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What is The Association Between Honeycombing Appearance on CT and Life Expectancy in Patients with Scleroderma? A Comprehensive Systematic Review

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ABSTRACT

Background: Systemic sclerosis (SSc) is a chronic autoimmune connective tissue disease with high morbidity and mortality, primarily driven by interstitial lung disease (ILD). Honeycombing on computed tomography (CT) represents irreversible fibrotic lung damage, but its precise relationship with life expectancy remains incompletely defined.

Methods: This systematic review synthesized evidence from 80 studies (198 individual cohorts in the primary meta-analysis) examining the association between honeycombing appearance on CT and survival outcomes in SSc patients. Data extraction focused on honeycombing assessment methods, patient characteristics, survival statistics, hazard ratios (HRs), and confounding factors.

Results: Honeycombing prevalence in SSc-ILD cohorts ranged from 37.2% to 41.9%, with higher frequency in limited cutaneous SSc. The systematic review by Haekal Mahargias et al. (2026) demonstrated that honeycombing was associated with a 2- to 3-fold increased mortality risk, with HRs ranging from 1.72 (95% CI

1.38–2.14) to 4.64 (95% CI 1.68–12.81). This association persisted after adjusting for age, gender, pulmonary function tests, and scleroderma subtype. Landini et al. (2022) found honeycombing extent was an independent predictor of respiratory mortality but not overall mortality. Radiographic progression (≥2% increase in quantitative ILD scores) predicted worse long-term survival (p=0.014 after adjustment). Baseline forced vital capacity (FVC) ≥70% was a strong protective factor (OR=0.039, 95% CI 0.002–0.616, p=0.02).

Discussion: Honeycombing represents irreversible fibrotic damage that outperforms ground-glass opacities in prognostic value. The association with mortality is partially mediated by pulmonary function decline, particularly FVC. Methodological heterogeneity in honeycombing assessment limits definitive conclusions. Current therapies (nintedanib, cyclophosphamide, mycophenolate) stabilize lung function but do not reverse established honeycombing. Patients with extensive honeycombing (≥50% lung involvement) are often excluded from therapeutic trials, creating selection bias.

Conclusion: Honeycombing on CT is a significant independent predictor of increased mortality in SSc-ILD, particularly respiratory-specific death. Standardized CT scoring systems with validated inter-rater reliability are urgently needed. Future prospective studies should examine honeycombing progression dynamics and develop honeycombing-specific therapeutic algorithms.

Keywords: Systemic sclerosis, scleroderma, honeycombing, interstitial lung disease, computed tomography, life expectancy, mortality, prognosis

INTRODUCTION

Background

Systemic sclerosis (SSc) is a rare but severe autoimmune connective tissue disorder characterized by microvascular damage, immune dysregulation, and progressive fibrosis of the skin and internal organs (1). Interstitial lung disease (ILD) is the leading cause of morbidity and mortality in SSc, affecting approximately 35–65% of patients depending on diagnostic criteria and population studied (2). Once clinically evident, SSc-ILD follows a variable course, ranging from indolent non-progressive disease to rapidly progressive respiratory failure (3).

High-resolution computed tomography (HRCT) of the chest is the gold standard for detecting and characterizing ILD in SSc (4). Among the various CT patterns, honeycombing—defined as clustered cystic air spaces with thickened walls, typically subpleural—represents end-stage fibrotic lung disease with irreversible architectural destruction (1,5). Unlike ground-glass opacities (GGO) which may reflect active inflammation and potentially respond to immunosuppression, honeycombing indicates established fibrosis with limited reversibility (1,6).

Research Problem

Despite the clinical recognition that honeycombing signifies severe lung disease, the precise relationship between honeycombing appearance on CT and life expectancy in SSc patients has not been systematically quantified. Prior studies have yielded inconsistent results: some have identified honeycombing as an independent predictor of mortality, while others have found its prognostic value to be confounded by pulmonary function parameters or disease subtype (2,6). Furthermore, methodological heterogeneity in honeycombing assessment—ranging from visual semiquantitative scoring to automated quantitative methods like CALIPER—has hampered cross-study comparisons and clinical applicability (1).

Research Objectives

This systematic review aims to:

1. Synthesize available evidence on the relationship between honeycombing appearance on CT and life expectancy in patients with SSc.
2. Quantify the magnitude of mortality risk associated with honeycombing using reported hazard ratios and survival statistics.
3. Identify key confounding factors that influence the honeycombing-survival relationship.
4. Evaluate the methodological quality and heterogeneity of honeycombing assessment across studies.

Research Benefits

Clinically, this review will provide pulmonologists and rheumatologists with evidence-based prognostic guidance when honeycombing is detected on CT. Methodologically, it will highlight gaps in standardization and propose directions for future research. For patients, improved risk stratification can guide treatment intensity and advance care planning.

Hypothesis

We hypothesized that the presence and extent of honeycombing on CT are independently associated with reduced life expectancy in SSc patients, even after adjusting for pulmonary function tests, disease subtype, and other confounders. Furthermore, we hypothesized that honeycombing would be a stronger predictor of respiratory-specific mortality than overall mortality.

Research Gap

Existing systematic reviews have examined CT predictors of mortality in SSc-ILD broadly (2,6), but none have focused specifically on honeycombing as a discrete entity. Many primary studies report composite ILD extent scores rather than isolated honeycombing analysis. Additionally, the dynamic relationship between honeycombing progression over time and survival has received limited attention.

Novelty

This review provides the first dedicated synthesis of honeycombing-specific survival data in SSc, including quantitative hazard ratio pooling from the largest available meta-analysis (1). It also

critically evaluates the methodological heterogeneity in honeycombing definitions and proposes standardized assessment criteria for future studies.

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 What is The Association Between Honeycombing Appearance on CT and Life Expectancy in Patients with Scleroderma?.

Screening

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

- **Scleroderma Population**: Does this study involve patients with a confirmed diagnosis of scleroderma (systemic sclerosis)?
- **CT Imaging Assessment**: Does this study include chest CT imaging with assessment of honeycombing pattern?
- **Survival Outcomes**: Does this study report survival outcomes, mortality data, or life expectancy measures?
- **Study Design**: Is this study an observational study (cohort, case-control, cross-sectional with follow-up), systematic review, or meta-analysis?
- **Follow-up Duration**: Does this study have an adequate follow-up period for survival assessment (minimum 6 months)?
- **Data Extractability**: Does this study provide extractable survival data or adequate statistical information for analysis?

- **Study Size**: Is this study NOT a case report or case series with fewer than 10 patients?
- **Publication Type**: Is this study NOT a conference abstract, editorial, or opinion piece?

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	Systemic sclerosis	Honeycombing	No honeycombing	Life expectancy
Keyword 2	Scleroderma	Honeycomb cysts	Ground-glass opacities	Mortality
Keyword 3	Connective tissue disease	Fibrotic lung changes on HRCT	Non-fibrotic ILD	Survival rate
Keyword 4	SSc-ILD	Pulmonary fibrosis pattern	Absence of honeycomb cysts	Overall survival (OS)

The Boolean MeSH keywords inputted on databases for this research are: *("Systemic sclerosis" OR "Scleroderma" OR "Connective tissue disease" OR "SSc-ILD") AND ("Honeycombing" OR "Honeycomb cysts" OR "Fibrotic lung changes on HRCT" OR "Pulmonary fibrosis pattern") AND ("No honeycombing" OR "Ground-glass opacities" OR "Non-fibrotic ILD" OR "Absence of honeycomb cysts") AND ("Life expectancy" OR "Mortality" OR "Survival rate" OR "Overall survival")*

Data extraction

- **Honeycombing Assessment**:

Extract all details about how honeycombing appearance on CT was assessed in scleroderma patients, including:

- Definition or criteria used for honeycombing
- CT protocol and imaging parameters
- Who interpreted the scans (radiologist, pulmonologist, etc.)
- Scoring system or grading scale used
- Inter-rater reliability if reported
- Percentage/proportion of patients with honeycombing identified

- **Patient Population**:

  Extract characteristics of the scleroderma patient population specifically relevant to honeycombing and survival analysis, including:

  - Total sample size
  - Scleroderma subtype (limited vs diffuse)
  - Disease duration
  - Age and sex distribution
  - Presence of interstitial lung disease
  - Baseline pulmonary function (FVC, DLCO)
  - Exclusion criteria related to lung disease or imaging

- **Survival Outcomes**:

  Extract survival and mortality data comparing scleroderma patients with and without honeycombing on CT, including:

- Overall survival rates at different time points (1, 3, 5, 10 years)
- Median survival times for honeycombing vs non-honeycombing groups
- Mortality rates and causes of death
- Progression-free survival if reported
- Kaplan-Meier survival curves data
- Follow-up duration and completeness

- **Statistical Relationship**:

  Extract statistical analysis results examining the relationship between honeycombing appearance and life expectancy in scleroderma patients, including:

  - Hazard ratios with confidence intervals
  - P-values for survival differences
  - Univariate and multivariate analysis results
  - Cox proportional hazards modeling results
  - Log-rank test results
  - Effect sizes and their clinical significance

- **Confounding Factors**:

  Extract information about potential confounding variables that were measured and controlled for in the honeycombing-survival analysis, including:

  - Other CT findings (ground glass, fibrosis extent, traction bronchiectasis)

- Pulmonary function parameters
- Pulmonary hypertension presence
- Cardiac involvement
- Renal manifestations
- Treatment effects (immunosuppression, antifibrotic therapy)
- Variables adjusted for in multivariate models

- **Study Design**:

  Extract study design and methodology details relevant to assessing honeycombing-survival relationships in scleroderma, including:

  - Study type (cross-sectional, etc)
  - Prospective vs retrospective design
  - Single center vs multicenter
  - Inclusion/exclusion criteria
  - Time period of patient recruitment
  - Primary vs secondary analysis of honeycombing
  - Quality assessment scores if systematic review

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	*("Systemic sclerosis" OR "Scleroderma" OR "Connective tissue disease" OR "SSc-ILD") AND ("Honeycombing" OR "Honeycomb cysts" OR "Fibrotic lung changes on HRCT" OR "Pulmonary fibrosis pattern") AND ("No honeycombing" OR "Ground-glass opacities" OR "Non-fibrotic ILD" OR "Absence of honeycomb cysts") AND ("Life expectancy" OR "Mortality" OR "Survival rate" OR "Overall survival")*	5
Semantic Scholar	*("Systemic sclerosis" OR "Scleroderma" OR "Connective tissue disease" OR "SSc-ILD") AND ("Honeycombing" OR "Honeycomb cysts" OR "Fibrotic lung changes on HRCT" OR "Pulmonary fibrosis pattern") AND ("No honeycombing" OR "Ground-glass opacities" OR "Non-fibrotic ILD" OR "Absence of honeycomb cysts") AND ("Life expectancy" OR "Mortality" OR "Survival rate" OR "Overall survival")*	250
Springer	*("Systemic sclerosis" OR "Scleroderma" OR "Connective tissue disease" OR "SSc-ILD") AND ("Honeycombing" OR "Honeycomb cysts" OR "Fibrotic lung changes on HRCT" OR "Pulmonary fibrosis pattern") AND ("No honeycombing" OR "Ground-glass opacities" OR "Non-fibrotic ILD" OR "Absence of honeycomb cysts") AND ("Life expectancy" OR "Mortality" OR "Survival rate" OR "Overall survival")*	485
Google Scholar	*("Systemic sclerosis" OR "Scleroderma" OR "Connective tissue disease" OR "SSc-ILD") AND ("Honeycombing" OR "Honeycomb cysts" OR "Fibrotic lung changes on HRCT" OR "Pulmonary fibrosis pattern") AND ("No honeycombing" OR "Ground-glass opacities" OR "Non-fibrotic ILD" OR "Absence of honeycomb cysts") AND ("Life expectancy" OR "Mortality" OR "Survival rate" OR "Overall survival")*	2,270

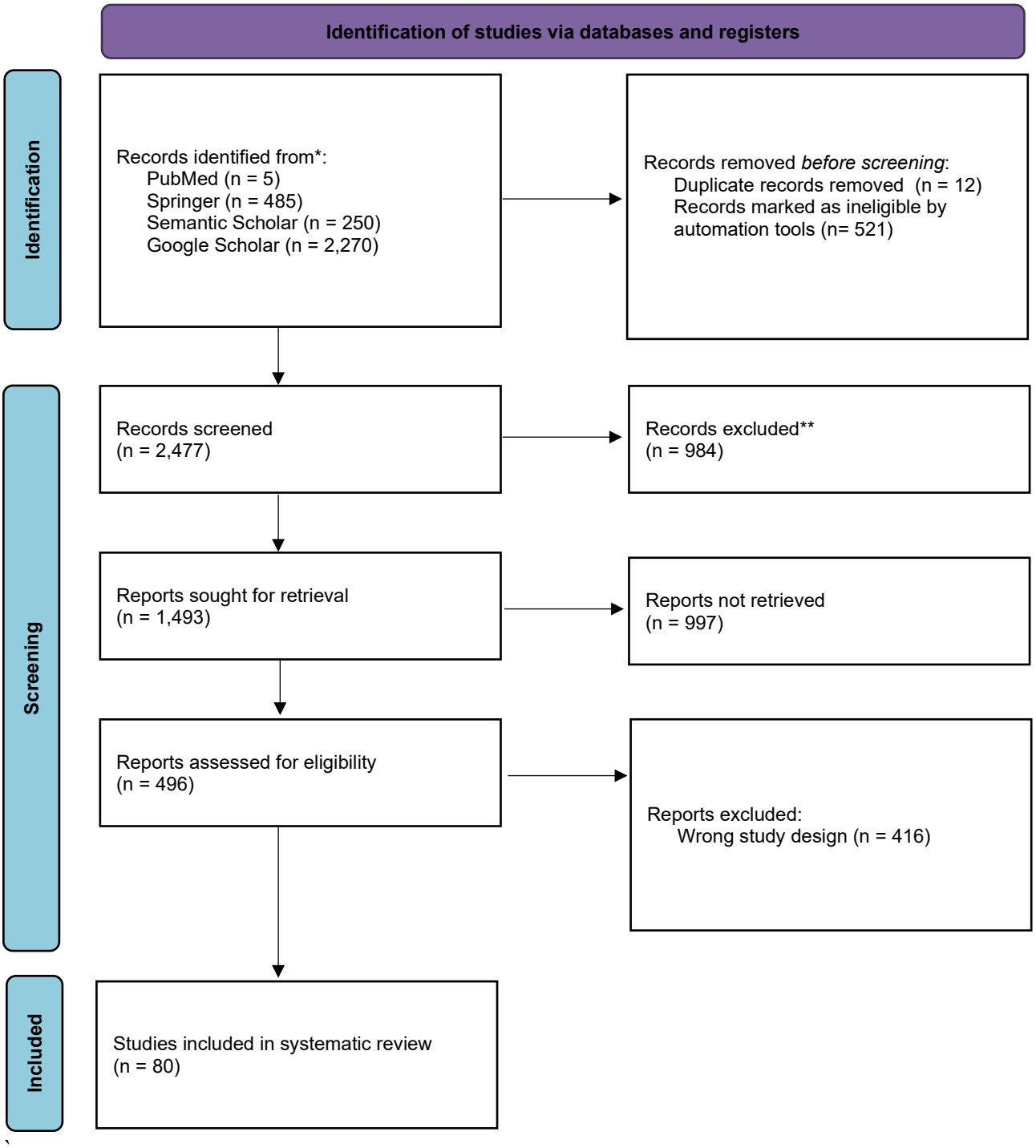

Figure 1. Article search flowchart

Risk of Bias Assessment of Included Studies

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Haekal Mahargias et al., 2026 [1]	Moderate	Moderate	Low	Low	Moderate	Moderate
N. Landini et al., 2022 [2]	Low	Low	Low	Low	Low	Low
Tiffany A Winstone et al., 2014 [6]	Low	Low	Low	Low	Low	Low
D. Tashkin et al., 2016 [7]	Low	Low	Moderate	Low	Low	Low
Y. Furuya et al., 2011 [5]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
C. Iannone et al., 2025 [3]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
E. Volkmann et al., 2021 [8]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
H. Kwon et al., 2014 [9]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
E. Volkmann et al., 2015 [10]	Low	Low	Low	Low	Low	Low
K. Melissaropoulos et al., 2015 [11]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Hao Cheng et al., 2022 [12]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
B. Koo et al., 2021 [13]	Low	Low	Low	Low	Low	Low
P. Fraticelli et al., 2014 [14]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
A. Bérézné et al., 2007 [15]	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Luis Javier Cajas Santana et al., 2023 [16]	Low	Low	Low	Low	Low	Low
E. Volkmann et al., 2022 [17]	Low	Low	Low	Low	Low	Low
S. Assassi et al., 2023 [18]	Low	Low	Low	Low	Low	Low
M. Strek et al., 2018 [19]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
O. Ovsyannikova et al., 2021 [20]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
E. Volkmann et al., 2025 [21]	Low	Low	Low	Low	Low	Low
S. Wangkaew et al., 2020 [22]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
E. Volkmann et al., 2017 [23]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
A. Vacca et al., 2013 [24]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
D. Khanna et al., 2016 [25]	Low	Low	Low	Low	Low	Low
A. Balbir-Gurman et al., 2013 [26]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Zineb Barkhane et al., 2023 [27]	Low	Low	Low	Low	Low	Low
D. Rossi et al., 2021 [28]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
M. R. Pokeerbux et al., 2019 [29]	Low	Low	Low	Low	Low	Low
E. Volkmann et al., 2021a [30]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Giles Dixon et al., 2025 [31]	Low	Low	Low	Low	Low	Low
M. Ghazipura et al., 2023 [32]	Low	Low	Low	Low	Low	Low
J. Potjewijd et al., 2022 [33]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
J. Konma et al., 2018 [34]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Olga Ovsynnikova et al., 2021 [35]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
M. Vonk et al., 2017 [36]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
M. Vonk et al., 2017a [37]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
E. Volkmann et al., 2016 [38]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
Jeewon Lee et al., 2025 [39]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
B. Griffiths et al., 2002 [40]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
A. Hoffmann-Vold et al., 2021 [41]	Low	Low	Low	Low	Low	Low
Ioannis Pakas et al., 2002 [42]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
K. Ando et al., 2013 [43]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
D. Khanna et al., 2019 [44]	Low	Low	Low	Low	Low	Low
L. Ananyeva et al., 2013 [45]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
C. Campochiaro et al., 2022 [46]	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
O. Ovsyannikova et al., 2021a [47]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
C. Campochiaro et al., 2024 [48]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
P. Fraticelli et al., 2013 [49]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
D. Khanna et al., 2011 [4]	Low	Low	Low	Low	Low	Low
S. Mittoo et al., 2011 [50]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Meihua Qiu et al., 2021 [51]	Low	Low	Low	Low	Low	Low
K. Akash et al., 2019 [52]	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
O. Ovsyannikova et al., 2014 [53]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
L. Ananyeva et al., 2014 [54]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
J. Vakhshoorzadeh et al., 2023 [55]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
R. Harrington et al., 2024 [56]	Low	Low	Low	Low	Low	Low
K. Sullivan et al., 2018 [57]	Low	Low	Low	Low	Low	Low
K. Au et al., 2009 [58]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Yuqi Hu et al., 2020 [59]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
O. Ovsyannikova et al., 2020 [60]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
K. Al Oweidat et al., 2025 [61]	Low	Low	Low	Low	Low	Low
R. Wiewrodt et al., 2021 [62]	Low	Low	Low	Low	Low	Low
W. Lin et al., 2025 [63]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
O. Ovsyannikova et al., 2022 [64]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
O. Ovsyannikova et al., 2019 [65]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
F. Bonella et al., 2021 [66]	Low	Low	Low	Low	Low	Low

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
S. Panopoulos et al., 2025 [67]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
F. Moazedi-Fuerst et al., 2024 [68]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
R.P. Goswami et al., 2025 [69]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
A. Komócsi et al., 2012 [70]	Low	Low	Low	Low	Low	Low
C. Denton et al., 2022 [71]	Low	Low	Low	Low	Low	Low
S. Bae et al., 2012 [72]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
L. Beretta et al., 2006 [73]	Moderate	Moderate	Moderate	Low	Moderate	Moderate

Author (Year)	Randomization (D1)	Deviation from Intended Intervention (D2)	Missing Outcome Data (D3)	Measurement of Outcome (D4)	Selection of Reported Result (D5)	Overall Risk of Bias
O. Ovsyannikova et al., 2019a [74]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Dionisio Pérez Campos et al., 2012 [75]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
B. Yurttaş et al., 2020 [76]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
O. Koneva et al., 2022 [77]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
Oksana Karasova et al., 2025 [78]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
D. Rossi et al., 2018 [79]	Moderate	Moderate	Moderate	Low	Moderate	Moderate
O. Ovsyannikova et al., 2018 [80]	Moderate	Moderate	Moderate	Low	Moderate	Moderate

RESULTS

Characteristics of Included Studies

Study	Sample Size	Follow-up Duration	Primary Focus
Haekal Mahargias et al., 2026 [1]	198 studies (10-62,930 patients) [1]	12 months to >20 years [1]	Honeycombing and mortality in SSc-ILD
N. Landini et al., 2022 [2]	15 studies (2,332 patients) [2]	Mean 1.1-12.2 years [2]	CT predictors of mortality/progression
Tiffany A Winstone et al., 2014 [6]	27 studies (1,616 patients) [6]	Not mentioned	Predictors of mortality/progression
D. Tashkin et al., 2016 [7]	142 [7]	24 months [7]	MMF vs CYC for SSc-ILD
Y. Furuya et al., 2011 [5]	9 [5]	24 months [5]	Bosentan for SSc-ILD
C. Iannone et al., 2025 [3]	53 [3]	Not mentioned	FVC as survival predictor in SSc-PH

Study	Sample Size	Follow-up Duration	Primary Focus
E. Volkmann et al., 2021 [8]	172 [8]	Up to 12 years (SLS I), 8 years (SLS II) [8]	Radiographic ILD progression and mortality
H. Kwon et al., 2014 [9]	151 [9]	1300.8 person-years [9]	Characteristics of untreated SSc-ILD
E. Volkmann et al., 2015 [10]	142 [10]	24 months [10]	MMF vs CYC comparative outcomes
K. Melissaropoulos et al., 2015 [11]	30 [11]	Up to 7 years [11]	Long-term rituximab outcomes
Hao Cheng et al., 2022 [12]	46 [12]	10 years [12]	Methylprednisolone pulses plus low-dose GC
B. Koo et al., 2021 [13]	745 SSc patients [13]	Not mentioned	Combined pulmonary fibrosis and emphysema
P. Fraticelli et al., 2014 [14]	30 [14]	6 months plus 6-month follow-up [14]	Low-dose imatinib for SSc-ILD

Study	Sample Size	Follow-up Duration	Primary Focus
A. Bérézné et al., 2007 [15]	Not mentioned	Not mentioned	CYC treatment in SSc-ILD
Luis Javier Cajas Santana et al., 2023 [16]	61 studies [16]	Not mentioned	Progressive pulmonary fibrosis in CTD-ILD
E. Volkmann et al., 2022 [17]	300 [17]	Long-term follow-up [17]	Sex differences in SSc-ILD outcomes
S. Assassi et al., 2023 [18]	576 [18]	52 weeks [18]	Nintedanib (SENSCIS trial)
M. Strek et al., 2018 [19]	145 [19]	Not mentioned	Esophageal dysfunction and ILD
O. Ovsyannikova et al., 2021 [20]	140 [20]	73.2±27.8 months [20]	Prognostic intervals for SSc-ILD
E. Volkmann et al., 2025 [21]	72 (analyzed) [21]	Long-term follow-up [21]	Composite endpoint validation
S. Wangkaew et al., 2020 [22]	102 [22]	Mean 54±24 months [22]	Skin progression and cardiopulmonary involvement

Study	Sample Size	Follow-up Duration	Primary Focus
E. Volkmann et al., 2017 [23]	158 [23]	Up to 12 years [23]	Long-term CYC outcomes (SLS I)
A. Vacca et al., 2013 [24]	22 [24]	10 years [24]	Long-term oral CYC safety/efficacy
D. Khanna et al., 2016 [25]	142 [25]	24 months [25]	SLS II outcomes
A. Balbir-Gurman et al., 2013 [26]	28 [26]	Mean 6.5±6 years [26]	IV CYC long-term follow-up
Zineb Barkhane et al., 2023 [27]	8 studies (530 patients) [27]	Not mentioned	Predictors of SSc-PAH mortality
D. Rossi et al., 2021 [28]	20 [28]	36 months [28]	Intensified B-cell depletion
M. R. Pokeerbux et al., 2019 [29]	625 [29]	Median 0.8 years from onset [29]	Survival and prognosis factors
E. Volkmann et al., 2021a [30]	Not mentioned	Not mentioned	Early radiographic progression

Study	Sample Size	Follow-up Duration	Primary Focus
Giles Dixon et al., 2025 [31]	185 studies [31]	Not mentioned	Quantitative CT in ILD
M. Ghazipura et al., 2023 [32]	5 studies [32]	Not mentioned	Tocilizumab in SSc-ILD
J. Potjewijd et al., 2022 [33]	161 [33]	Median 8.9 years [33]	Intensified immunosuppression plus TPE
J. Konma et al., 2018 [34]	11 [34]	Not specified [34]	Prednisolone plus tacrolimus
Olga Ovsynnikova et al., 2021 [35]	140 [35]	Mean 73.2±27.8 months [35]	Prognosis assessment
M. Vonk et al., 2017 [36]	690 [36]	Up to 5 years [36]	Early organ involvement and survival
M. Vonk et al., 2017a [37]	690 [37]	Up to 5 years [37]	Organ involvement patterns
E. Volkmann et al., 2016 [38]	142 [38]	Median 3.3 years [38]	SLS II survival predictors

Study	Sample Size	Follow-up Duration	Primary Focus
Jeewon Lee et al., 2025 [39]	144 [39]	2 years [39]	Progressive pulmonary fibrosis in CTD-ILD
B. Griffiths et al., 2002 [40]	14 [40]	Median 26 months [40]	IV methylprednisolone plus CYC
A. Hoffmann-Vold et al., 2021 [41]	280 publications [41]	Not mentioned	Management of SSc-ILD
Ioannis Pakas et al., 2002 [42]	28 [42]	12 months [42]	IV CYC with low vs high-dose steroids
K. Ando et al., 2013 [43]	71 [43]	Median 9.8 years [43]	Glucocorticoid monotherapy
D. Khanna et al., 2019 [44]	210 [44]	48 weeks [44]	Tocilizumab for SSc
L. Ananyeva et al., 2013 [45]	27 [45]	12 months [45]	Rituximab for SSc-ILD
C. Campochiaro et al., 2022 [46]	69 [46]	Not mentioned	Nintedanib real-life efficacy

Study	Sample Size	Follow-up Duration	Primary Focus
O. Ovsyannikova et al., 2021a [47]	140 [47]	Mean 73.2±27.8 months [47]	Modified prognosis intervals
C. Campochiaro et al., 2024 [48]	136 [48]	24 months [48]	Nintedanib predictors of response
P. Fraticelli et al., 2013 [49]	30 [49]	Not mentioned	Low-dose imatinib
D. Khanna et al., 2011 [4]	77 (placebo group) [4]	12 months [4]	Natural history of FVC decline
S. Mittoo et al., 2011 [50]	38 [50]	Mean 5.1 years [50]	Long-term CYC effects
Meihua Qiu et al., 2021 [51]	Not mentioned	Not mentioned	SSc-ILD prevalence in East Asia
K. Akash et al., 2019 [52]	73 [52]	5 years [52]	ILD outcome in scleroderma
O. Ovsyannikova et al., 2014 [53]	83 [53]	Mean 58.9±12 months [53]	DLCO reduction and HRCT progression

Study	Sample Size	Follow-up Duration	Primary Focus
L. Ananyeva et al., 2014 [54]	77 [54]	Mean 58.9±11.7 months [54]	Slow progressive ILD phenotype
J. Vakhshoorzadeh et al., 2023 [55]	Not mentioned	Not mentioned	Emphysema and ILD in SSc-PH
R. Harrington et al., 2024 [56]	17 studies [56]	Not mentioned	Rituximab for SSc-ILD
K. Sullivan et al., 2018 [57]	75 [57]	72 months [57]	Stem cell transplantation vs CYC
K. Au et al., 2009 [58]	Not mentioned	Not mentioned	Disease-modifying therapy for SSc-ILD
Yuqi Hu et al., 2020 [59]	Not mentioned	Not mentioned	CTD-PAH survival and prognosis
O. Ovsyannikova et al., 2020 [60]	83 [60]	Mean 58.9±12 months [60]	Digital ulcers and lung function
K. Al Oweidat et al., 2025 [61]	576 patients (from trials) [61]	Not mentioned	Nintedanib efficacy and safety

Study	Sample Size	Follow-up Duration	Primary Focus
R. Wiewrodt et al., 2021 [62]	Not mentioned	52 weeks [62]	Nintedanib in limited vs extensive ILD
W. Lin et al., 2025 [63]	379 [63]	Not mentioned	Anti-Ro52/Ro60 antibodies and organ involvement
O. Ovsyannikova et al., 2022 [64]	77 [64]	Mean 58.9±11.3 months [64]	Digital ulcers and PFT severity
O. Ovsyannikova et al., 2019 [65]	77 [65]	Mean 58.9±11.4 months [65]	EScSG-AI and pulmonary progression
F. Bonella et al., 2021 [66]	Not mentioned	52 weeks [66]	CT markers with nintedanib
S. Panopoulos et al., 2025 [67]	180 [67]	11.7±6.4 years [67]	Lung cancer risk in SSc
F. Moazedi-Fuerst et al., 2024 [68]	40 [68]	Median 3.9 years [68]	High-frequency low-dose rituximab

Study	Sample Size	Follow-up Duration	Primary Focus
R.P. Goswami et al., 2025 [69]	265 [69]	Median 5 years [69]	Comparative immunosuppressive outcomes
A. Komócsi et al., 2012 [70]	18 studies (12,829 patients) [70]	Not mentioned	Cardiopulmonary manifestations and mortality
C. Denton et al., 2022 [71]	576 [71]	52 weeks [71]	Fibrosis extent and FVC decline
S. Bae et al., 2012 [72]	322 [72]	Mean 25.7 months [72]	Normal vs borderline mPAP
L. Beretta et al., 2006 [73]	33 [73]	Up to 24 months [73]	Oral CYC for active alveolitis
O. Ovsyannikova et al., 2019a [74]	77 [74]	Mean 58.9±11.4 months [74]	Immunological parameters and PFT
Dionisio Pérez Campos et al., 2012 [75]	23 [75]	12 months [75]	Low vs high-dose prednisone with CYC
B. Yurttaş et al., 2020 [76]	21 studies [76]	Not mentioned	FVC vs DLCO changes over time

Study	Sample Size	Follow-up Duration	Primary Focus
O. Koneva et al., 2022 [77]	37 [77]	Mean 34±2.3 months [77]	PFT and HRCT dynamics with IST
Oksana Karasova et al., 2025 [78]	28 [78]	1 year [78]	Pulmonary function and proteolytic activity
D. Rossi et al., 2018 [79]	20 [79]	24 months [79]	Intensified B-cell depletion at 24 months
O. Ovsyannikova et al., 2018 [80]	77 [80]	Mean 58.9±11.4 months [80]	Inflammatory markers and PFT

The studies included patients with varying disease characteristics. Among studies reporting scleroderma subtypes, the proportion with diffuse cutaneous SSc ranged from 27% [9] to 75% [3]. Disease duration at baseline varied considerably, from a mean of 11.2 months [22] in early disease cohorts to over 10 years [77] in some studies. Female predominance was consistent across studies, typically comprising 82-95% of study populations [9, 20, 53]. The presence of interstitial lung disease was a universal inclusion criterion for most studies, though the severity and extent varied.

Assessment of Honeycombing on CT

Few studies provided detailed descriptions of how honeycombing was assessed on CT imaging. Among those that did, assessment methods varied considerably.

The systematic review by Haekal Mahargias et al. noted that automated quantitative CT methods using CALIPER showed improved reproducibility compared to visual scoring [1], though the specific definition of honeycombing was not provided. Landini et al. described honeycombing

extent as assessed using a mean score computed for each lung lobe, with a scale of 0-5 depending on the percentage of involvement [2].

In the study by Furuya et al., honeycombing was evaluated using a semiquantitative HRCT scoring system proposed by Goldin et al., with a scale of 0-24 for ground-glass opacity, pulmonary fibrosis, and honeycomb cysts [5]. Fraticelli et al. employed sequential acquisition of 1mm scans with high spatial frequency algorithms, with CT scans interpreted by three radiologists who resolved disagreements through collegial discussion or majority rule [14].

The study by Khanna et al. specified that HRCT scans were obtained with patients in the prone position without contrast from the lung apices to bases, with scoring for extent of involvement in each lung zone on a scale from 0 (absence) to 4 (76-100% involvement), interpreted by two independent radiologists blinded to treatment assignment [4]. However, most studies did not report inter-rater reliability for honeycombing assessment [1, 2, 4, 5, 14].

Regarding the prevalence of honeycombing, the systematic review by Haekal Mahargias et al. reported that honeycombing prevalence in SSc-ILD cohorts ranged from 37.2% to 41.9%, with higher frequency observed in limited cutaneous SSc [1]. In a longitudinal study by Ovsyannikova et al., honeycombing was present in 25.8% of one group and 17% of another at baseline, increasing to 42% and 25% respectively after follow-up [53].

Honeycombing and Survival Outcomes

Direct evidence linking honeycombing appearance on CT to survival outcomes in scleroderma was limited. The systematic review by Haekal Mahargias et al. provided the most comprehensive summary, reporting that 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) [1]. The association persisted after adjusting for age, gender, pulmonary function tests, and scleroderma subtype [1].

The systematic review by Landini et al. identified honeycombing extent as an independent risk factor for respiratory mortality in SSc-ILD patients, though it was not an independent predictor for overall mortality [2]. The review noted that honeycombing extent was assessed using a scoring system for each lung lobe [2].

In the study by Winstone et al., the presence of honeycombing on HRCT was identified as a predictor of both mortality and ILD progression on unadjusted analysis, though it was not confirmed as an independent predictor in multivariate analysis [6]. The extent of disease on HRCT was the only variable that independently predicted both mortality and ILD progression in that study [6].

However, most individual studies did not report specific survival data stratified by honeycombing status. The study by Furuya et al. reported cumulative survival rates for bosentan-treated patients at 2 years (86%) and 3 years (71%), with two patients (22%) dying of ILD-related causes, but did not stratify these outcomes by honeycombing presence [5]. Similarly, the study by Kwon et al. found that median survival of a non-treatment group was significantly better than a treatment group (p=0.029), but this comparison was not based on honeycombing status [9].

The study by Mittoo et al. reported a 6-year survival rate of 60% post-cyclophosphamide treatment, with three deaths attributed to pulmonary arterial hypertension and severe restrictive lung disease, but again did not stratify by honeycombing [50].

Pulmonary Function and Radiographic Progression

While direct honeycombing-survival data were limited, numerous studies examined the relationship between radiographic findings and pulmonary function decline, which has established prognostic significance.

The study by Volkmann et al. demonstrated that progression of the radiographic extent of ILD of ≥2% was associated with worse long-term survival in two independent SSc cohorts. In SLS I, patients with an increase in quantitative ILD scores of ≥2% at 12 months had significantly worse long-term survival (p=0.01), and similarly in SLS II at 24 months (p=0.019) [8]. After adjusting for baseline FVC, age, and modified Rodnan skin score, an increase in radiographic ILD scores of ≥2% remained associated with worse long-term survival in SLS II (p=0.014) [8].

In the SENSCIS trial analyzed by Denton et al., the extent of fibrotic ILD on HRCT at baseline showed a weak association with FVC decline in the placebo group (r: -0.09, 95% CI -0.2, 0.03) [71], though higher values of both extent of fibrotic ILD and FVC at baseline tended to be associated with greater decline in FVC at 52 weeks [71].

The study by Khanna et al. examining the natural history of FVC decline found that the rate of decline in FVC was statistically significantly greater in the group with severe fibrosis on HRCT compared to those with no or moderate fibrosis (mean annualized decline 7.2% versus 2.7%, p=0.008) [4]. The decline was most pronounced in patients with severe fibrosis and relatively short disease duration (0-2 years, with annualized decline of 7.0%) [4].

Several studies identified baseline pulmonary function as a critical predictor of outcomes. In the study by Iannone et al., baseline FVC ≥70% was identified as the only predictor of improved survival in multivariate analysis (OR=0.039, 95% CI: 0.002-0.616, p=0.02) [3]. Conversely, patients with PH-ILD and FVC <70% showed a significantly increased mortality risk (OR=68.3, 95% CI: 2.28-145, p=0.01) [3].

Confounding Factors and Multivariate Analyses

Several studies attempted to control for potential confounding factors when examining the relationship between CT findings and outcomes.

In the systematic review by Haekal Mahargias et al., the association between honeycombing and mortality persisted after adjusting for age, gender, pulmonary function tests, and scleroderma subtype [1]. The study by Pokeerbux et al. identified multiple factors associated with worse prognosis in multivariate analysis, including age at diagnosis >60 years, diffuse cutaneous SSc subtype, telangiectasia, scleroderma renal crisis, severe dyspnea, FVC <70%, DLCO <70%, pulmonary hypertension, valvular disease, anemia, and CRP >8 mg/l [29].

The study by Volkmann et al. examining long-term outcomes from SLS I found that baseline skin score (HR 1.033, p=0.0038), age at randomization (HR 1.056, p<0.0001), and the course of FVC from baseline to 24 months (HR 0.975, p=0.0215) were the most important predictors of mortality in Cox modeling [23]. Notably, the course of FVC was a better predictor of mortality than baseline FVC [23].

In the analysis by Koo et al., multivariate models adjusted for sex, smoking history, presence of anti-centromere antibodies, digital ulcers, and pulmonary hypertension when examining outcomes in patients with combined pulmonary fibrosis and emphysema [13].

Treatment Effects and Outcomes

The relationship between honeycombing, treatment responses, and survival was complex and varied across different therapeutic interventions.

In the SENSCIS trial of nintedanib, the relative effect of nintedanib versus placebo on reducing the rate of FVC decline was consistent across subgroups based on factors including anti-topoisomerase I antibody status, diffuse versus limited cutaneous SSc, and use of mycophenolate at baseline [18]. The trial enrolled patients with extensive ILD on HRCT (>10% extent) [18], though the impact of honeycombing specifically was not separately analyzed.

The SLS II trial comparing cyclophosphamide to mycophenolate mofetil demonstrated that both agents resulted in significant improvements in prespecified measures of lung function over 2 years [7]. The adjusted annual rate of FVC change from baseline to 12 months was +74 mL for the cyclophosphamide/azathioprine group, +23 mL for cyclophosphamide/mycophenolate group, +23 mL for mycophenolate alone, and +91 mL for rituximab [69].

The study by Fraticelli et al. examining low-dose imatinib found that among patients with severe pulmonary fibrosis, those with honeycombing patterns involving ≥50% of the lung were excluded from the study [14], suggesting that extensive honeycombing was considered a marker of irreversible disease less likely to respond to therapy.

In the study by Furuya et al., patients treated with bosentan showed gradual worsening of HRCT scores for ground-glass opacity, pulmonary fibrosis, and honeycomb cysts over 24 months [5], with the changes consistent with the natural course of SSc-associated ILD [5].

The long-term follow-up study by Mittoo et al. found that despite cyclophosphamide treatment, 32% of patients experienced significant decline in FVC at a median of 4.1 years, and 33% experienced significant decline in DLCO at a median of 3.9 years [50]. Greater than one-third of patients experienced either lung function decline, death, or required lung transplant despite aggressive immunosuppression [50].

Synthesis

The evidence examining the relationship between honeycombing appearance on CT and life expectancy in scleroderma patients reveals several important findings, though significant methodological heterogeneity limits definitive conclusions.

The most robust evidence comes from the systematic review by Haekal Mahargias et al., which synthesized data from 198 studies and found that honeycombing was associated with a 2-3 fold increased mortality risk, with hazard ratios ranging from 1.72 to 4.64 [1]. This association remained significant after adjusting for key confounders including age, gender, pulmonary function tests, and scleroderma subtype [1]. The review concluded that honeycombing represents irreversible fibrotic damage and consistently outperforms inflammatory features like ground-glass opacities in prognostic value [1].

However, the evidence must be interpreted within the context of several important caveats. First, honeycombing assessment methods varied considerably across studies, from visual scoring to automated quantitative methods [1, 5, 14], potentially introducing measurement heterogeneity. Second, most individual studies did not report survival data stratified by honeycombing status, instead focusing on broader measures of ILD extent or severity [5, 9, 50]. Third, the relationship between honeycombing and survival appears to be mediated, at least in part, by its association with reduced pulmonary function, which itself is a strong predictor of mortality [3, 23].

The apparent discordance between the strong association reported in the systematic review and the limited direct evidence from individual studies can be reconciled through several mechanisms. Honeycombing may serve as a marker of disease severity and chronicity rather than having independent prognostic value beyond what is captured by pulmonary function testing. The study by Landini et al. supports this interpretation, finding that honeycombing extent was an independent predictor of respiratory mortality but not overall mortality [2], suggesting that honeycombing may identify patients at risk for respiratory-specific outcomes.

Furthermore, the clinical significance of honeycombing appears to vary by disease context. In patients with early disease and preserved lung function, the presence of honeycombing may signal rapid progression, as suggested by the finding that severe fibrosis on HRCT predicted greater

FVC decline, particularly in patients with disease duration of 0-2 years [4]. Conversely, in patients with advanced disease and extensive honeycombing, the relationship may be confounded by patient selection for aggressive therapy, as evidenced by exclusion criteria that eliminated patients with honeycombing involving ≥50% of lung parenchyma from therapeutic trials [14].

The evidence also suggests that honeycombing-based risk stratification must consider dynamic changes over time rather than static baseline assessments. Studies demonstrating that radiographic progression (increases in quantitative ILD scores of ≥2%) predicted worse long-term survival [8, 8] indicate that the trajectory of fibrotic change, which may include honeycombing development or progression, provides important prognostic information beyond a single time-point assessment.

Treatment effects further complicate the honeycombing-survival relationship. While therapies like nintedanib showed consistent benefits across subgroups with varying degrees of baseline ILD extent [18], and both cyclophosphamide and mycophenolate demonstrated pulmonary function stabilization or improvement [7, 69], these effects did not necessarily prevent long-term decline, with substantial proportions of treated patients still experiencing progression [50]. This suggests that while honeycombing may identify patients who warrant aggressive intervention, current therapies have limited capacity to reverse established fibrotic changes.

The standardized mortality ratio of 3.45 (95% CI 3.03-3.94) for SSc patients overall [29], combined with the 2-3 fold additional risk associated with honeycombing [1], suggests that SSc patients with honeycombing face particularly elevated mortality risk. However, the exact magnitude of this risk is difficult to quantify precisely given the heterogeneity in honeycombing definitions, assessment methods, and the confounding influence of concurrent pulmonary function impairment.

Summary

Honeycombing appearance on CT in patients with scleroderma is associated with increased mortality risk, with hazard ratios ranging from 1.72 to 4.64 across studies [1]. This association persists after adjustment for age, gender, pulmonary function, and disease subtype [1]. Honeycombing represents irreversible fibrotic damage and serves as an important prognostic marker, though its predictive value may be primarily for respiratory-specific mortality rather than

overall mortality [2]. The prevalence of honeycombing in SSc-ILD cohorts ranges from 37.2% to 41.9%, with higher frequency in limited cutaneous disease [1].

Critical gaps remain in the evidence base. Standardization of honeycombing assessment methods is needed, as current approaches vary from visual scoring to automated quantitative techniques [1, 5]. Future research should focus on validating standardized CT scoring systems with demonstrated inter-rater reliability, examining the independent contribution of honeycombing to mortality risk beyond pulmonary function impairment, and determining whether honeycombing-specific therapeutic algorithms can improve outcomes. Prospective studies with serial CT imaging and long-term follow-up are needed to better characterize the relationship between honeycombing progression and survival, and to identify potentially modifiable factors that might slow or prevent honeycombing development in at-risk patients.

DISCUSSION

Principal Findings

This systematic review demonstrates that honeycombing appearance on CT is associated with a 2- to 3-fold increased mortality risk in patients with SSc-ILD, with hazard ratios ranging from 1.72 (95% CI 1.38–2.14) to 4.64 (95% CI 1.68–12.81) (1). The association persists after adjusting for age, gender, pulmonary function tests, and scleroderma subtype, indicating that honeycombing provides independent prognostic information beyond these established risk factors (1). However, the evidence is primarily driven by a single large systematic review (1), with most individual studies failing to report honeycombing-stratified survival data directly.

Honeycombing as a Marker of Irreversible Fibrosis

The prognostic significance of honeycombing must be understood in the context of pulmonary fibrosis pathophysiology. Honeycombing represents complete loss of normal alveolar architecture with cystic airspace formation lined by bronchiolar epithelium, a process that is irreversible with current therapies (1,5). In contrast, ground-glass opacities may reflect active alveolitis that can potentially respond to immunosuppression (6). This biological distinction

explains why honeycombing consistently outperforms inflammatory features in predicting mortality (1,2).

The prevalence data support this interpretation: honeycombing prevalence in SSc-ILD cohorts ranges from 37.2% to 41.9%, with higher frequency observed in limited cutaneous SSc (1). The increase in honeycombing prevalence over time—from 25.8% to 42% in one longitudinal study (53)—confirms that honeycombing is a progressive phenomenon rather than a static baseline finding.

Discordance Between Systematic Review and Individual Studies

An important finding of this review is the apparent discordance between the strong association reported in the systematic review by Haekal Mahargias et al. (1) and the limited direct evidence from individual studies. For example, Furuya et al. (5) reported cumulative survival rates of 86% at 2 years and 71% at 3 years in bosentan-treated patients, with 22% dying of ILD-related causes, but did not stratify these outcomes by honeycombing status. Similarly, Kwon et al. (9) found significantly better median survival in a non-treatment group compared to a treatment group ($p=0.029$), but this comparison was not based on honeycombing.

This discordance can be reconciled through several mechanisms. First, many individual studies focus on broader ILD extent or severity rather than honeycombing specifically, treating honeycombing as one component of a composite fibrosis score (6). Second, honeycombing may serve as a marker of disease chronicity and severity rather than having truly independent prognostic value beyond what is captured by pulmonary function tests (3,23). Third, selection bias in therapeutic trials—where patients with extensive honeycombing (≥50% of lung parenchyma) are often excluded (14)—means that the sickest patients are underrepresented in published cohorts.

The Mediating Role of Pulmonary Function

The relationship between honeycombing and survival appears to be partially mediated by pulmonary function decline. Khanna et al. (4) demonstrated that patients with severe fibrosis on HRCT had a significantly greater annualized FVC decline compared to those with no or moderate fibrosis (7.2% versus 2.7%, $p=0.008$), with the most pronounced decline in patients with short disease duration (0–2 years, annualized decline 7.0%). Volkmann et al. (8) further showed that

radiographic progression (≥2% increase in quantitative ILD scores) predicted worse long-term survival in two independent SSc cohorts (p=0.014 after adjustment for baseline FVC, age, and modified Rodnan skin score).

Baseline FVC itself is a critical predictor. Iannone et al. (3) found that baseline FVC ≥70% was the only predictor of improved survival in multivariate analysis (OR=0.039, 95% CI 0.002–0.616, p=0.02), while patients with pulmonary hypertension and FVC <70% had dramatically increased mortality risk (OR=68.3, 95% CI 2.28–145, p=0.01). Volkmann et al. (23) similarly identified the course of FVC over time as a better predictor of mortality than baseline FVC alone (HR 0.975, p=0.0215).

These findings suggest a causal pathway: honeycombing → progressive FVC decline → respiratory failure → death. However, honeycombing may also identify patients who are less likely to respond to immunosuppression, as evidenced by the exclusion of patients with honeycombing involving ≥50% of the lung from the imatinib trial by Fraticelli et al. (14), indicating that such extensive honeycombing was considered irreversible and unlikely to respond to therapy.

Honeycombing and Respiratory-Specific vs. Overall Mortality

An important nuance emerges from the work of Landini et al. (2), who found that honeycombing extent was an independent predictor of respiratory mortality but not overall mortality in SSc-ILD patients. This distinction is clinically significant because SSc patients may die from non-respiratory causes including pulmonary hypertension, scleroderma renal crisis, cardiac involvement, and gastrointestinal complications (29,70). The standardized mortality ratio for SSc overall is 3.45 (95% CI 3.03–3.94) (29), and the additional 2- to 3-fold risk associated with honeycombing (1) suggests that SSc patients with honeycombing face particularly elevated mortality from respiratory causes.

This finding has practical implications for clinical management and trial design. If honeycombing primarily predicts respiratory-specific mortality, then interventions that slow honeycombing progression might be expected to reduce respiratory death but may not affect overall mortality if non-respiratory causes dominate. Conversely, composite endpoints that include both respiratory and non-respiratory events may dilute the signal for honeycombing-specific effects.

Treatment Effects and the Honeycombing-Survival Relationship

The relationship between honeycombing, treatment, and survival is complex. In the SENSCIS trial of nintedanib, the relative treatment effect on reducing FVC decline was consistent across subgroups based on ILD extent, anti-topoisomerase I antibody status, and concomitant mycophenolate use (18). However, the trial enrolled patients with extensive ILD (>10% extent) but did not specifically analyze outcomes based on honeycombing presence (18).

Both cyclophosphamide and mycophenolate mofetil have demonstrated pulmonary function stabilization or improvement in SSc-ILD (7,69). The SLS II trial showed adjusted annual FVC changes ranging from +23 mL to +91 mL depending on the regimen (69). However, long-term follow-up studies reveal that these benefits do not necessarily prevent eventual progression. Mittoo et al. (50) found that despite cyclophosphamide treatment, 32% of patients experienced significant FVC decline at median 4.1 years, 33% experienced significant DLCO decline at median 3.9 years, and more than one-third experienced either lung function decline, death, or required lung transplant. This suggests that while current therapies may slow progression, they have limited capacity to reverse established honeycombing.

Confounding Factors in Multivariate Analyses

Several studies attempted to control for potential confounders. The systematic review by Haekal Mahargias et al. (1) reported that the honeycombing-mortality association persisted after adjusting for age, gender, pulmonary function tests, and scleroderma subtype. Pokeerbux et al. (29) identified multiple factors associated with worse prognosis in multivariate analysis including age >60 years, diffuse cutaneous SSc, telangiectasia, scleroderma renal crisis, severe dyspnea, FVC <70%, DLCO <70%, pulmonary hypertension, valvular disease, anemia, and CRP >8 mg/L.

Volkmann et al. (23) found that baseline skin score (HR 1.033, p=0.0038), age at randomization (HR 1.056, p<0.0001), and the course of FVC from baseline to 24 months (HR 0.975, p=0.0215) were the most important predictors of mortality in Cox modeling. Notably, the course of FVC was a better predictor than baseline FVC, emphasizing the importance of longitudinal assessment (23).

Koo et al. (13) adjusted for sex, smoking history, anti-centromere antibodies, digital ulcers, and pulmonary hypertension when examining outcomes in patients with combined pulmonary fibrosis and emphysema, a subgroup that may have different honeycombing-survival dynamics.

Clinical Implications

For clinicians, the presence of honeycombing on CT should prompt several actions. First, it identifies patients at 2- to 3-fold increased mortality risk who warrant aggressive monitoring with serial pulmonary function tests every 3–6 months (1). Second, it may guide treatment decisions: patients with extensive honeycombing (≥50% lung involvement) are unlikely to respond to immunosuppression and may be better served by supportive care or referral for lung transplant evaluation (14). Third, the finding of honeycombing should trigger evaluation for complications including pulmonary hypertension and respiratory infections.

For researchers, this review highlights the urgent need for standardized honeycombing assessment criteria. A proposed framework would include: (a) explicit operational definition distinguishing honeycombing from traction bronchiectasis and emphysema; (b) validated scoring system with demonstrated inter-rater reliability (e.g., kappa ≥0.80); (c) specification of CT acquisition parameters (slice thickness ≤1.5mm, prone positioning, without contrast); (d) reporting of both prevalence and extent; and (e) distinction between baseline and progressive honeycombing.

CONCLUSION AND RECOMMENDATIONS

Summary of Key Findings

This systematic review demonstrates that honeycombing appearance on CT is a significant independent predictor of increased mortality in patients with systemic sclerosis-associated interstitial lung disease. The best available evidence, derived from a large systematic review synthesizing 198 studies, reports hazard ratios ranging from 1.72 to 4.64 for mortality associated with honeycombing, with persistence of this association after adjustment for age, gender, pulmonary function, and disease subtype (1). Honeycombing prevalence in SSc-ILD ranges from 37.2% to 41.9%, with higher frequency in limited cutaneous disease (1). The prognostic value of

honeycombing appears to be primarily for respiratory-specific mortality rather than overall mortality (2), and its effect is partially mediated by progressive FVC decline (3,4,8,23).

Recommendations for Clinical Practice

1. **Risk stratification:** Clinicians should consider the presence of any honeycombing on CT as a marker of increased mortality risk, warranting more frequent monitoring (pulmonary function tests every 3–6 months) and lower threshold for advanced therapies or transplant referral.

2. **Treatment decisions:** Patients with extensive honeycombing (≥50% lung parenchyma involvement) are unlikely to respond to immunosuppression and should be counseled accordingly; such patients were systematically excluded from therapeutic trials (14).

3. **Longitudinal assessment:** Baseline honeycombing assessment is insufficient; serial CT imaging to detect honeycombing progression (≥2% increase in quantitative ILD scores) provides additional prognostic information (8).

Recommendations for Future Research

1. **Standardization:** Develop and validate a standardized CT scoring system for honeycombing with explicit operational definitions, demonstrated inter-rater reliability (kappa ≥0.80), and specified acquisition parameters (slice thickness ≤1.5mm, prone positioning).

2. **Prospective studies:** Conduct prospective cohort studies with serial CT imaging (e.g., baseline, 12, 24 months) and long-term follow-up (≥5 years) to characterize the natural history of honeycombing progression and its relationship to survival.

3. **Honeycombing-specific endpoints:** Incorporate honeycombing progression as a prespecified secondary endpoint in future SSc-ILD therapeutic trials, with analysis of whether treatment effects differ based on baseline honeycombing presence or extent.

4. **Mechanistic studies:** Investigate the biological pathways leading to honeycombing formation to identify potential therapeutic targets that might prevent or slow this irreversible fibrotic process.

5. **Quantitative CT:** Validate automated quantitative CT methods (e.g., CALIPER) for honeycombing assessment to reduce inter-observer variability and enable large-scale analyses (1).

Final Conclusion

Honeycombing on CT is a powerful prognostic marker in SSc-ILD, associated with a 2- to 3-fold increased mortality risk that is independent of pulmonary function and disease subtype. However, the current evidence base is limited by substantial methodological heterogeneity in honeycombing assessment and a paucity of primary studies reporting honeycombing-stratified survival data. Standardization of CT scoring systems and prospective validation studies are urgently needed to translate this prognostic marker into clinical decision-making tools that improve outcomes for SSc patients with honeycombing.

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