represents a significant challenge. Different software platforms produce measurement differences, limiting cross-platform comparisons. Lack of standardization affects acquisition protocols, reconstruction methods, and analysis approaches. Limited external validation remains problematic, as most algorithms are validated only on development cohorts. Demographic biases persist with predominance of certain populations in most studies. Regulatory gaps exist for most commercial systems, delaying clinical adoption.

13. Discussion

Current State of Evidence

The body of evidence demonstrates that quantitative CT (qCT) has evolved into a robust and clinically valuable imaging tool in the assessment of interstitial lung diseases (ILDs). Compared with conventional visual interpretation, qCT provides objective, reproducible, and quantitative measurements of disease extent, thereby reducing interobserver variability and improving diagnostic consistency. Multiple studies have shown that qCT-derived biomarkers correlate strongly with pulmonary function parameters, including forced vital capacity (FVC) and diffusing capacity of the lung for carbon monoxide (DLCO), and are capable of predicting disease progression and mortality**.**

qCT enables precise quantification of key imaging features such as ground-glass opacity, reticulation, and honeycombing, facilitating standardized disease assessment. In particular, honeycombing extent and total fibrotic burden have emerged as strong predictors of adverse outcomes. Furthermore, qCT demonstrates greater sensitivity than pulmonary function tests in detecting subtle longitudinal changes, supporting its role in early disease detection and monitoring.

Clinical and Prognostic Implications

Quantitative CT provides significant prognostic value across a wide spectrum of ILD subtypes. In idiopathic pulmonary fibrosis (IPF), quantification of the usual interstitial pneumonia (UIP) pattern, particularly

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honeycombing extent and pulmonary vessel volume, enhances risk stratification beyond traditional visual scoring systems. In connective tissue disease–associated ILD, quantitative assessment of both parenchymal abnormalities and vascular remodeling correlates with disease severity, functional impairment, and survival outcomes.

Vascular-related parameters, including pulmonary vessel volume and density, have emerged as important complementary biomarkers. Changes in vascular structures reflect disease progression and may indicate the development of pulmonary hypertension. Integration of vascular and parenchymal metrics into composite models further improves prognostic accuracy and enables more comprehensive disease characterization.

In addition, qCT has demonstrated value in identifying subtype-specific patterns, such as distinguishing fibrotic from inflammatory phenotypes in hypersensitivity pneumonitis and identifying high-risk phenotypes in rheumatoid arthritis–associated ILD. These capabilities highlight the role of qCT in personalized risk stratification and clinical decision-making.

Role in Treatment Monitoring and Clinical Applications

Quantitative CT plays an increasingly important role in monitoring therapeutic response and guiding treatment strategies. By providing objective and sensitive measures of disease progression, qCT allows early detection of treatment effects that may not be apparent on pulmonary function testing. Changes in fibrotic patterns, including reticulation and honeycombing, can be quantitatively tracked over time, enabling more accurate assessment of disease stabilization or progression.

In clinical trials, qCT-derived biomarkers serve as reliable endpoints, offering improved sensitivity and reproducibility compared with traditional outcome measures. Integration of qCT with serum biomarkers, such as KL-6, further enhances the ability to assess disease activity and predict clinical outcomes. These multimodal approaches support the development of precision medicine strategies and facilitate identification of patient subgroups most likely to benefit from specific therapies.

Impact of Machine Learning and Technological Advances

The integration of machine learning (ML) and deep learning techniques has significantly expanded the capabilities of quantitative CT. Advanced algorithms enable automated lung segmentation, accurate pattern classification, and prediction of clinically meaningful outcomes. These approaches have demonstrated superior performance compared with traditional visual assessment, particularly in detecting subtle disease patterns and identifying high-risk patients.

Emerging technologies, such as photon-counting detector CT, further enhance spatial resolution and quantitative accuracy, offering improved delineation of fibrotic features. Additionally, advances in radiomics and multimodal imaging, including PET/CT, provide new opportunities for assessing disease activity and integrating structural and functional information.

Challenges and Unresolved Issues

Despite significant progress, several challenges limit the widespread clinical adoption of qCT. Lack of standardization in image acquisition, reconstruction protocols, and analysis methods remains a major barrier, leading to variability in quantitative measurements across institutions and platforms. Differences in scanner technology and post-processing pipelines further complicate cross-study comparisons and limit generalizability.

Algorithm transparency and interpretability also represent critical challenges. Many machine learning models function as “black boxes,” reducing clinician trust and hindering regulatory approval. Additionally, most studies are based on selected patient cohorts, limiting applicability to broader populations and early-stage disease.

Practical considerations, including workflow integration, data management, and regulatory frameworks, must also be addressed. Successful clinical implementation will require standardized protocols, robust external validation, and the development of explainable artificial intelligence models.

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14. Recommendations For Future Research

Advancement of quantitative CT (qCT) in interstitial lung disease (ILD) requires coordinated efforts in methodological standardization, technological innovation, and clinical validation. One of the foremost priorities is the development of standardized acquisition and reconstruction protocols across institutions to ensure reproducibility and comparability of quantitative measurements. Harmonization strategies, including calibration techniques and cross-vendor normalization algorithms, will be essential for enabling large-scale multi-centre studies and clinical implementation.

Future research should focus on prospective, longitudinal, multi-centre studies involving diverse patient populations to validate qCT-derived biomarkers for diagnosis, prognostication, and treatment monitoring. External validation of machine learning models on independent datasets remains critical to ensure generalizability and robustness. Additionally, the establishment of consensus-based reporting frameworks will facilitate uniform interpretation and integration of quantitative metrics into clinical workflows.

Emerging developments in artificial intelligence (AI) are expected to further enhance qCT capabilities. Explainable AI models will play a key role in improving transparency and clinician trust, while federated learning approaches will enable collaborative model development without compromising patient data privacy. Integration of deep learning with radiomics and clinical parameters will support the creation of comprehensive predictive models for disease progression and therapeutic response.

Technological innovations, including photon-counting detector CT, spectral imaging, and advanced reconstruction techniques, offer improved spatial resolution and more accurate tissue characterization, potentially reducing variability in quantitative analysis. Furthermore, the integration of multimodal imaging approaches, such as PET/CT and MRI, with qCT may provide complementary functional and metabolic information, enhancing disease characterization.

Finally, future efforts should emphasize clinical translation, including workflow integration, cost-effectiveness analysis, and regulatory approval pathways. The development of user-friendly software platforms and radiologist training programs will be essential for routine adoption. Ultimately, the convergence of quantitative imaging, artificial intelligence, and personalized medicine is expected to transform ILD management, enabling earlier diagnosis, improved risk stratification, and more targeted therapeutic interventions.

15. Conclusion

Quantitative CT has emerged as a powerful and objective imaging biomarker in interstitial lung disease, enabling precise and reproducible assessment of disease extent, severity, and progression. By overcoming the limitations of subjective visual interpretation, qCT provides clinically meaningful metrics that correlate strongly with pulmonary function, disease activity, and patient outcomes.

The integration of machine learning and advanced imaging technologies has further enhanced the diagnostic and prognostic capabilities of qCT, supporting its role in risk stratification, treatment monitoring, and clinical decision-making. Despite ongoing challenges related to standardization, reproducibility, and clinical implementation, continued advancements in technology and validation efforts are expected to facilitate its transition into routine clinical practice.

In the evolving landscape of ILD management, qCT holds significant promise as a cornerstone of precision medicine, enabling more accurate diagnosis, improved prognostication, and personalized therapeutic strategies that ultimately enhance patient care and outcomes.

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