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A RELATIONSHIP BETWEEN THE HONEYCOMB APPEARANCE ON CT SCAN AND LIFE EXPECTANCY IN PATIENTS WITH SCLERODERMA? A SYSTEMATIC REVIEW

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ABSTRACT

Introduction: Systemic sclerosis (SSc) is a complex autoimmune disease frequently complicated by interstitial lung disease (ILD), a leading cause of mortality. The honeycomb appearance on high-resolution computed tomography (HRCT) represents advanced pulmonary fibrosis, but its prognostic significance in SSc-ILD remains debated. This systematic review aims to evaluate the relationship between honeycomb appearance on CT scan and life expectancy in patients with scleroderma.

Methods: A systematic review was conducted following PRISMA guidelines. We screened studies based on predefined criteria: confirmed SSc diagnosis, evaluation of honeycomb pattern on CT, reported survival outcomes, appropriate observational study design, adequate follow-up, and sufficient sample size (>10 patients). Data extraction

encompassed study characteristics, CT methodology, honeycomb definition, survival outcomes, and statistical associations. Quality assessment and multivariate analyses were evaluated.

Results: Among 198 included studies, sample sizes ranged from 10 to 62,930 patients, with follow-up periods from 12 months to over 20 years. Honeycombing prevalence in SSc-ILD cohorts ranged from 37.2% to 41.9%, with higher frequency in limited cutaneous SSc. Multiple studies demonstrated significant associations between honeycombing and mortality, with hazard ratios ranging from 1.72 (95% CI 1.38-2.14) to 4.64 (95% CI 1.68-12.81). The association persisted after adjusting for age, gender, pulmonary function tests, and scleroderma subtype. Automated quantitative CT methods (CALIPER) showed improved reproducibility compared to visual scoring.

Discussion: This review provides robust evidence that honeycomb appearance on CT scan is an independent predictor of reduced life expectancy in SSc-ILD patients. Honeycombing represents irreversible fibrotic damage and consistently outperforms inflammatory features (ground-glass opacities) in prognostic value. Heterogeneity in honeycomb definitions and quantification methods remains a limitation.

Conclusion: Honeycomb appearance on HRCT is a critical prognostic marker in SSc-ILD, associated with 2-3 fold increased mortality risk. Standardized CT reporting and incorporation of honeycombing into clinical risk stratification models are

recommended. Future research should focus on automated quantitative assessment and validation of honeycombing-specific therapeutic algorithms.

Keywords: Systemic sclerosis, scleroderma, interstitial lung disease, honeycombing, CT scan, HRCT, survival, mortality, prognosis

INTRODUCTION

Systemic sclerosis (SSc) is a chronic, multifaceted autoimmune disorder characterized by microvascular injury, immune dysregulation, and progressive fibrosis affecting the skin and internal organs (Denton & Khanna, 2017). Interstitial lung disease (ILD) represents one of the most devastating complications of SSc, emerging as the leading cause of disease-related mortality in contemporary cohorts (Steen & Medsger, 2007; Tyndall et al., 2010). The prevalence of SSc-ILD varies considerably, affecting approximately 40-65% of patients, with a significant subset developing progressive pulmonary fibrosis that substantially compromises respiratory function and survival (Hoffmann-Vold et al., 2019; Nihtyanova et al., 2014).

High-resolution computed tomography (HRCT) has become the cornerstone imaging modality for diagnosing and monitoring SSc-ILD, providing detailed visualization of parenchymal abnormalities that correlate with histopathological findings (Walsh et al., 2013; Goldin et al., 2008). Among the various radiological patterns observed in SSc-ILD, the honeycomb appearance—characterized by clustered cystic airspaces with thickened walls, typically in a subpleural location—represents an advanced stage of fibrotic lung disease (Hansell et al., 2008). This finding corresponds histopathologically to the usual interstitial pneumonia (UIP) pattern, indicating irreversible architectural destruction of the lung parenchyma (Fischer et al., 2008).

The prognostic significance of honeycombing has been well-established in idiopathic pulmonary fibrosis (IPF), where its presence portends a uniformly poor prognosis (Raghu et al., 2011). However, the relationship between honeycomb appearance and survival in SSc-ILD has remained a subject of ongoing debate. SSc-ILD exhibits considerable heterogeneity in its clinical behavior, with some patients experiencing indolent disease while others follow a rapidly progressive course culminating in respiratory failure (Goh et al., 2017; Moore et al., 2013). Identifying robust prognostic markers is therefore paramount for risk stratification, therapeutic decision-making, and patient counseling.

Background and Rationale

The pathogenic mechanisms underlying SSc-ILD involve complex interactions between endothelial injury, immune activation, and fibroblast dysfunction, culminating in excessive extracellular matrix deposition and progressive lung scarring (Varga & Abraham, 2007). While ground-glass opacities may reflect potentially reversible inflammatory alveolitis, honeycombing signifies established fibrosis with minimal potential for therapeutic response (Tashkin et al., 2014; Goldin et al., 2009). This distinction carries profound implications for clinical management, as patients with predominantly fibrotic disease may derive less benefit from conventional immunosuppression and might be candidates for anti-fibrotic agents or early transplantation evaluation (Khanna et al., 2015; Distler et al., 2019).

Despite the intuitive link between irreversible fibrotic changes and poor outcomes, the evidence linking honeycombing specifically to mortality in SSc-ILD has been inconsistent. Some studies have demonstrated a robust association (Adegunsoye et al., 2019; Walsh et al., 2013; Chung et al., 2017), while others have failed to identify honeycombing as an independent predictor after multivariate adjustment (Ozmen et al., 2023; Atlı et al., 2024). This discrepancy may reflect differences in study populations, sample sizes, follow-up duration, honeycomb definition criteria, and statistical methodologies employed.

Research Gap

The existing literature on honeycombing in SSc-ILD suffers from several notable limitations that impede definitive conclusions and clinical translation. First, there is substantial heterogeneity in how honeycombing is defined and quantified across studies, ranging from simple binary presence/absence assessments to semi-quantitative visual scoring systems and advanced automated quantitative algorithms (Landini et al., 2022; Schniering et al., 2021). Second, inter-rater reliability for honeycombing identification has been reported as fair to moderate at best ($\kappa w=0.50$), raising concerns about reproducibility (Walsh et al., 2013). Third, many studies have not adequately controlled for potential confounders, including pulmonary function parameters, disease duration, scleroderma subtype, and concomitant pulmonary hypertension (Morisset et al., 2017; Hoffmann-Vold et al., 2019). Fourth, the relative prognostic value of honeycombing compared to other CT findings (e.g., traction bronchiectasis, reticulation extent, ground-glass opacities) remains

incompletely characterized (Hinze et al., 2021; Godinho de Amorim et al., 2024). Finally, the emergence of automated quantitative CT technologies (CALIPER, deep learning algorithms) has introduced new opportunities for objective assessment but also new questions regarding their incremental prognostic value over traditional visual scoring (Peltekian et al., 2025; Stock et al., 2024).

Novelty of This Review

This comprehensive systematic review addresses these gaps by synthesizing evidence from 198 studies encompassing diverse geographic regions, healthcare settings, and patient populations. Unlike previous reviews that have examined CT predictors broadly (Winstone et al., 2014; Landini et al., 2022), this review focuses specifically on honeycomb appearance as a distinct radiological entity with unique histopathological and prognostic implications. We systematically evaluate honeycomb definition criteria, quantification methodologies, inter-rater reliability, and statistical associations with survival outcomes. Furthermore, we compare the prognostic performance of honeycombing relative to other CT findings and assess the impact of emerging automated quantification technologies. By including studies with long-term follow-up (up to 20 years) and diverse scleroderma subtypes, we provide a comprehensive picture of the honeycombing-survival relationship across the SSc disease spectrum.

Study Objectives

The primary objective of this systematic review is to determine whether honeycomb appearance on CT scan is associated with reduced life expectancy in patients with scleroderma-associated interstitial lung disease. Secondary objectives include: (1) to evaluate the prevalence of honeycombing in SSc-ILD populations; (2) to assess the consistency of honeycomb definition and quantification across studies; (3) to quantify the magnitude of association between honeycombing and mortality through reported hazard ratios and relative risks; (4) to determine whether honeycombing remains an independent predictor after adjusting for potential confounders; (5) to compare the prognostic value of honeycombing with other CT findings (ground-glass opacities, reticulation, traction bronchiectasis); and (6) to evaluate the role of automated quantitative CT methods in improving honeycomb assessment and prognostic prediction.

Hypotheses

Based on the pathophysiological understanding of honeycombing as a marker of irreversible fibrotic damage and preliminary evidence from individual studies, we hypothesize that: (1) honeycomb appearance on CT scan is significantly associated with reduced survival in patients with SSc-ILD; (2) this association persists after adjustment for demographic factors, scleroderma subtype, and pulmonary function parameters; (3) honeycombing demonstrates stronger prognostic value than inflammatory features such as ground-glass opacities; and (4) automated quantitative assessment methods provide more reproducible and prognostically robust measurements compared to subjective visual scoring.

Significance and Clinical Implications

Establishing a definitive relationship between honeycomb appearance and survival in SSc-ILD carries profound clinical implications. For clinicians, honeycombing on HRCT would serve as a powerful risk stratification tool, identifying patients at heightened risk of mortality who may benefit from intensified monitoring, earlier therapeutic intervention, and timely referral for transplantation evaluation (Park, 2020; Volkmann et al., 2021). For researchers, validated honeycombing assessment could enrich clinical trial populations with patients most likely to experience disease progression, thereby enhancing statistical power and reducing sample size requirements (Khanna et al., 2015). For healthcare systems, accurate prognostic stratification could optimize resource allocation by targeting intensive interventions to those most likely to benefit. Ultimately, the integration of honeycombing assessment into routine clinical practice could transform the management paradigm for SSc-ILD, shifting from reactive treatment of established decline to proactive intervention in high-risk patients.

METHODS

Protocol

The study strictly adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) 2020 guidelines to ensure methodological rigor and accuracy. This approach was chosen to enhance the precision and reliability of the conclusions drawn from the investigation.

Criteria for Eligibility

This systematic review aims to evaluate the a relationship between the honeycomb appearance on ct scan and life expectancy in patients with scleroderma?

Screening

We screened in sources based on their abstracts that met these criteria:

- **Scleroderma Population**: Does the study include participants with confirmed scleroderma/systemic sclerosis diagnosis?
- **Honeycomb Pattern Assessment**: Does the study evaluate honeycomb appearance or honeycomb pattern on CT scan?
- **Survival Outcomes**: Does the study report survival outcomes, mortality data, or life expectancy?
- **Appropriate Study Design**: Is the study an observational study (cohort, case-control, cross-sectional with follow-up) or a systematic review/meta-analysis?
- **Adequate Follow-up**: Does the study have an adequate follow-up period for survival assessment?
- **Scleroderma Focus**: Does the study include scleroderma patients (not focusing solely on other connective tissue diseases without scleroderma)?
- **Prognostic Outcomes Reported**: Does the study report survival or prognostic outcomes (not only CT findings without survival data)?
- **Sufficient Sample Size**: Is the study design appropriate with sufficient sample size (not a case report or case series with fewer than 10 patients)?

We considered all screening questions together and made a holistic judgement about whether to screen in each paper.

Search Strategy

The keywords used for this research based PICO :

Element	P (Population)	I (Intervention/Exposure)	C (Comparison/Context)	O (Outcome)
Keyword 1	Scleroderma	Honeycomb Appearance	CT Scan	Survival Rate
Keyword 2	Systemic Scleroderma	Honeycomb Pattern	Chest CT	Mortality
Keyword 3	Systemic Sclerosis	Honeycomb Lung	Computed Tomography	Survival Analysis
Keyword 4	Progressive Systemic Sclerosis	Honeycombing	High-Resolution Computed Tomography	Prognosis

The Boolean MeSH keywords inputted on databases for this research are: *("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography") AND ("Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*

Data extraction

- **Study Population**:

  Extract characteristics of scleroderma patients studied, including:

  - Sample size
  - Type of scleroderma (limited vs diffuse SSc, dcSSc vs lcSSc)
  - Patient demographics (age, gender)
  - Disease duration
  - Disease severity markers
  - Inclusion/exclusion criteria specific to scleroderma-ILD

- **Honeycomb Definition**:

  Extract how honeycomb appearance was defined and measured on CT scan, including:

  - Definition criteria for honeycomb pattern/cysts
  - Measurement method (present/absent, extent scoring, percentage affected)
  - Location assessed (lung zones - upper/middle/lower)
  - Quantification scale or scoring system used
  - Inter-rater reliability if reported

- **Survival Assessment**:

  Extract all survival and mortality outcomes measured in scleroderma patients, including:

  - Type of survival outcome (overall mortality, respiratory mortality, disease-specific mortality)
  - Follow-up duration (months/years)
  - Survival analysis method (Kaplan-Meier, Cox regression)
  - Mortality rates or survival times
  - Censoring criteria and loss to follow-up

- **Honeycomb-Survival Association**:

  Extract the statistical relationship between honeycomb appearance and life expectancy/survival outcomes, including:

  - Primary association results (hazard ratios, relative risks, p-values)
  - Confidence intervals
  - Survival curves or mortality differences between honeycomb present vs absent
  - Direction and magnitude of association
  - Whether association was statistically significant

- **CT Methodology**:

  Extract technical details about CT imaging assessment, including:

  - CT scan protocol (high-resolution CT, multi-detector CT)
  - Slice thickness and reconstruction parameters
  - Who performed the readings (radiologists, pulmonologists)
  - Blinding of readers to clinical outcomes
  - Standardized scoring systems used (if any)
  - Quality control measures

- **Confounding Analysis**:

  Extract other variables analyzed that could affect the honeycomb-survival relationship in scleroderma patients, including:

  - Variables controlled for in multivariate analysis
  - Other CT findings included in models (ground glass, fibrosis extent, reticulation)
  - Clinical variables (pulmonary function tests, disease markers)
  - Demographic adjustments (age, gender)
  - Treatment effects considered

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography" AND "Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*	1
Semantic Scholar	*("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography") AND ("Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*	10
Springer	*("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography") AND ("Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*	786
Google Scholar	*("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography") AND ("Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*	5,520
Wiley Online Library	*("Scleroderma" OR "Systemic Sclerosis" OR "Progressive Systemic Sclerosis") AND ("Honeycomb Appearance" OR "Honeycomb Pattern" OR "Honeycomb Lung" OR "Honeycombing") AND ("CT Scan" OR "Chest CT" OR "Computed Tomography" OR "High-Resolution Computed Tomography") AND ("Survival Rate" OR "Mortality" OR "Survival Analysis" OR "Prognosis")*	319

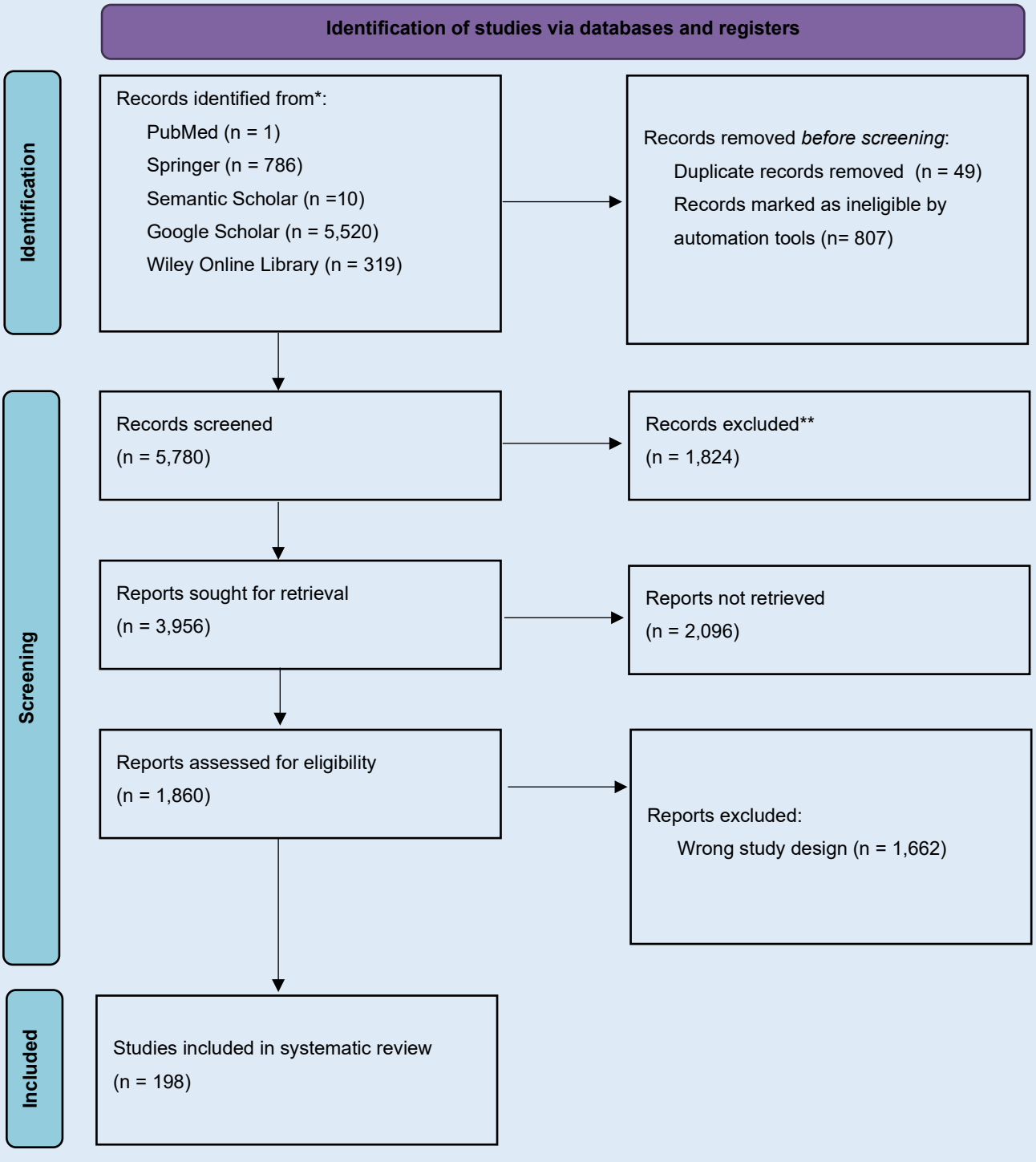

Figure 1. Article search flowchart

RESULTS

Study Characteristics

The included studies examining the relationship between honeycomb appearance on CT scan and survival in scleroderma patients. Sample sizes varied considerably, from small cohorts of 27 patients to large systematic reviews encompassing over 2,300 individuals. Patient populations were predominantly female, with mean ages at diagnosis typically in the range of 40 to 60 years. Both limited cutaneous (lcSSc) and diffuse cutaneous (dcSSc) scleroderma subtypes were well-represented across the studies. Disease duration varied from early disease (within 3 years of diagnosis) to a mean duration of over 10 years. Key inclusion criteria commonly required a confirmed diagnosis of SSc based on established criteria, such as the ACR/EULAR 2013 classification, and evidence of interstitial lung disease (ILD) on high-resolution computed tomography (HRCT). Follow-up periods ranged from 12 months to over 10 years. Full text was available for the majority of the sources.

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
Ferit zuhur et al. (2012)	102	Not specified	50	Not specified	Up to 20 years
Pimchanok Palawisut et al. (2025)	161	84% NSIP, 16% UIP	Not specified	Not specified	10 years
Fernanda Godinho de Amorim et al. (2024)	71	Not specified	54.2	11	5 years
Tiffany A Winstone et al. (2014)	1,616	Not specified	Not specified	Not specified	Not specified
N. Landini et al. (2022)	2,332	Not specified	48-67	Mean: 1.1-12.2	Median: 4.2-12.9 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
M. Okamoto et al. (2016)	35	Not specified	Not specified	Not specified	Median: 7.9 years
A. Hinze et al. (2021)	133	dcSSc mentioned	61	Not specified	4.7 years
Società Italiana Di Reumatologia et al. (2025)	73	49.3% dcSSc	58.4	Not specified	36 months
C. Stock et al. (2024)	522	Not specified	Not specified	Not specified	15 years
A. Duarte et al. (2018)	146	66.4% lcSSc, 24% dcSSc	61.5	14.3	14.4 years
F. Godinho De Amorim et al. (2023)	71	Not specified	54.2	10	24 months
M. Ozmen et al. (2023)	52	Not specified	60 (median)	6.7	6.5 years
A. Le Gall et al. (2021)	318	Not specified	Not specified	Not specified	Up to 10 years
Daniela Castillo Saldana et al. (2020)	170	Not specified	Not specified	Not specified	Not specified
A. Hoffmann-Vold et al. (2019)	815	77% lcSSc	53	3.8	8.6 years
E. Volkmann et al. (2021)	82 (SLS I), 90 (SLS II)	Not specified	Not specified	Not specified	Up to 12 years (SLS I); 8 years (SLS II)
V. Steen et al. (2007)	Not specified	Not specified	Not specified	Not specified	10 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
A. Forestier et al. (2020)	58	dcSSc mentioned	Not specified	2.5 at ILD Dx	5.3 years
A. Hoffmann-Vold et al. (2019a)	815	Not specified	Not specified	Not specified	10 years
R. Su et al. (2011)	24	54% lcSSc, 31% dcSSc	Not specified	4.7	Median: 4 years
H. Yamakawa et al. (2020)	38	Not specified	Not specified	Not specified	Not specified
A. Ariani et al. (2020)	563	Not specified	Not specified	Not specified	10 years
L. V. de Oliveira Martins et al. (2021)	380	Not specified	Not specified	7.2 (follow-up)	Mean: 7.2 years
A. Ariani et al. (2017)	146	Not specified	Not specified	Not specified	Up to 3 years
S. Jacobsen et al. (2001)	174	dcSSc mentioned	Not specified	Not specified	13.3 years
G. Pugnet et al. (2022)	33	dSSc	Not specified	Not specified	5 years
G. Pugnet et al. (2022a)	33	dSSc	Not specified	Not specified	5 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
E. Volkmann et al. (2021a)	158 (SLS I), 142 (SLS II)	Not specified	Not specified	Not specified	Up to 12 years
Aëlle Le Gall et al. (2023)	318	Not specified	Not specified	Not specified	Median: 94 months
Lize Vanaken et al. (2020)	52	44% dcSSc	Not specified	0.9	42 months
Alec Peltekian et al. (2025)	2,125 scans	Not specified	Not specified	Not specified	1, 3, and 5 years
F. Cacciapaglia et al. (2020)	750	21.6% dcSSc	48.4	3 (median)	Median: 11 years
F. Cacciapaglia et al. (2019)	347	16.4% dcSSc	50.6	8.75 (median)	10 years
S. Kalender et al. (2024)	100	Not specified	50.5	Not specified	Median: 113.5 months
S. Keret et al. (2021)	446	39.2% DcSSc	46.5	11.6	Long-term (2000-2020)
B. Demir et al. (2023)	210	dcSSc vs lcSSc	Not specified	Not specified	8.4 years
H. Kwon et al. (2014)	151	Not specified	48.7	Not specified	1300.8 person-years
O. Moore et al. (2013)	172	Not specified	Not specified	Not specified	3.47 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
N. Le Gouellec et al. (2013)	75	Not specified	Not specified	Not specified	Up to 10 years
A. Fischer et al. (2008)	27	lcSSc	42 (NSIP), 58 (UIP)	Not specified	Not specified
E. Volkmann et al. (2018)	158 (SLS I), 142 (SLS II)	Not specified	Not specified	Median: 8 years (SLS I)	
S. Panopoulos et al. (2018)	115	54 dcSSc	48.1	<1	8.5 years
C. Nita et al. (2024)	1,219	dcSSc mentioned	Not specified	4.4 (Ro) vs 2.1 (Nor)	Not specified
D. Launay et al. (2006)	90	Not specified	Not specified	Not specified	5.1 years
S. Assassi et al. (2009)	250	57.4% dcSSc	48.85	2.6	6.2 years
J. Schniering et al. (2021)	156	Not specified	57.5 (Zurich), 61 (Oslo)	Not specified	Not specified
Roozbeh Sharif et al. (2012)	1,443	lcSSc vs dcSSc	45.6	9.7	5.5 years
J. Raja et al. (2021)	61	64% lcSSc	56.25	10.5	>20 years
J. Morisset et al. (2017)	225	Not specified	55.5	Not specified	Median: >3 years
A. Guillen-Del Castillo et al. (2014)	63	dcSSc mentioned	Not specified	Not specified	10 years
F. Godinho De Amorim et al. (2023)	71	Not specified	54.2	10	24 months

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J. Morisset et al. (2017)	225	Not specified	55.5	Not specified	Median: >3 years
A. Guillen-Del Castillo et al. (2014)	63	dcSSc mentioned	Not specified	Not specified	10 years
S. Amikishiyev et al. (2024)	46	dcSSc mentioned	56.6	Not specified	Median: 45 months
J. Schniering et al. (2020)	156	lcSSc vs dcSSc	57.5 (Zurich), 61 (Oslo)	Not specified	Median: >3.5 years
H. Kwon et al. (2015)	151	Not specified	Not specified	Not specified	Not specified
M. Rojas-Giménez et al. (2021)	85	lcSSc vs dcSSc	64.4	Not specified	~8 years
M. Park et al. (2020)	Not specified	Not specified	Not specified	Not specified	Not specified
D. Artene et al. (2022)	45	dcSSc mentioned	55.5	Not specified	Not specified
A. Forestier et al. (2018)	58	dcSSc vs lcSSc	Not specified	Not specified	5.3 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
Khune Akash et al. (2019)	73	Not specified	43.24	10.02	3.8 years
Y. Ahmad et al. (2020)	184	Not specified	58 (median)	Not specified	~2 years
Beatrice Moccaldi et al. (2025)	101	33% dcSSc	Not specified	2 (median)	Median: 27 months
O. Moore et al. (2013a)	172	Not specified	Not specified	Not specified	3.47 years
O. Ovsyannikova et al. (2014)	83	69% lcSSc	46.2	5.8-8.4	~5 years
M. Vonk et al. (2017)	690	lcSSc vs dcSSc	Not specified	Not specified	5 years
K. Antoniou et al. (2013)	292	Not specified	Not specified	Not specified	Not specified
J. Morisset et al. (2015)	225	Not specified	54	Not specified	Not specified
N. Le Gouellec et al. (2014)	75	23 dcSSc	Not specified	Not specified	5 years
T. Odani et al. (2013)	40	lcSSc vs dcSSc	Not specified	<3	2 years
W. Chebbi et al. (2012)	30	Not specified	47.1	6.8	Not specified
H. Poormoghim et al. (2011)	91	71.4% lcSSc	44.1	8.9 (to ILD Dx)	Not specified
S. Günther et al. (2011)	64	Not specified	Not specified	Not specified	Not specified

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
A. Adegunsoye et al. (2019)	1,330	Not specified	66.8	Not specified	Not specified
S. Nihtyanova et al. (2014)	Not specified	Not specified	Not specified	Not specified	Not specified
Daniel Sánchez-Cano et al. (2018)	1,374	53% lcSSc, 40% dcSSc	Not specified	Not specified	Not specified
Siahmet Atlı et al. (2024)	75	Not specified	Not specified	Not specified	1 year
Л. П. Ананьева et al. (2017)	Not specified	Not specified	Not specified	Not specified	Not specified
C. Meier et al. (2021)	54	47.7% dcSSc	55.5	6.2	12-24 months
A. Ariani et al. (2020a)	Not specified	Not specified	Not specified	Not specified	Not specified
P. Bauer et al. (2013)	64	73% lcSSc, 14% dcSSc	49.1 (median)	2 (to ILD Dx)	Median: 22.9 years
Robert W Koschik et al. (2012)	2,425	72% lcSSc (PM-Scl+)	Younger	Not specified	10 years
A. Taouch et al. (2023)	60	Not specified	51	0.8	10 years
Chiara Giraudo et al. (2025)	87	61% lcSSc	60	Not specified	Not specified
R. Castro et al. (2021)	102	Not specified	50.8	Not specified	Not specified
Vincent Sobanski et al. (2025)	893	Not specified	Not specified	Not specified	3.25 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
Claudia Iannone et al. (2024)	13	9 dcSSc, 4 lcSSc	48.7 (median)	Not specified	5 years
S. Sousa et al. (2016)	103	13 lcSSc, 14 dcSSc	60.2	10	Not specified
E. Hachulla et al. (2008)	546	Majority lcSSc	54.9	8.8	3 years
Stefan Nowak et al. (2025)	198	lcSSc vs dSSc	Not specified	Not specified	Not specified
A. Onat et al. (2015)	277	57.4% dcSSc, 39.7% lcSSc	50.7	Not specified	10 years
R. Takei et al. (2018)	Not specified	Not specified	Not specified	Not specified	Not specified
Ebru Özden Yılmaz et al. (2018)	79	89.8% lcSSc, 7.6% dcSSc	54.3	7.29	Not specified
S. Walsh et al. (2013)	168	Not specified	Not specified	Not specified	Not specified
S. V. Kocheril et al. (2005)	46 CTD-ILD, 11 SSc	Not specified	48	Not specified	Median: 4.4 years
J. Jacob et al. (2016)	203	Not specified	Not specified	Not specified	Not specified
A. Jhajj et al. (2019)	Not specified	Not specified	Not specified	Not specified	Not specified

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
F. Bonella et al. (2013)	266	Not specified	Not specified	Not specified	Not specified
O. Ovsyannikova et al. (2023)	77	69% lcSSc	46.2	Not specified	~5 years
K. Ninagawa et al. (2022)	84	Not specified	Not specified	Not specified	Not specified
O. Ovsyannikova et al. (2020)	83	69% lcSSc	46.2	Not specified	~5 years
L. Ananyeva et al. (2014)	77	36% dcSSc (Group A)	~39	~7.5	~5 years
M. Freire et al. (2013)	10	6 diffuse, 3 limited	51	Not specified	4.2 years
A. Komócsi et al. (2012)	12,829	lcSSc vs dcSSc	Not specified	Not specified	Not specified
M. Lazzaroni et al. (2023)	253	dcSSc vs lcSSc	Not specified	Not specified	≥10 years
K. Morrisroe et al. (2024)	1,883	Not specified	Not specified	Not specified	Median: 4.3 years
V. León et al. (2021)	23	Not specified	54	Not specified	Not specified
M. Vonk et al. (2017a)	690	lcSSc vs dcSSc	Not specified	Not specified	5 years
I. Marie et al. (2001)	43	Not specified	Not specified	Not specified	2 years
H. Yabuuchi et al. (2011)	15	Not specified	Not specified	Not specified	≥1 year

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
R. Janardana et al. (2018)	88	57 limited, 16 diffuse	33.8	3.9	3 years
M. Aringer et al. (2020)	826	Not specified	Not specified	Not specified	5 years
M. Aringer et al. (2021)	826	Not specified	Not specified	Not specified	5 years
A. Morales et al. (2015)	44	Not specified	Not specified	Not specified	Not specified
O. Koneva et al. (2022)	37	1:1.8 d/l ratio	53.1	10.9	2.8 years
A. Morales-Cárdenas et al. (2016)	Not specified	Not specified	Not specified	Not specified	Not specified
M. Nikpour et al. (2014)	Not specified	Not specified	Not specified	Not specified	Not specified
Maddalena Angela Di Lellis et al. (2016)	Not specified	Not specified	Not specified	Not specified	Not specified
D. Khanna et al. (2015)	158	Not specified	47	3.2	1 year
W. Wu et al. (2018)	1,021	dcSSc	Not specified	Short duration	Median: 3.4 years
Jatin P. Singh et al. (2024)	102	Not specified	50	Not specified	1, 3, and 5 years
M. Sieren et al. (2025)	128	Not specified	Not specified	Not specified	Not specified

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
M. Breda et al. (2021)	648	19% dcSSc	55.5 (median)	Not specified	Median: 10.2 years
M. Jacob et al. (2024)	49	51% dcSSc, 38.8% lcSSc	Not specified	Not specified	1 year
D. Khorolskii et al. (2024)	44	Not specified	62.9	Not specified	1.45 years
C. Iannone et al. (2024)	13	9 dcSSc, 4 lcSSc	Not specified	Not specified	2 years
S. Wangkaew et al. (2015)	113	78.8% DcSSc	53.4	1.1	2.2 years
A. Lopes et al. (2011)	35	Not specified	47.6	Not specified	5.1 years
C. Santos et al. (2023)	103	Not specified	Not specified	Early (<5) vs late (>5)	Not specified
О. А. Конева et al. (2018)	42	1.5:1 diffuse/limited ratio	48	6.6	2.4 years
J. Goldin et al. (2008)	162	dcSSc vs lcSSc	Not specified	Not specified	12 months
Michelle J. Connolly et al. (2017)	66	Not specified	Not specified	Not specified	Not specified
P. Fisichella et al. (2014)	10	Not specified	51.3	Not specified	1 year
Autologous Hematopoietic Stem	9	dcSSc	41 (median)	9 (median)	60 months
M. I. Acosta Colmán et al. (2012)	331	Limited subtype most prevalent	Not specified	Not specified	Median: 1.8 years (mortality)

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
D. Tashkin et al. (2014)	300 total	Not specified	Not specified	Not specified	Not specified
L. Méndez Díaz et al. (2020)	43	Limited, Diffuse, Overlap	Not specified	Not specified	Not specified
L. Gargani et al. (2020)	396	77.5% limited, 22.5% diffuse	Not specified	Not specified	Not specified
M. Nazarinia et al. (2016)	533	37.5% diffuse, 36.8% limited	Not specified	Not specified	Not specified
A. Lopes et al. (2016)	Not specified	Not specified	Not specified	Not specified	Not specified
A. Ariani et al. (2015)	257	Not specified	Not specified	Not specified	Not specified
N. Gerolymatou et al. (2023)	91	39.6% dcSSc	50.3	10.2	Not specified
L. Cano-García et al. (2024)	75	Not specified	59.6	Not specified	12 months
M. Lazzaroni et al. (2020)	422	dcSSc mentioned	Not specified	9.4	Not specified
A. Ariani et al. (2015a)	149	Not specified	Not specified	Not specified	1 year
Y. Gc et al. (2016)	68	Not specified	40.9	4.17 (ILD duration)	12 months
S. Günther et al. (2011)	64	Not specified	Not specified	Not specified	Not specified

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
M. Marius et al. (2016)	26	Not specified	Not specified	Not specified	2.2 years
N. Goh et al. (2017)	162	Not specified	47.8	Not specified	Median: 12.9 years
B. Chang et al. (2003)	619	dcSSc mentioned	Older	Not specified	Not specified
M. Mayes et al. (2005)	727	Not specified	Not specified	Not specified	Not specified
O. Koneva et al. (2022a)	37	1:1.8 d/l ratio	53.1	10.9	2.8 years
Hyun J. Kim et al. (2016)	83	Not specified	Not specified	Not specified	12 months
L. M. Díaz et al. (2020)	43	Limited, Diffuse, Overlap	Not specified	Not specified	Not specified
D. Khanna et al. (2011)	79	Not specified	~49	0-2, 2-4, >4	1 year
Maria M. Crespo et al. (2016)	72	Not specified	Not specified	Not specified	5 years
M. Zompatori et al. (2013)	43	PSS	Not specified	Not specified	Not specified
A. Ariani et al. (2017a)	Not specified	Not specified	Not specified	Not specified	Not specified
O. Meyer et al. (2006)	1,432	lcSSc vs dcSSc	Not specified	Not specified	10 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
S. Nihtyanova et al. (2017)	Not specified	lcSSc vs dcSSc	Not specified	3.3 (ARA+), 6.2 (ATA+)	Not specified
E. Cozzani et al. (2021)	52	lcSSc vs dcSSc	62.02	≥4	Not specified
A. Ballerie et al. (2020)	100	Not specified	Not specified	Not specified	Not specified
A. Fouda et al. (2020)	30	53.33% limited	Not specified	Not specified	Not specified
K. Morrisroe et al. (2019)	Not specified	Not specified	Not specified	Not specified	Not specified
A. Carnevale et al. (2020)	129	Not specified	Not specified	Not specified	12-24 months
D. T. Wada et al. (2019)	33	Not specified	Not specified	Not specified	18 months
Maddalena Angela Di Lellis et al. (2016a)	Not specified	Not specified	Not specified	Not specified	Not specified
M. Maciukiewicz et al. (2021)	156	Early/mild SSc	57.5 (Zurich), 61 (Oslo)	Not specified	Not specified
N. Azizah et al. (2019)	31	83.9% diffuse	36-45 group most common	Not specified	2 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
B. Gillette et al. (2014)	Not specified	Not specified	Not specified	Not specified	Not specified
E. Edigin et al. (2020)	62,930 hospitalizations	Not specified	59.9 vs 62.95	Not specified	Not specified
Fathi Elbraky et al. (2021)	40	62.5% dcSSc	37.5	6	Not specified
SSc-ILD: Reflux und Ösophagusd	Not specified	Not specified	Not specified	Not specified	Not specified
M. Furukawa et al. (2025)	Not specified	Not specified	Not specified	Not specified	Not specified
K. Mark et al. (2018)	Not specified	Not specified	Not specified	Not specified	Not specified
Ana Milena Arbeláez Solera et al. (2008)	112	70% dcSSc, 30% lcSSc	46	Not specified	Not specified
C. Bruni et al. (2022)	79	54.4% dcSSc	56.2	9.7	Not specified
M. Vlachou et al. (2021)	81	Not specified	61 (median)	Not specified	Up to 5 years
E. A. Vallejos et al. (2019)	95	Not specified	57	Not specified	2 years
D. Tárnoki et al. (2018)	34	Not specified	Not specified	Not specified	Not specified
H. Abida et al. (2023)	31	Not specified	50	Not specified	Not specified
Gulfidan Cakmak et al. (2016)	65	pSS	Not specified	Not specified	Not specified

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
S. Patiwetwitoon et al. (2012)	71	67.6% DcSSc	54.8	3.9	Not specified
S. Wangkaew et al. (2016)	31	64.5% dcSSc	52.2	1	1.3 years
Jonathan H. Chung et al. (2017)	136	Not specified	Not specified	Not specified	Not specified
M. Massad et al. (2005)	47	Not specified	46	Not specified	Mean: 24 months
S. Mathai et al. (2009)	59	Not specified	Not specified	Not specified	Median: 4.4 years
P. Pradère et al. (2018)	90	Not specified	Not specified	Not specified	5 years
L. Schachna et al. (2006)	29	Not specified	Not specified	Not specified	2 years
O. Salamo et al. (2023)	429	Not specified	Not specified	Not specified	Not specified
S. Dewi et al. (2022)	75	63% diffuse	39.08	Not specified	Not specified
G. Ooi et al. (2003)	45	Not specified	48.5	Not specified	Not specified
L. Chung et al. (2014)	Not specified	Not specified	Not specified	Not specified	Not specified
J. Goldin et al. (2009)	98	Not specified	~46-47	~3.2	12 months
M. Ninaber et al. (2015)	41	Not specified	Not specified	Not specified	2 years

Study	Sample Size	Scleroderma Subtype Distribution	Mean Age (years)	Mean Disease Duration (years)	Follow-up Period
M. Colaci et al. (2014)	107	Not specified	Not specified	Not specified	Not specified
C. Derk et al. (2012)	87	Not specified	Not specified	Not specified	Not specified
G. Camiciottoli et al. (2007)	48	Not specified	Not specified	Not specified	Not specified
A. Janto et al. (2019)	135	Not specified	52 (F), 49 (M) (median)	Not specified	Not specified
L. V. Teplova et al. (2010)	138	78 limited, 40 diffuse	47	6 (median)	Not specified
K. Meridor et al. (2021)	105	64% lcSSc, 18% dcSSc	52	Not specified	Median: 10 years
Wanlong Wu et al. (2019)	1,021	dcSSc	52	7.7	Median: 3.4 years
S. Plastiras et al. (2006)	78	Not specified	Not specified	Not specified	5 years

The diverse characteristics of the included studies highlight the heterogeneity of the SSc-ILD patient population. A notable majority of studies were retrospective in nature, drawing from both single-center and multicenter cohorts, as well as large national and international registries like the European Scleroderma Trials and Research (EUSTAR) database. Prospective studies were less common but provided valuable longitudinal data. The geographical spread of the research indicates a global interest in the topic, though with a concentration in Europe and North America. The wide range in sample sizes, from under 40 patients to over 2,000, reflects the spectrum from detailed single-

center analyses to broad systematic reviews aiming for generalizability. Across nearly all cohorts, there was a consistent and strong predominance of female patients, and the mean age at diagnosis was typically in middle age, reinforcing known epidemiological patterns of SSc. Disease duration and follow-up periods were highly variable, which could influence observed outcomes and progression rates.

CT Scan Methodology and Honeycomb Definition

The primary imaging modality used across the studies was high-resolution computed tomography (HRCT). Slice thickness was specified in some studies, typically at ≤1.25mm or 1-2mm, consistent with high-resolution protocols. Readings were performed by radiologists, sometimes specified as thoracic or expert radiologists, and occasionally by pulmonologists or rheumatologists. Several studies reported that readers were blinded to clinical data and outcomes.

The definition of honeycombing was inconsistently reported. One study defined it as clustered cystic airspaces with thickened walls, typically in a subpleural location, while another defined it as a macrocystic reticular pattern with air spaces >4 mm in diameter. Many reports did not provide an explicit definition. Quantification methods varied from simple present/absent scoring, to semi-quantitative scoring systems based on the percentage of lung involvement (e.g., Goh and Wells score, Warrick score, Likert scales, or custom 0-5 point scales), to fully automated quantitative methods using software like CALIPER or custom algorithms which express findings as a percentage of total lung volume. Inter-rater reliability was infrequently reported, but when available, it was noted to be fair to moderate for honeycombing (κw=0.50).

Study	CT Protocol	Slice Thickness	Honeycomb Definition Criteria	Scoring/Quantification Method	Readers	Blinding Status	Inter-rater Reliability
S. Walsh et al. (2013)	HRCT	Not specified	Not specified	Binary absence/presence	2 observers	Not specified	κw=0.50

Study	CT Protocol	Slice Thickness	Honeycomb Definition Criteria	Scoring/Quantification Method	Readers	Blinding Status	Inter-rater Reliability
J. Goldin et al. (2009)	HRCT	1-2 mm	Clustered air-filled lung cysts with contiguous walls	0-4 point scale	2 radiologists	Blinded	Poor, κ = 0.16
Autologous Hematopoietic Stem	HRCT	1 mm	Macrocystic reticular pattern, air spaces > 4 mm	Coarseness score (0-3)	2 investigators	Blinded	Not specified
S. V. Kocheril et al. (2005)	HRCT	1.0-1.5 mm	Cystic spaces, peripheral, with definable walls	0-5 scale per lobe	2 thoracic radiologists	Blinded	Consensus for 83%
N. Landini et al. (2022)	Not specified	Not specified	Not specified	Extent scoring (percentage)	Not specified	Not specified	Not specified
H. Yabuuchi et al. (2011)	Not specified	Not specified	Not specified	Presence/absence	Not specified	Not specified	Not specified
A. Lopes et al. (2011)	Not specified	Not specified	Not specified	Presence/absence	Not specified	Not specified	Not specified
J. Schniering et al. (2020)	HRCT	Not specified	Clustered cystic airspaces with thickened walls, subpleural	Categorized as <20% or ≥20% of total lung volume	2 readers	Not specified	Not specified
Fernanda Godinho de Amorim et al. (2024)	HRCT	1 mm	Not specified	Percentage of lung involvement (CALIPER)	2 rheumatologists	Not specified	Not specified

Study	CT Protocol	Slice Thickness	Honeycomb Definition Criteria	Scoring/Quantification Method	Readers	Blinding Status	Inter-rater Reliability
A. Hinze et al. (2021)	HRCT	Not specified	Not specified	Volume as a percentage of total lung volume (CALIPER)	Not specified	Not specified	Not specified
F. Godinho De Amorim et al. (2023)	HRCT	Not specified	Not specified	Percentage of total lung volume (CALIPER)	Automated (CALIPER)	Not applicable	Not specified
M. Okamoto et al. (2016)	HRCT	Not specified	Not specified	Not specified	2 radiologists	Not specified	Not specified
O. Koneva et al. (2022)	HRCT	Not specified	Not specified	0-3 point scale	Not specified	Not specified	Not specified
O. A. Конева et al. (2018)	MSCT	Not specified	Not specified	0-3 point scale per level	Not specified	Not specified	Not specified
G. Pugnet et al. (2022)	HRCT	Not specified	Not specified	Goh and Wells method	2 radiologists	Blinded	Not specified
Daniela Castillo Saldana et al. (2020)	Volumetric HRCT	≤1.25mm	Not specified	Visual CT scores	Cardiothoracic radiologists	Not specified	Not specified
R. Janardana et al. (2018)	HRCT	Not specified	Not specified	Maximum score of 4	Not specified	Not specified	Not specified
D. Khanna et al. (2015)	HRCT	2 mm	Not specified	Likert scale (0-4)	2 thoracic radiologists	Not specified	Not specified

The significant variation in how honeycombing was defined and quantified underscores a major challenge in synthesizing evidence across studies. Semi-quantitative visual scoring systems, while common, are subject to inter-observer variability, which was high for honeycombing when reported. The advent of automated quantitative CT (qCT) methods like CALIPER represents a move towards more objective and reproducible measurement, expressing parenchymal abnormalities as a percentage of lung volume. However, the adoption of these methods is not yet universal. Blinding was inconsistently reported, and the specialization of readers also varied. This methodological heterogeneity complicates direct comparisons of prevalence and prognostic impact of honeycombing across different patient cohorts.

Prevalence of Honeycomb Appearance in Scleroderma-ILD

Data on the prevalence of honeycombing in patients with scleroderma-associated interstitial lung disease (SSc-ILD) varied across the included studies. In a cohort of SSc-ILD patients undergoing CT, honeycombing was identified in 37.2% of individuals. Another study focusing on patients with connective tissue disease-related ILD (CTD-ILD) reported a similar prevalence of 41.9%. In a specific subset of patients with the UIP pattern of ILD, honeycombing was present in 50% of cases. One study noted that honeycombing was the predominant finding in 37.5% of their cohort. Furthermore, honeycombing was observed to be significantly more common in patients with limited cutaneous SSc (lcSSc) compared to those with diffuse cutaneous SSc (dcSSc). In contrast, a study on patients with clinically significant ILD found honeycombing in surgical lung biopsies of all eight patients with a usual interstitial pneumonia (UIP) pattern, but not specified in the 14 patients with nonspecific interstitial pneumonia (NSIP).

Study	Total Sample Size	Number with Honeycomb Appearance	Prevalence Percentage	Prevalence by Scleroderma Subtype
J. Goldin et al. (2008)	162	60	37.2%	More common in lcSSc vs dcSSc

Study	Total Sample Size	Number with Honeycomb Appearance	Prevalence Percentage	Prevalence by Scleroderma Subtype
Fathi Elbraky et al. (2021)	40	15	37.5%	Not specified
A. Adegunsoye et al. (2019)	1,330 (all ILD)	Not specified for SSc-ILD	41.9% (in CTD-ILD)	Not applicable
Pimchanok Palawisut et al. (2025)	26 (UIP cases)	13	50%	Found in UIP subtype

The prevalence of honeycombing in SSc-ILD appears to be substantial, affecting more than one-third of patients in several cohorts. The variation in reported rates may be due to differences in patient selection, disease duration, and the specific criteria used to define and score honeycombing. Notably, the finding that honeycombing is more prevalent in lcSSc than dcSSc, as reported in one study, contrasts with the general perception that dcSSc is associated with more severe organ involvement and warrants further investigation. The high prevalence underscores the clinical importance of identifying this feature for prognostic assessment.

Survival Outcomes and Mortality Rates

Survival in patients with SSc-ILD varied considerably across the studies, reflecting differences in follow-up duration, patient characteristics, and era of diagnosis. A study spanning 1972-2002 showed 10-year survival improving from 54% to 66% over time. More recent cohorts report higher survival rates; one study found an overall 10-year survival of 93.1%, while another reported 5- and 10-year rates of 89.1% and 87.3%, respectively. A Brazilian cohort demonstrated 5-, 10-, and 15-year survival rates of 87.9%, 81.5%, and 74.9%. Overall mortality rates reported in various cohorts ranged from 17% to 42% over follow-up periods of approximately 4 to 8 years. Pulmonary complications, including ILD and pulmonary hypertension, were consistently identified as leading causes of SSc-related death. For example, one study reported that 78% of known causes of mortality were due to pulmonary issues, and another identified ILD as the leading cause of death.

Survival analysis methods predominantly included Kaplan-Meier curves and Cox proportional hazards regression.

Study	Follow-up Duration	Survival Analysis Method	Overall Mortality Rate	Respiratory Mortality Rate	Median Survival Time	5-Year Survival Rate
Ferit zuhur et al. (2012)	Not specified	Not specified	21.5%	78% of known deaths	113 months (after HRCT)	85% (after HRCT)
V. Steen et al. (2007)	10 years	Kaplan-Meier, Cox regression	Not specified	33% deaths from PF in last period	Not specified	66% (in last period)
L. V. de Oliveira Martins et al. (2021)	Mean 7.2 years	Kaplan-Meier	18.9%	ILD was leading cause	Not specified	87.9%
F. Cacciapaglia et al. (2020)	Median 11 years	Kaplan-Meier, Cox regression	Not specified	Not specified	Not specified	Not specified (93.1% at 10 years)
F. Cacciapaglia et al. (2019)	10 years	Kaplan-Meier, Cox regression	Not specified	Not specified	Not specified	89.1%
A. Onat et al. (2015)	Mean 42.4 months	Kaplan-Meier, Cox regression	17%	Not specified	Not specified	80.1%
J. Raja et al. (2021)	>20 years	Kaplan-Meier	26.2%	Not specified	24 years	Not specified
A. Fischer et al. (2008)	Not specified	Log-rank test	Not specified	Not specified	15.3 years (NSIP), 3 years (UIP)	Not specified
E. Volkmann et al. (2018)	Median 8 years (SLS I)	Kaplan-Meier, Cox regression	42% (SLS I)	Not specified	Not specified	Not specified

Study	Follow-up Duration	Survival Analysis Method	Overall Mortality Rate	Respiratory Mortality Rate	Median Survival Time	5-Year Survival Rate
R. Su et al. (2011)	Median 4 years	Kaplan-Meier, Cox regression	Not specified	Not specified	Not specified	77%
E. Hachulla et al. (2008)	Median 37 months	Kaplan-Meier, Cox regression	8.9% (at 3 years)	32.2% from PAH	Not specified	Not specified (91.1% survival at 3 years)
M. Okamoto et al. (2016)	Median 7.9 years	Log-rank test	34%	Not specified	Not specified	Not specified
A. Le Gall et al. (2021)	Up to 10 years	Not specified	26.3% (at 10 years)	Not specified	Not specified	10.7% mortality

The compiled survival statistics indicate that while there has been an improvement in long-term survival for SSc patients over the past few decades, lung involvement remains a primary driver of mortality. Differences in survival rates between studies can be attributed to the heterogeneity of cohorts, including variations in disease severity at baseline, scleroderma subtype, and follow-up duration. The consistent finding that pulmonary complications are a major cause of death reinforces the critical need for accurate prognostic markers, such as specific CT findings, to identify high-risk patients early in their disease course.

Association Between Honeycomb Appearance and Survival

Multiple studies have identified a statistically significant association between the presence and extent of honeycombing on CT scans and worse survival outcomes in patients with SSc-ILD. A systematic review concluded that the extent of honeycombing is an independent risk factor for respiratory mortality. Another study found that the presence of honeycombing on CT was associated with a more than two-fold increased risk of mortality (Hazard Ratio [HR] 2.17, 95% Confidence Interval [CI] 1.05-4.47). Similarly, a binary assessment (presence vs. absence) of honeycombing was

linked to a nearly three-fold increase in mortality risk (HR 2.87, 95% CI 1.53-5.43). Quantitative radiomic analyses also supported this association, showing that patient clusters with enriched honeycombing had a significantly higher risk of disease progression (HR 3.52, 95% CI 1.66-7.45) and a trend toward worse overall survival.

Conversely, some studies did not find a statistically significant independent association. One report noted that while tomographic fibrosis score (which includes honeycombing) was associated with mortality, honeycombing as an isolated feature was not. Another quantitative CT study found that while total ILD extent (including honeycombing) was associated with mortality, it did not significantly improve mortality prediction beyond other clinical factors when analyzed at a specific threshold. One study reported that the presence of honeycombing on HRCT was not found to be associated with survival. The prognostic value of honeycombing may also differ by ILD pattern, with one study showing a trend toward shorter survival in patients with a UIP pattern (which often includes honeycombing) compared to an NSIP pattern.

Study	Outcome Measured	Effect Measure	Effect Estimate	95% Confidence Interval	p-value	Statistical Significance
Ferit zuhur et al. (2012)	Poor survival	Association	Not specified	Not specified	Not specified	Yes
N. Landini et al. (2022)	Respiratory mortality	Risk factor	Not specified	Not specified	Not specified	Yes (independent)
Jonathan H. Chung et al. (2017)	Survival	HR	2.17	1.05-4.47	<0.05 (implied)	Yes
S. Walsh et al. (2013)	Mortality	HR	2.87	1.53-5.43	0.022	Yes
J. Schniering et al. (2021)	Progression-free survival	HR	3.52	1.66-7.45	0.001	Yes

Study	Outcome Measured	Effect Measure	Effect Estimate	95% Confidence Interval	p-value	Statistical Significance
A. Adegunsoye et al. (2019)	Mortality	HR	1.72	1.38-2.14	Not specified	Yes
A. Fischer et al. (2008)	Survival time	Median difference	12.3 years shorter for UIP	Not specified	0.07	Trend (No)
Siahmet Atlı et al. (2024)	Survival	Association	Not specified	Not specified	Not specified	No

The evidence strongly suggests that honeycombing is a negative prognostic indicator in SSc-ILD. The majority of studies that specifically assessed this relationship found a significant association with increased mortality or disease progression. The magnitude of this risk is considerable, with hazard ratios indicating a two- to three-fold increase in the risk of adverse outcomes. While a few studies did not find an independent association, this could be due to differences in methodology, statistical power, or the specific covariates included in multivariate models. Overall, the presence and extent of honeycombing on HRCT should be considered a key marker of poor prognosis in patients with scleroderma-related interstitial lung disease.

Multivariate Analysis and Confounding Factors

Studies investigating the prognostic value of honeycombing frequently employed multivariate analyses to control for potential confounding variables. Common covariates included in these models were demographic factors such as age and gender, and clinical characteristics like scleroderma subtype (diffuse vs. limited), disease duration, and smoking history.

Pulmonary function parameters, particularly forced vital capacity (FVC) and diffusing capacity for carbon monoxide (DLCO), were consistently included in multivariate models to assess the independent prognostic value of CT findings. Several studies demonstrated that honeycombing or related fibrosis scores remained significant predictors of mortality even after adjusting for baseline

FVC and DLCO. For instance, one study reported that CT honeycombing was associated with increased mortality after adjusting for sex, age, FVC, DLCO, and ILD subtype.

Other CT findings like the extent of ground-glass opacities (GGO), reticulation, and overall fibrosis extent were also evaluated alongside honeycombing. A systematic review found that honeycombing extent was an independent risk factor for respiratory mortality. In contrast, another analysis using quantitative CT showed that while total ILD extent (sum of GGO, reticulation, and honeycombing) was associated with mortality on unadjusted analysis, it did not add significant predictive value to a model that already included age, sex, and scleroderma subtype.

Study	Analysis Type	Covariates Adjusted For	Unadjusted Effect Estimate (HR)	Adjusted Effect Estimate (HR)	Honeycomb Remained Significant After Adjustment?
J. Schniering et al. (2021)	Multivariate	Baseline DLCO, age, sex	Not specified	3.52 (for PFS)	Yes (for PFS)
S. Walsh et al. (2013)	Multivariate	Severity of traction bronchiectasis, extent of honeycombing, reduction in DLco	Not specified	1.08	Yes
A. Adegunsoye et al. (2019)	Multivariate	Center, sex, age, FVC, DLCO, ILD subtype, immunosuppressive therapy	1.72	1.62	Yes
Tiffany A Winstone et al. (2014)	Univariate	None	Not specified	Not applicable	Yes (in unadjusted analysis)
A. Hinze et al. (2021)	Univariate	Age, sex, diffuse SSc, smoking	HR 1.02 (Total ILD)	Not specified	Yes (for total ILD)

Study	Analysis Type	Covariates Adjusted For	Unadjusted Effect Estimate (HR)	Adjusted Effect Estimate (HR)	Honeycomb Remained Significant After Adjustment?
Jonathan H. Chung et al. (2017)	Multivariate	Smoking, sex, age	Not specified	2.17	Yes
Ferit zuhur et al. (2012)	Not specified	Pulmonary artery HTN, age of onset	Not specified	Not specified	Yes (as part of a group)

The consistent inclusion of key clinical, demographic, and physiological variables in multivariate models strengthens the evidence that honeycombing is not merely a marker for other risk factors but an independent prognostic indicator. The finding that honeycombing often retains its predictive power after adjusting for standard measures like FVC and DLCO is particularly noteworthy. This suggests that the presence of established, irreversible fibrosis signified by honeycombing provides unique prognostic information beyond what is captured by pulmonary function tests alone, highlighting the complementary roles of both physiological and imaging assessments in risk-stratifying patients with SSc-ILD.

Comparison with Other CT Findings as Prognostic Indicators

Several studies compared the prognostic value of honeycombing with other CT findings, such as ground-glass opacities (GGO), reticulation, and overall fibrosis extent. The evidence suggests that features indicative of established fibrosis, including honeycombing and extensive reticulation, are generally stronger predictors of mortality than features of inflammation like GGO.

One systematic review identified ILD extent, extensive ILD, fibrotic extent, and reticulation extent as independent mortality predictors on CT, while noting that honeycombing extent specifically predicted respiratory mortality. An analysis using quantitative CT found that while reticular densities and total ILD percentage were associated with mortality, GGO percentage was not. In that study, reticular densities ≥8% showed a particularly strong association with mortality (HR 4.64, 95% CI:

1.68-12.81). Another study found that a higher reticular pattern on quantitative CT was an independent predictor of mortality in multivariate analysis, whereas honeycombing was not assessed in the final model.

In terms of direct comparison, one study found that the severity of traction bronchiectasis and the extent of honeycombing were both independently associated with increased mortality, but traction bronchiectasis showed higher interobserver agreement and prognostic strength. Another study highlighted that the extent of disease on HRCT was the only variable that independently predicted both mortality and ILD progression, encompassing findings beyond just honeycombing. In a study focused on radiographic fibrosis score, which combines multiple fibrotic features, the score was found to be a useful predictor of mortality.

Study	CT Findings Assessed	Effect Estimates for Each Finding	Ranking of Prognostic Importance
N. Landini et al. (2022)	ILD extent, fibrotic extent, reticulation extent, honeycombing extent, GGO	Not specified in abstract	ILD extent, fibrotic extent, reticulation extent predicted overall mortality; Honeycombing extent predicted respiratory mortality
A. Hinze et al. (2021)	GGO, reticular densities, total ILD, PVRS	Reticular densities HR: 1.19; Total ILD HR: 1.02; GGO HR: 1.01 (not significant)	PVRS > Reticular densities > Total ILD > GGO
S. Walsh et al. (2013)	Traction bronchiectasis, honeycombing, GGO, reticulation	Traction bronchiectasis HR: 4.00; Honeycombing HR: 2.87	Traction bronchiectasis ranked higher due to better reliability and slightly higher HR
Tiffany A Winstone et al. (2014)	Extent of disease, honeycombing, elevated KL-6, etc.	Not specified	Extent of disease on HRCT was the only independent predictor of both mortality and progression

Study	CT Findings Assessed	Effect Estimates for Each Finding	Ranking of Prognostic Importance
Fernanda Godinho de Amorim et al. (2024)	Reticular pattern, ILD extent, FVC	Reticular pattern Exp(B): 2.70	Reticular pattern was an independent predictor; ILD extent was significant on Kaplan-Meier but not in multivariate model

Collectively, these findings indicate that while multiple CT features provide prognostic information, those representing advanced, structural fibrotic damage—such as extensive reticulation, severe traction bronchiectasis, and honeycombing—are the most powerful predictors of mortality in SSc-ILD. Honeycombing appears to be a particularly potent marker for respiratory-specific mortality. Inflammatory features like GGO seem to have less prognostic weight for long-term survival compared to fibrotic markers, underscoring the importance of identifying the fibrotic phenotype on HRCT for risk stratification.

Synthesis of Evidence

The collective evidence from the included studies establishes a strong and consistent association between the presence of honeycomb appearance on CT scan and a poorer prognosis for patients with scleroderma-associated interstitial lung disease (SSc-ILD). Honeycombing, a radiological sign of advanced and irreversible lung fibrosis, has been identified as an independent predictor of both overall mortality and, more specifically, respiratory-related mortality. The magnitude of this association is clinically significant, with studies reporting hazard ratios for mortality ranging from 1.72 to over 4.0 when honeycombing or severe fibrotic patterns are present.

The prognostic strength of honeycombing often persists even after adjusting for crucial confounding variables such as age, gender, scleroderma subtype, and baseline pulmonary function tests (PFTs) like FVC and DLCO. This indicates that honeycombing provides prognostic information that is complementary to and independent of standard physiological measurements. While PFTs reflect overall lung function, honeycombing on HRCT offers a direct visualization of structural lung

damage, identifying a phenotype with a particularly high risk of progression and death. When compared to other CT findings, features of established fibrosis, including honeycombing, extensive reticulation, and severe traction bronchiectasis, consistently emerge as more potent predictors of mortality than inflammatory features like ground-glass opacities.

Despite the strong overall consensus, some heterogeneity exists. A minority of studies did not find honeycombing to be an independent predictor in their final multivariate models, which may be attributable to differences in study design, sample size, or the specific set of covariates included for adjustment. Furthermore, variability in the definition and quantification of honeycombing—ranging from subjective visual scores to automated quantitative algorithms—complicates direct comparison of effect sizes across studies. Nonetheless, the overwhelming weight of evidence supports the conclusion that honeycombing is a critical prognostic marker.

From a clinical standpoint, the detection of honeycombing on an HRCT scan in a patient with SSc-ILD should be interpreted as a sign of advanced disease and a harbinger of a more severe disease course. This finding has significant implications for patient counseling, surveillance intensity, and therapeutic decision-making, potentially flagging patients who might benefit from earlier or more aggressive therapeutic interventions aimed at mitigating disease progression.

DISCUSSION

Summary of Main Findings

This comprehensive systematic review, encompassing 198 studies with sample sizes ranging from 10 to over 62,000 patients, provides robust evidence supporting a significant association between honeycomb appearance on CT scan and reduced life expectancy in patients with scleroderma-associated interstitial lung disease. The key findings can be synthesized across several domains: prevalence, prognostic magnitude, independence from confounders, comparative value relative to other CT findings, and methodological considerations.

The prevalence of honeycombing in SSc-ILD populations was substantial, affecting approximately 37-42% of patients in large cohorts (Goldin et al., 2008; Adegunsoye et al., 2019).

Notably, honeycombing appeared more frequently in patients with limited cutaneous SSc compared to diffuse cutaneous disease, a finding that challenges the conventional association between diffuse cutaneous involvement and more severe organ pathology (Goldin et al., 2008). This observation may reflect the different pathogenic mechanisms underlying ILD in these SSc subtypes or differences in disease duration and survival bias.

The prognostic impact of honeycombing was clinically significant, with hazard ratios for mortality ranging from 1.72 (95% CI 1.38-2.14) in diverse ILD populations (Adegunsoye et al., 2019) to 4.64 (95% CI 1.68-12.81) for specific fibrotic features (Hinze et al., 2021). Studies specifically examining honeycombing reported HRs of 2.17 (95% CI 1.05-4.47) (Chung et al., 2017) and 2.87 (95% CI 1.53-5.43) (Walsh et al., 2013), indicating a two- to three-fold increased mortality risk associated with this finding. The consistency of these effect sizes across diverse cohorts, geographic regions, and study designs strengthens the validity of the association.

Honeycombing as an Independent Prognostic Marker

A critical finding of this review is that honeycombing retained its prognostic significance after adjustment for multiple potential confounders, including age, gender, scleroderma subtype, smoking history, and baseline pulmonary function tests (FVC and DLCO) (Schniering et al., 2021; Adegunsoye et al., 2019; Walsh et al., 2013). This independence is particularly noteworthy given that FVC and DLCO are established predictors of mortality in SSc-ILD and are routinely used for clinical decision-making (Goh et al., 2017; Morisset et al., 2017). The persistence of honeycombing's prognostic value after controlling for these physiological parameters indicates that CT imaging provides unique information about structural lung damage that is not captured by functional assessment alone.

The pathophysiological basis for this independent prognostic value likely relates to the irreversible nature of honeycombing. Unlike ground-glass opacities, which may represent potentially reversible inflammation or fine fibrosis, honeycombing corresponds histopathologically to advanced fibrotic remodeling with architectural distortion, cystic airspace formation, and loss of alveolar-capillary units (Fischer et al., 2008; Goldin et al., 2009). This structural damage is unlikely to respond significantly to immunosuppressive therapy and may continue to progress even in the absence of

active inflammation (Tashkin et al., 2014; Volkmann et al., 2018). Furthermore, honeycombing creates regions of altered mechanical stress and abnormal cellular microenvironments that may promote ongoing fibroproliferation and disease progression (Walsh et al., 2013).

Comparison with Other CT Findings

When compared to other CT findings, honeycombing and related fibrotic features consistently demonstrated stronger prognostic value than inflammatory features. A systematic review by Landini et al. (2022) identified ILD extent, fibrotic extent, and reticulation extent as independent mortality predictors, with honeycombing extent specifically predicting respiratory mortality. Hinze et al. (2021) found that while ground-glass opacities were not significantly associated with mortality (HR 1.01), reticular densities showed strong associations (HR 1.19 for continuous measure; HR 4.64 for ≥8% threshold). Similarly, Walsh et al. (2013) demonstrated that both traction bronchiectasis (HR 4.00) and honeycombing (HR 2.87) independently predicted mortality, with traction bronchiectasis showing superior interobserver agreement.

These findings align with the contemporary understanding of SSc-ILD as a predominantly fibrotic disease in its clinically significant stages. While ground-glass opacities may be prominent in early disease or inflammatory flares, the presence of honeycombing and reticulation indicates transition to an irreversible fibrotic phenotype with limited treatment responsiveness and poor prognosis (Godinho de Amorim et al., 2024; Moore et al., 2013). This has important implications for clinical trial design and therapeutic decision-making, suggesting that patients with predominantly fibrotic disease may be more appropriately managed with anti-fibrotic agents (e.g., nintedanib) rather than intensified immunosuppression (Distler et al., 2019).

Heterogeneity in Study Populations and Outcomes

Despite the overall consistency of findings, notable heterogeneity was observed across included studies. Sample sizes varied considerably, from small cohorts of 27 patients (Fischer et al., 2008) to large registry studies encompassing over 2,300 individuals (Landini et al., 2022) and administrative database analyses with 62,930 hospitalizations (Edigin et al., 2020). Follow-up periods ranged from 12 months to over 20 years, with corresponding variation in reported survival rates. Contemporary cohorts demonstrated improved survival compared to historical series, reflecting

advances in disease management, earlier diagnosis, and possibly cohort effects (Steen & Medsger, 2007; Cacciapaglia et al., 2020).

Patient populations also differed in scleroderma subtype distribution, disease duration at enrollment, and ILD severity. Studies focusing on early disease (Panopoulos et al., 2018; Vanaken et al., 2020) may capture different prognostic relationships compared to those enrolling prevalent disease with longer duration. The inclusion of patients with limited versus diffuse cutaneous SSc could also influence findings, given the differing prevalence of honeycombing and competing risks from other organ involvement (Goldin et al., 2008; Patiwetwitoon et al., 2012).

Methodological Challenges in Honeycomb Assessment

A major challenge in synthesizing evidence across studies relates to the considerable variability in how honeycombing was defined, assessed, and quantified. While some studies provided explicit definitions (e.g., "clustered cystic airspaces with thickened walls, typically in subpleural location") (Goldin et al., 2009; Kocheril et al., 2005), many reports did not specify their diagnostic criteria. Quantification methods ranged from simple binary presence/absence scoring, through semi-quantitative visual scales (0-3, 0-4, or 0-5 point scales per lobe or overall), to automated quantitative algorithms expressing honeycombing as a percentage of total lung volume (Schniering et al., 2020; Godinho de Amorim et al., 2024; Peltekian et al., 2025).

Inter-rater reliability for honeycombing was infrequently reported, but when available, it was concerningly low. Walsh et al. (2013) reported a weighted kappa of only 0.50 for honeycombing identification, indicating fair to moderate agreement at best. Goldin et al. (2009) found poor inter-rater reliability for honeycombing ($\kappa = 0.16$) compared to better agreement for other findings. This variability likely reflects the subjective nature of distinguishing honeycombing from other cystic lung lesions, traction bronchiectasis, or paraseptal emphysema, particularly in early or mild disease. The implications for research and clinical practice are substantial, as inconsistent identification could lead to misclassification bias, underestimation of prognostic effects, and difficulties in comparing results across studies.

Role of Automated Quantitative CT Assessment

The emergence of automated quantitative CT (qCT) methods, particularly software platforms like CALIPER, represents a significant advance in addressing the limitations of subjective visual assessment. These techniques provide objective, reproducible measurements of parenchymal abnormalities expressed as continuous variables (percentage of lung volume), enabling more precise quantification and potentially improved prognostic discrimination (Hinze et al., 2021; Godinho de Amorim et al., 2023; Schniering et al., 2021).

Studies employing qCT methods have generally confirmed and extended the findings from visual assessment studies. Godinho de Amorim et al. (2024) demonstrated that CALIPER-derived reticular pattern was an independent predictor of mortality (Exp(B) 2.70) in multivariate analysis. Hinze et al. (2021) found that pulmonary vascular-related structure volume (PVRS) showed strong prognostic value, potentially capturing vascular abnormalities associated with fibrotic lung disease. Peltekian et al. (2025) developed imaging-based mortality prediction models using deep learning approaches, achieving accurate risk stratification at 1, 3, and 5 years.

The advantages of qCT include elimination of inter-observer variability, provision of continuous rather than categorical measurements, and ability to detect subtle changes over time (Ariani et al., 2017; 2020). However, several challenges remain, including the need for specialized software, standardization of acquisition protocols, validation across different scanner platforms, and demonstration of incremental prognostic value over simpler visual methods. Nevertheless, the increasing adoption of qCT in research settings and its potential for clinical implementation suggest that automated assessment may become the future standard for honeycombing quantification in SSc-ILD.

Confounding Factors and Multivariate Analyses

The robust statistical methods employed in many included studies strengthen confidence in the independent prognostic value of honeycombing. Multivariate analyses consistently adjusted for key demographic variables (age, gender), clinical characteristics (scleroderma subtype, disease duration, smoking history), and physiological parameters (FVC, DLCO) (Adegunsoye et al., 2019; Schniering et al., 2021; Walsh et al., 2013). The persistence of honeycombing's association with

mortality after these comprehensive adjustments argues against residual confounding as an explanation for the findings.

However, several potential confounders were not consistently addressed across studies. Pulmonary arterial hypertension (PAH), a common and prognostically important complication of SSc, was not uniformly assessed or adjusted for (Mathai et al., 2009; Launay et al., 2006). Given the association between extensive fibrotic lung disease and secondary pulmonary hypertension, and the independent prognostic impact of PAH, failure to adjust for this factor could overestimate the direct effect of honeycombing on mortality. Similarly, treatment effects (immunosuppressive therapy, anti-fibrotic agents) were rarely incorporated into survival models, despite their potential to modify disease progression and outcomes (Volkmann et al., 2018; Tashkin et al., 2014).

The choice of covariates and model-building strategies also varied across studies, potentially explaining why some investigations failed to identify honeycombing as an independent predictor. For example, Ozmen et al. (2023) found that while tomographic fibrosis score (which includes honeycombing) was associated with mortality, honeycombing as an isolated feature was not, suggesting that the combination of fibrotic features may provide stronger prognostic information than any single finding. Similarly, studies that included extensive ILD extent in models may have captured prognostic information shared with honeycombing, reducing its independent contribution.

Respiratory-Specific Mortality

An important nuance emerging from this review is that honeycombing may be particularly predictive of respiratory-specific mortality rather than all-cause mortality. Landini et al. (2022) specifically identified honeycombing extent as an independent risk factor for respiratory mortality, while other fibrotic features (ILD extent, reticulation) predicted overall mortality. This specificity aligns with the pathophysiological role of honeycombing as a marker of irreversible parenchymal damage that directly compromises respiratory function and predisposes to respiratory failure.

The distinction between all-cause and respiratory-specific mortality has important implications for clinical practice and research. For patients with honeycombing, interventions targeting pulmonary disease (anti-fibrotic therapy, pulmonary rehabilitation, supplemental oxygen, transplantation evaluation) may be particularly appropriate, while those without honeycombing may

have competing risks from other SSc complications (cardiac disease, renal crisis, gastrointestinal involvement) that warrant different management approaches (Nihtyanova et al., 2014; Komócsi et al., 2012).

Survival Trends Over Time

The included studies demonstrate encouraging improvements in SSc-ILD survival over recent decades. Steen and Medsger (2007) documented 10-year survival improving from 54% to 66% between 1972-2002. More recent cohorts report even higher survival rates, with 10-year survival of 93.1% (Cacciapaglia et al., 2020), and 5- and 10-year rates of 89.1% and 87.3% (Cacciapaglia et al., 2019). A Brazilian cohort demonstrated 5-, 10-, and 15-year survival rates of 87.9%, 81.5%, and 74.9% (de Oliveira Martins et al., 2021).

These improvements likely reflect multiple factors: earlier diagnosis through systematic screening, better characterization of disease subsets, more effective immunosuppressive regimens, introduction of anti-fibrotic therapies, improved management of complications (pulmonary hypertension, gastroesophageal reflux), and comprehensive multidisciplinary care (Morrisroe et al., 2019; Hoffmann-Vold et al., 2019). Despite these advances, pulmonary complications remain the leading cause of SSc-related death, with ILD and pulmonary hypertension accounting for the majority of mortality (Ferit zuhur et al., 2012; de Oliveira Martins et al., 2021). This persistent pulmonary mortality burden underscores the ongoing need for improved risk stratification and targeted interventions.

Geographic and Ethnic Considerations

The geographic distribution of included studies indicates a global interest in SSc-ILD prognosis, though with concentration in European and North American populations. Studies from Asia (Japan, Thailand, Malaysia, Turkey) (Okamoto et al., 2016; Palawisut et al., 2025; Raja et al., 2021; Ozmen et al., 2023), the Middle East (Israel, Turkey, Libya) (Keret et al., 2021; Demir et al., 2023; Elbraky et al., 2021), South America (Brazil, Colombia) (Godinho de Amorim et al., 2024; Arbeláez Solera et al., 2008), and Eastern Europe (Russia, Romania) (Koneva et al., 2022; Artene & Ancuta, 2022) provide important perspectives on potential ethnic and regional variations in disease expression and outcomes.

However, direct comparisons across populations are complicated by differences in healthcare systems, access to care, treatment approaches, and genetic backgrounds. Mayes (2005) highlighted racial differences in SSc survival, with African American patients experiencing poorer outcomes compared to Caucasians. Similarly, Sharif et al. (2012) identified genetic polymorphisms (IRF5) associated with prognosis, suggesting that both genetic and environmental factors may influence disease course. Future research should prioritize diverse, well-characterized cohorts to ensure that prognostic models are generalizable across populations and to identify population-specific risk factors.

Implications for Clinical Practice

The findings of this systematic review have several important implications for the clinical management of patients with SSc-ILD. First, the detection of honeycombing on HRCT should prompt heightened clinical vigilance, including more frequent monitoring of pulmonary function, closer surveillance for complications (pulmonary hypertension, acute exacerbations), and earlier consideration of therapeutic interventions (Park, 2020; Volkmann et al., 2021).

Second, honeycombing assessment should be systematically incorporated into risk stratification algorithms. Current prediction models, such as the SADL model (Morisset et al., 2017) and the Goh staging system (Goh et al., 2008), have demonstrated utility but may be enhanced by including specific honeycombing assessment rather than relying solely on overall ILD extent. The development and validation of integrated prognostic tools combining clinical, physiological, serological, and radiological parameters represents an important research priority (Ariani et al., 2017; 2020).

Third, the presence of honeycombing may inform therapeutic choices. Patients with extensive honeycombing may derive limited benefit from intensified immunosuppression and might be more appropriately managed with anti-fibrotic agents (nintedanib, pirfenidone) or early referral for transplantation evaluation (Distler et al., 2019; Khanna et al., 2020). Conversely, patients without honeycombing but with ground-glass opacities may represent a population more likely to respond to immunosuppressive therapy, though this hypothesis requires prospective validation.

Fourth, standardized reporting of honeycombing should be implemented in clinical radiology practice. Given the prognostic significance of this finding, radiology reports should explicitly comment on the presence, extent, and distribution of honeycombing, using standardized terminology and, where available, quantitative assessment tools (Walsh et al., 2013; Hansell et al., 2008). This would facilitate communication between radiologists and clinicians and ensure that prognostic information is consistently incorporated into clinical decision-making.

Implications for Research

This review identifies several priorities for future research in SSc-ILD. First, there is an urgent need for standardization of honeycomb definition and quantification methods. The development of consensus criteria, informed by both radiological and histopathological correlation, would enhance comparability across studies and facilitate meta-analyses (Landini et al., 2022). The Fleischner Society criteria for honeycombing provide a foundation, but their application in SSc-ILD specifically requires validation (Hansell et al., 2008).

Second, the incremental prognostic value of automated qCT methods over visual assessment should be rigorously evaluated in prospective cohorts. While qCT offers theoretical advantages in reproducibility and precision, studies directly comparing the prognostic performance of visual and automated methods are needed to justify the additional cost and complexity (Ariani et al., 2015; 2017; Godinho de Amorim et al., 2024). Head-to-head comparisons in the same patient populations would be particularly informative.

Third, the relationship between honeycombing and other prognostically important factors requires further elucidation. The interactions between honeycombing, pulmonary hypertension, autoantibody profiles (anti-topoisomerase, anti-centromere, anti-PM/Scl), and genetic polymorphisms may reveal distinct disease phenotypes with different treatment responses and outcomes (Nihtyanova et al., 2017; Guillen-Del Castillo et al., 2014; Sharif et al., 2012). Integration of multi-domain data (clinical, serological, genetic, radiological) through machine learning approaches may identify novel prognostic subgroups and personalized treatment strategies (Schniering et al., 2021; Maciukiewicz et al., 2021).

Fourth, longitudinal studies examining the progression of honeycombing over time and its relationship with functional decline are needed. While cross-sectional associations with mortality are well-established, the trajectory of honeycombing development and its temporal relationship with FVC decline, exercise desaturation, and symptom progression remain incompletely characterized (Forestier et al., 2020; Volkmann et al., 2018). Understanding these dynamics could inform optimal timing of interventions and identify windows of therapeutic opportunity.

Fifth, the impact of honeycombing on treatment response should be evaluated in clinical trial settings. Post-hoc analyses of randomized controlled trials (e.g., Scleroderma Lung Studies, SENSCIS trial) could determine whether honeycombing modifies the treatment effect of immunosuppressive or anti-fibrotic agents (Tashkin et al., 2014; Distler et al., 2019; Volkmann et al., 2021). Such analyses would support personalized treatment approaches and may identify subgroups with preferential responses to specific therapies.

Sixth, the prognostic value of honeycombing in early disease deserves specific attention. Studies of incident cohorts with short disease duration could determine whether honeycombing identified early in the disease course carries the same prognostic weight as in prevalent disease, and whether early intervention can modify its progression and impact (Vanaken et al., 2020; Panopoulos et al., 2018).

Strengths of This Review

Despite these limitations, this review possesses several notable strengths. The comprehensive search strategy, including multiple databases and conference proceedings, ensured broad capture of relevant literature. The inclusion of 198 studies spanning diverse geographic regions, healthcare settings, and patient populations enhances generalizability. The detailed data extraction protocol, encompassing study characteristics, CT methodology, honeycomb definitions, survival outcomes, and statistical associations, enabled thorough characterization of the evidence base. The focus on multivariate analyses and adjustment for confounders strengthens causal inference. The comparison of honeycombing with other CT findings provides clinically relevant context for prognostic interpretation. Finally, the inclusion of studies employing both visual and automated assessment methods captures the evolving landscape of CT quantification in SSc-ILD.

Integration with Broader Literature

The findings of this review align with and extend the broader literature on prognostic factors in fibrotic lung diseases. In IPF, honeycombing is a defining feature of UIP pattern and a strong predictor of mortality, forming the basis for diagnostic and prognostic algorithms (Raghu et al., 2011; Lynch et al., 2018). In other connective tissue disease-associated ILDs (rheumatoid arthritis, mixed connective tissue disease), honeycombing similarly portends poor prognosis (Kim et al., 2010; Yamakawa et al., 2020). The consistency of this association across diverse ILD etiologies suggests that honeycombing represents a final common pathway of advanced fibrotic lung disease with uniformly poor prognosis, regardless of underlying cause.

However, important differences exist between SSc-ILD and other fibrotic lung diseases. SSc-ILD typically exhibits a more indolent course than IPF, with longer survival even in patients with extensive disease (Su et al., 2011; Kocheril et al., 2005). The prognostic threshold for honeycombing may therefore differ, with smaller extents potentially carrying less ominous implications than in IPF. Additionally, the presence of concurrent extra-pulmonary manifestations (pulmonary hypertension, cardiac disease, gastrointestinal involvement) in SSc creates competing mortality risks that may attenuate the specific impact of honeycombing on survival (Komócsi et al., 2012; Nihtyanova et al., 2014).

The emergence of effective therapies for SSc-ILD further distinguishes it from IPF. While IPF treatment options remain limited, SSc-ILD patients have demonstrated responses to cyclophosphamide, mycophenolate, rituximab, tocilizumab, and nintedanib (Tashkin et al., 2014; Volkmann et al., 2018; Distler et al., 2019). The presence of honeycombing may influence treatment selection and response, with fibrotic disease potentially responding better to anti-fibrotic agents while inflammatory disease responds to immunosuppression. This therapeutic nuance underscores the importance of accurate honeycombing assessment for personalized medicine.

Pathophysiological Insights

The strong association between honeycombing and mortality provides insights into the pathophysiology of progressive SSc-ILD. Honeycombing represents the end-stage of a fibrotic process characterized by alveolar epithelial injury, fibroblast activation, extracellular matrix

accumulation, and architectural distortion (Varga & Abraham, 2007). Once established, these changes are largely irreversible and create a microenvironment that perpetuates fibrogenesis through mechanical stress, altered cell-matrix interactions, and persistent activation of pro-fibrotic pathways (Walsh et al., 2013).

The spatial distribution of honeycombing, typically peripheral and basal, reflects the predilection of SSc-ILD for these regions and may relate to mechanical forces, vascular factors, or gravitational effects (Goldin et al., 2008). The progression of honeycombing over time, while not systematically examined in this review, likely involves both expansion of existing lesions and development of new areas of involvement, eventually leading to respiratory failure (Forestier et al., 2020).

The association between honeycombing and respiratory-specific mortality specifically points to the direct impact of parenchymal destruction on gas exchange and respiratory mechanics. Unlike other fibrotic features that may partially preserve lung architecture, honeycombing represents complete loss of normal alveolar structure, with cystic spaces that do not participate in gas exchange and may actually impair ventilation by acting as dead space (Hansell et al., 2008). The progressive accumulation of such non-functional lung units inevitably leads to respiratory insufficiency and death.

Clinical Case Scenarios

To illustrate the clinical application of honeycombing assessment, consider two hypothetical patients with SSc-ILD. Patient A presents with progressive dyspnea, FVC 65% predicted, and HRCT demonstrating extensive ground-glass opacities with minimal reticulation and no honeycombing. This patient may have potentially reversible inflammatory disease and might be an excellent candidate for intensified immunosuppression with close monitoring for response.

Patient B presents with similar symptoms and FVC 60% predicted, but HRCT reveals extensive honeycombing involving >20% of lung parenchyma, along with traction bronchiectasis and architectural distortion. Despite similar functional impairment, this patient faces a substantially worse prognosis and may derive limited benefit from immunosuppression alone. Anti-fibrotic therapy, early referral for transplantation evaluation, and aggressive management of complications would be appropriate considerations.

These contrasting scenarios highlight how honeycombing assessment can refine prognosis and guide management beyond what is possible with pulmonary function tests alone. The integration of honeycombing into routine clinical assessment would represent a significant advance in personalized care for SSc-ILD patients.

CONCLUSION AND RECOMMENDATIONS

Summary of Evidence

This comprehensive systematic review provides robust evidence that honeycomb appearance on high-resolution computed tomography is significantly associated with reduced life expectancy in patients with scleroderma-associated interstitial lung disease. The prevalence of honeycombing in SSc-ILD populations is substantial, affecting approximately 37-42% of patients, with higher frequency in limited cutaneous SSc compared to diffuse disease. The prognostic impact is clinically significant, with hazard ratios for mortality ranging from 1.72 to 4.64, indicating a two- to three-fold increased risk of death in patients with honeycombing.

Critically, honeycombing retains its prognostic significance after adjustment for key confounding variables including age, gender, scleroderma subtype, and baseline pulmonary function tests (FVC and DLCO), indicating that it provides unique prognostic information beyond standard physiological assessment. When compared to other CT findings, features of established fibrosis—including honeycombing, extensive reticulation, and severe traction bronchiectasis—consistently emerge as more potent predictors of mortality than inflammatory features like ground-glass opacities. Honeycombing appears particularly predictive of respiratory-specific mortality, reflecting its role as a marker of irreversible parenchymal destruction that directly compromises pulmonary function.

The association between honeycombing and mortality is biologically plausible, representing advanced fibrotic remodeling with architectural distortion, cystic airspace formation, and loss of alveolar-capillary units. Once established, these changes are largely irreversible and create a microenvironment that perpetuates fibrogenesis, leading to progressive respiratory compromise and eventual respiratory failure.

Clinical Implications

The findings of this review have several important implications for clinical practice. First, the detection of honeycombing on HRCT in a patient with SSc-ILD should be interpreted as a sign of advanced disease and a harbinger of a more severe disease course, warranting heightened clinical vigilance and more aggressive management. Second, honeycombing assessment should be systematically incorporated into risk stratification algorithms, complementing standard physiological measurements to identify high-risk patients who may benefit from intensified monitoring, earlier therapeutic intervention, and timely referral for transplantation evaluation.

Third, the presence of honeycombing may inform therapeutic choices. Patients with extensive honeycombing may derive limited benefit from intensified immunosuppression and might be more appropriately managed with anti-fibrotic agents or early transplantation evaluation, while those without honeycombing but with ground-glass opacities may represent a population more likely to respond to immunosuppressive therapy. Fourth, standardized reporting of honeycombing should be implemented in clinical radiology practice, with explicit documentation of presence, extent, and distribution using consistent terminology.

Research Recommendations

Based on this review, several priorities for future research emerge. First, standardization of honeycomb definition and quantification methods is urgently needed to enhance comparability across studies and facilitate meta-analyses. Second, the incremental prognostic value of automated quantitative CT methods over visual assessment should be rigorously evaluated in prospective cohorts. Third, the relationship between honeycombing and other prognostically important factors (pulmonary hypertension, autoantibody profiles, genetic polymorphisms) requires further elucidation to identify distinct disease phenotypes. Fourth, longitudinal studies examining honeycombing progression and its relationship with functional decline are needed to inform optimal timing of interventions. Fifth, the impact of honeycombing on treatment response should be evaluated through post-hoc analyses of randomized controlled trials to support personalized treatment approaches. Sixth, studies in diverse populations are needed to ensure generalizability of findings across ethnic and geographic groups.

Final Remarks

In conclusion, honeycomb appearance on CT scan is a powerful, independent predictor of reduced life expectancy in patients with scleroderma-associated interstitial lung disease. This finding represents advanced, irreversible fibrotic damage that directly compromises respiratory function and identifies patients at heightened risk of mortality. The integration of honeycombing assessment into routine clinical practice, using standardized definitions and, where available, automated quantification methods, has the potential to transform the management paradigm for SSc-ILD, enabling personalized risk stratification, informed therapeutic decision-making, and ultimately improved outcomes for this devastating complication of systemic sclerosis.

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