ORIGINAL ARTICLE

# Effectiveness of Cyclophosphamide and Immunosuppressants in Systemic Sclerosis-associated Interstitial Lung Disease: A Meta-analysis

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## Abstract

**Objective:** The present meta-analysis compares the effectiveness of cyclophosphamide (CYC) as an immunosuppressant in systemic sclerosis-associated interstitial lung disease (SSc-ILD) with placebo, and other immunosuppressants.

**Methodology:** The study involved randomized trials and observational studies identified through a systematic literature search using various databases, such as Elton B Stephens Company (EBSCO) Medline/PubMed, Scopus, Web of Science, Google Scholar, PubMed Central, Cochrane Library, and ScienceDirect. These studies compared the effectiveness of CYC with placebo or other immunosuppressants in terms of lung parameters. Meta-analysis and network meta-analysis were conducted to evaluate the effectiveness of the treatments.

**Results:** Upon comparison, azathioprine (AZA) was favored over CYC for forced vital capacity (FVC) ($d = 1.02$, $p = 0.00$) and diffusing capacity of the lungs for carbon monoxide (DLCO) ($d = 0.88$, $p = 0.00$). No significant difference in FVC between CYC and mycophenolate mofetil (MMF) was found, although CYC was slightly preferred ($d = -0.12$, $p = 0.60$). CYC was beneficial over placebo in reducing the Dyspnea Index score ($d = 0.78$, $p = 0.00$) but not in improving DLCO. Network analysis revealed that CYC had the highest FVC outcome *p*-scores (0.6559), while rituximab (RTX) had the lowest (0.3410). For DLCO, AZA had the highest *p*-score (0.5707), followed by placebo (0.5180).

**Conclusion:** While suggesting the potential benefits of CYC and AZA, the study findings do not decisively support the superiority of CYC over other treatments for most SSc-ILD lung function parameters. This emphasizes the need for rigorous, ongoing research to refine treatment strategies and address unresolved questions regarding the efficacy and safety profile of CYC.


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## Introduction

Scleroderma or systemic sclerosis (SSc) is an autoimmune disease characterized by microvascular damage, excessive skin fibrosis, and distinct visceral alterations that may impact organs such as the lungs, heart, kidneys, and gastrointestinal tract.[1] The global incidence is 8.64 per 1,00,000 person-years, with 0.67 million new cases annually, and the global prevalence is 18.87 per 1,00,000 persons, with 1.47 million affected individuals.[2] The disease prevalence is higher in females, adults, and high-income countries.[3]

Systemic sclerosis is a rare disease, but it significantly affects the quality of life, and affected subjects have increased mortality rates compared to the general population.[4] The primary causes of mortality and decreased survival are rapid progression, pulmonary fibrosis, cardiac complications, and gastrointestinal involvement. Pulmonary complications like interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH) are prevalent in SSc and are the primary contributors to SSc-related morbidity and mortality, surpassing other connective tissue disorders.[5–7]

Interstitial lung disease, a group of lung conditions characterized by noninfectious infiltrates, is noted in 30–70% of the patients with SSc.[8,9] It can cause architectural distortion and irreversible fibrosis and pose the highest risk within the initial 4–5 years of SSc diagnosis. Symptoms range from minor lung involvement to severe pulmonary disease, progressing to respiratory failure and mortality.[10] Over 35% of SSc-related deaths are attributed to ILD, and it correlates with a decreased survival rate.[6,11,12]

Clinical assessments for lung disease in scleroderma include pulmonary function tests (PFTs) measuring forced vital capacity (FVC), total lung capacity (TLC), and diffusing capacity of the lungs for carbon monoxide (DLCO), chest radiography, and high-resolution computed tomography (HRCT).[13,14] The European Alliance of Associations for Rheumatology recommends cyclophosphamide (CYC) for treating systemic sclerosis-associated interstitial lung disease (SSc-ILD), while mycophenolate mofetil (MMF), rituximab (RTX), or azathioprine (AZA) may be considered based on individual patient characteristics.[15–18] The latest guidelines from the American College of Rheumatology offer a conditional recommendation endorsing the use of MMF, RTX, CYC, and AZA as primary treatment options for SSc-ILD.[19]

Cyclophosphamide has been used in the treatment of cancer and immune disorders for several decades. However, its clinical use has been reduced with the advent of newer therapies. Recent evidence suggests that CYC may still hold promise for certain patients, particularly those refractory to alternative treatments. One of the key advantages is its affordability. It is also widely available. Through meticulous scrutiny and additional research, CYC could offer therapeutic benefits for select patients. Recognizing the paucity of comparative studies and the rarity of the disease, leading to smaller sample sizes in studies, the present study conducted a meta-analysis to evaluate the effectiveness of CYC in comparison to various immunosuppressants in SSc-ILD, aiming to elucidate their effectiveness in this patient cohort.

## Methodology

This meta-analysis study was conducted following the guidelines set by the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).[20]

### Inclusion and Exclusion Criteria

The research encompassed randomized controlled trials (RCTs) and observational

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studies, admitting individuals of all age-groups above 18 years diagnosed with SSc-ILD. Studies comparing the efficacy of CYC against placebo and immunosuppressants in patients with SSc-ILD and containing complete data for meta-analysis were considered. There were no restrictions on dosage, administration method, or treatment duration. Abstracts, reviews, animal studies, editorials, case reports, duplicate or irrelevant studies, studies lacking data on the outcome of interest, and those with incomplete data for conducting a meta-analysis were excluded.

### Search Strategy

A comprehensive exploration spanning from 1968 to 2023 was conducted on Elton B Stephens Company (EBSCO) Medline/PubMed, Scopus, Web of Science, Google Scholar, PubMed Central, Cochrane Library, and ScienceDirect databases to identify pertinent literature. The search strategy involved a combination of indexed terms such as SSc, scleroderma, ILD, lung parameters, ILD, CYC, MMF, and RTX. The final search was concluded on November 19, 2023. Principal outcome indicators comprised percent predicted FVC, TLC, DLCO, and score on the Dyspnea Index. Studies reporting any of the above primary outcomes were considered.

### Study Screening and Data Extraction

Following the search, the three reviewers independently evaluated titles and abstracts to eliminate papers failing to meet the inclusion criteria. Duplicate entries across databases were removed, and full-text articles meeting the criteria were procured. Data extraction was carried out by the investigator, encompassing study details such as name, publication year, study design, participant count, drugs administered, treatment duration, age demographics, baseline and posttreatment metrics including percentage predicted FVC, TLC, DLCO, and score on the Dyspnea Index. For studies that presented data in forms other than mean and standard deviation (SD), the reported statistics were converted to the mean and SD format using standard statistical methods.[21,22]

### Quality Assessment of Selected Studies

The RCTs were evaluated based on their quality using the Jadad score. The Jadad score is made up of three items: randomization (0–2 points), blinding (0–2 points), and dropouts and withdrawals (0–1 point). For each item, a "yes" answer earned 1 point and a "no" answer earned 0 points. The final score ranged from 0 to 5 points, with higher scores indicating better reporting. Studies with a Jadad score of ≤2 were considered to be of low quality, while those with a score of ≥3 were considered to be of high quality.[23,24] The quality of observational studies was assessed using the Newcastle–Ottawa Scale (NOS). This scale consists of three items: selection, comparability, and outcome. The NOS has three categorical criteria with a maximum score of 9 points. Based on these criteria, the quality of each study was rated as follows: a score of ≥7 points was considered "good," a score of 2–6 points was considered "fair," and a score of ≤1 point was considered "poor" quality.[25,26]

### Sensitivity Analysis

The sensitivity analysis aimed to explore variations in key characteristics and outcomes across the studies included in the meta-analysis. This process assessed the impact of age, sample size, study design, treatment regimens, and baseline measurements of the outcomes.

### Statistical Analysis

#### *Meta-analysis*

A meta-analysis was conducted using SPSS version 29.0.2.0. The common procedure for both fixed and random effects models involved selecting meta-analysis from the analyze menu and choosing continuous outcomes with raw data. Treatment (CYC) and control groups were defined, with Cohen's *d* used to calculate effect sizes and a 95% confidence interval. Missing data were excluded on a case-by-case basis, including user-defined missing values. Iterations were set with a maximum of 100, a step size of 5, and a convergence criterion of 0.000001. Outputs for both models included tests of homogeneity, heterogeneity measures, and effect sizes for individual studies. A forest plot was generated, displaying effect size, standard error, confidence interval limits, *p*-values, and study weights, with annotations for homogeneity and heterogeneity tests. Reference lines for overall and null effect sizes were also included.

The fixed effects model was initially used for the meta-analysis, applying Cohen's *d* with an adjusted standard error. Egger's regression-based test was utilized to assess publication bias, using age and baseline treatment (mean and SD) as covariates, along with posttreatment values. The analysis also incorporated the regression intercept, dispersion parameter, and *t*-distribution-based statistics. For sensitivity-analysis, a random effects model was applied to compare results with the fixed effects model, using restricted maximum likelihood (REML) estimation without adjusting the standard error. Additionally, a prediction interval was provided under the random effects model to capture between-study variability.

#### *Network Meta-analysis*

For the network meta-analysis, RStudio version 2024.04.0 was employed, with CYC as the reference treatment. The effect size was calculated as the difference between posttreatment and baseline means. Variances were estimated using the posttreatment and baseline SDs, accounting for the number of patients. Pairwise treatment effects and their standard errors were computed by comparing the effect sizes and variances of CYC and the respective treatments. The *P*-scores, representing the probability of being the best treatment, were derived for both common and random effects models. The *P*-score (common) was used for the final analysis.

Network graphs and comparative results for the treatments, using CYC as the reference, were obtained by running the appropriate R code in RStudio. The effect size was calculated by subtracting the baseline mean from the posttreatment mean, while the variance was obtained by summing the squared posttreatment SD divided by the number of patients and the squared baseline SD divided by the same number. The pairwise treatment effect was defined as the difference between the treatment effects of CYC and the comparator treatment. The pairwise standard error of the treatment effect was calculated as the square root of the sum of the squared standard errors for both CYC and the comparator treatment.[27]

A $p$-value $< 0.05$ was considered statistically significant for all the analyses. Visual representations, including forest plots and network graphs, were generated to facilitate the interpretation of the results.

## Results

### Study Selection

An initial search of the literature in the databases yielded a total of 1,123 studies. Of these, 453 articles were excluded due to duplication, leaving 674 studies. Subsequently, 584 studies were excluded after reviewing the synopses or article titles. Overall, 44 studies were selected after a thorough evaluation of entire texts. A total of 28 studies were excluded due to a lack of comparative study design. An additional two studies were excluded as they were already meta-analysis articles. Furthermore, six studies were excluded because they did not provide sufficient data to perform the intended analysis. Finally, eight studies, consisting of four RCTs and

four observational studies, met the criteria and were considered for the analysis.[1,28–34] The progression of study selection, detailing the attrition from the initial search to the final studies included in the data synthesis, is depicted as a PRISMA flow diagram (Fig. 1). These studies collectively involved 484 patients, with a mean age ranging from 34 to 83.5 years. Notably, females were more prevalent among the patient cohorts. The basic characteristics and the lung function outcomes are presented in Tables 1 and 2.[1,28–34]

## Quality Assessment of Selected Studies

The Jadad score was used to assess the quality of four RCTs, and the results are presented in Supplementary Table 1. According to the Jadad scale, two studies scored 3, one study scored 4, and one study scored 0. The four observational studies were assessed by the NOS scale; three studies scored 9, and one study scored 8 (Supplementary Table 2). The funnel plot analysis for detecting publication bias was not performed since there were fewer than 10 studies and insufficient power to yield reliable results.[35]

## Efficacy Outcome for Forced Vital Capacity

The CYC group comprised a total of 57 patients, while the AZA group included 45 patients. There was a significant difference in FVC upon comparison between the two groups. The fixed-effect analysis favored AZA [overall (Cohen's *d* standard, 1.02; standard error, 0.31; 95% CI: 0.42–1.62; $p$ = 0.00)]. Homogeneity was not present in the population of studies included in the above analysis (Fig. 2).

The CYC group consisted of 33 patients, whereas the MMF group included 44 patients. No significant difference in FVC was found upon comparison of CYC with MMF. However, the fixed-effect analysis indicated a slight preference for CYC [overall (Cohen's *d* standard, −0.12; standard error, 0.23; 95% CI: −0.58 to 0.33; $p$ = 0.60)]. Homogeneity was maintained below 50% (3.6% among the two studies included) (Fig. 2).

The CYC group comprised 64 patients, while the RTX group included 57 patients. A mild but insignificant difference was observed in FVC on comparison between CYC and RTX, yet the analysis leaned toward favoring CYC [overall (Cohen's *d* standard, −0.31; standard error, 0.19; 95% CI: −0.68 to 0.05; $p$ = 0.09)]. Homogeneity was not maintained below 50% (54% among the two studies included) (Fig. 2).

Both the CYC and placebo groups consisted of 95 patients each. No significant difference in FVC was found in the comparison between CYC and placebo. However, the fixed-effect analysis slightly favored the placebo [overall (Cohen's *d* standard, 0.11; standard error, 0.15; 95% CI: −0.17 to 0.40; $p$ = 0.44)]. Homogeneity was maintained below 50% (3.1% between the two studies included) (Fig. 2).

## Efficacy Outcome for Diffusing Capacity of the Lung for Carbon Monoxide

The CYC group consisted of 57 patients, while the AZA group included 45 patients. Comparison between CYC demonstrated a significant difference in DLCO%, and this was confirmed by the fixed effect analysis favoring AZA [overall (Cohen's *d* standard, 0.88; standard error, 0.31; 95% CI: 0.28–1.48; $p$ = 0.00)]. Homogeneity was not maintained at all and was above 50% (93.74% among the two studies included). Both the CYC and placebo groups consisted of 95 patients each. Comparison of CYC with placebo did not show a significant difference in DLCO% predicted [overall (Cohen's *d* standard, −0.11; standard error, 0.15; 95% CI: −0.39 to 0.18; $p$ = 0.46)]. Homogeneity was maintained below 50% (0.6% among the two studies included) (Fig. 3).

## Efficacy Outcome for Total Lung Capacity

Both the CYC and placebo groups consisted of 95 patients each. Comparison between CYC and placebo demonstrated significant improvement in TLC predicted, favoring placebo [overall (Cohen's d standard, 0.37; standard error, 0.15; 95% CI: 0.08–0.66; $p$ = 0.01)]. Homogeneity was maintained below 50% (0.4% among the two studies included) (Supplementary Fig. 1).

## Efficacy Outcome for Dyspnea Index Score

Both the CYC and placebo groups consisted of 95 patients each. Comparison with placebo demonstrated a significant difference in the Dyspnea Index score, favoring CYC [overall (Cohen's *d* standard, 0.78; standard error, 0.15; 95% CI: 0.48–1.08; $p$ = 0.00)]. CYC notably reduced breathlessness among patients with SSc-ILD. Homogeneity was maintained below 50% (35.8% among the two studies included) (Supplementary Fig. 2).

## Network Analysis of Treatment Effects on Lung Function in Ssc-ILD

### *Forced Vital Capacity Outcomes*

The network analysis of FVC outcomes in patients with SSc-ILD indicated that CYC and AZA had the highest *P*-scores (0.6559 and 0.6296, respectively). These elevated *P*-scores suggest that CYC and AZA are the most central or influential treatments in the network, significantly impacting the maintenance or improvement of FVC

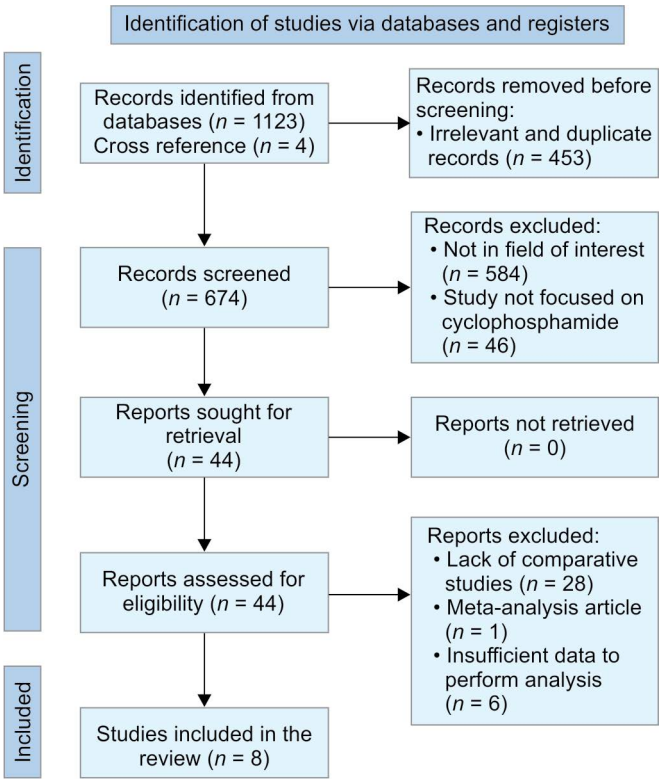



**Fig. 1:** PRISMA chart summarizing the selection of studies

**Table 1:** Basic characteristics and outcomes of the included studies

| *Author and year* | *Study design* | *No. of patients (n)* | *Drugs used* | *Dosing protocol* | *F(%)* | *Age (year, mean)* | *Treatment duration (months)* |
|---|---|---|---|---|---|---|---|
| Nadashkevich et al., 2006[28] | RCT | 30 | CYC | 2 mg/kg daily for 12 months and maintained on 1 mg/kg daily | 90 | 38 ± 11.25 | 18 |
| | | 30 | AZA | 2.5 mg/kg daily for 12 months and maintained on 2 mg/kg daily | 87 | 36 ± 11 | 18 |
| Poormoghim et al., 2014[29] | Retrospective observational study | 21 | CYC | 2 mg/kg/day (50–100 mg/day) for 12 months | 85.7 | 34 ± 14 | 12 |
| | | 15 | AZA | 1.5–2 mg/kg/day (50–150 mg) | 80 | 42 ± 14.07 | 12 |
| Shenoy et al., 2016[30] | Retrospective observational study | 23 | CYC | 600 mg/m$^2$ administered *via* intravenous (IV) infusion. About 6 monthly cycles of CYC were administered, with the dose increased to 1.2 g as tolerated | 78.2 | 46 ± 10.34 | 6 |
| | | 34 | MMF | Administered 500 mg once daily and increased to the maximum tolerable dose, not exceeding a total of 3 gm/day | 91.18 | 45.24 ± 13.87 | 6 |
| Panopoulos et al., 2013[31] | Observational study | 10 | CYC | Mean daily dose of 90 mg, with durations ranging from 17 to 55 months. Eight patients received treatment for over 24 months, while four completed 17 and 19 months, respectively | 90 | 47.6 ± 12.2 | 24 |
| | | 10 | MMF | Initiated at 2000 mg/day, with a mean daily dose of 1500 mg. Duration ranged from 22 to 72 months. Eight patients treated for over 24 months, while four received 22 and 23 months, respectively | 90 | 47 ± 11.2 | 24 |
| Sircar et al., 2018[32] | RCT | 30 | CYC | 500 mg/m$^2$ IV pulses every 4 weeks for 24 weeks | 83 | 36.50 ± 9.73 | 6 |
| | | 30 | RTX | Two pulses of 1000 mg IV at 0 and 15 days | 83 | 34.67 ± 8.13 | 6 |
| Yılmaz et al., 2021[33] | Retrospective observational study | 34 | CYC | Administered parenterally at a dosage of 1 gm once a month for the first 6 months. If the patient responded to the treatment, it continued at a dosage of 1 gm every 2 months for the next 12 months, followed by once every 4 months for the subsequent 12 months | 97.05 | 49.0 ± 11.8 | 24 |
| | | 27 | RTX | Provided in sessions every 6 months, each course will consist of two doses (500–1000 mg IV) separated by a 2-week interval | 85.18 | 52.5 ± 12.6 | 24 |
| Tashkin et al., 2006[1] | RCT | 73 | CYC | 1 mg/kg of body weight per day. The dosage was raised by one capsule each month until reaching 2 mg/kg | 75.6 | 48.2 ± 12.44 | 12 |
| | | 72 | Placebo | 1 mg/kg of body weight per day. The dosage was raised by one capsule each month until reaching 2 mg/kg | 64.6 | 47.5 ± 12.44 | 12 |
| Hoyles et al., 2006[34] | RCT | 22 | CYC | 600 mg/m$^2$ (mean dose 1050 mg) administered every 4 weeks | 77.3 | 83.5 ± 14.25 | 12 |
| | | 23 | Placebo | 600 mg/m$^2$ (placebo group was given placebo formulations that were identical to the active treatment) | 65.2 | 83.5 ± 14.25 | 12 |

AZA, azathioprine; CYC, cyclophosphamide; F, female; IV, intravenous; MMF, mycophenolate mofetil; No, number; NR, not reported; RTX, rituximab

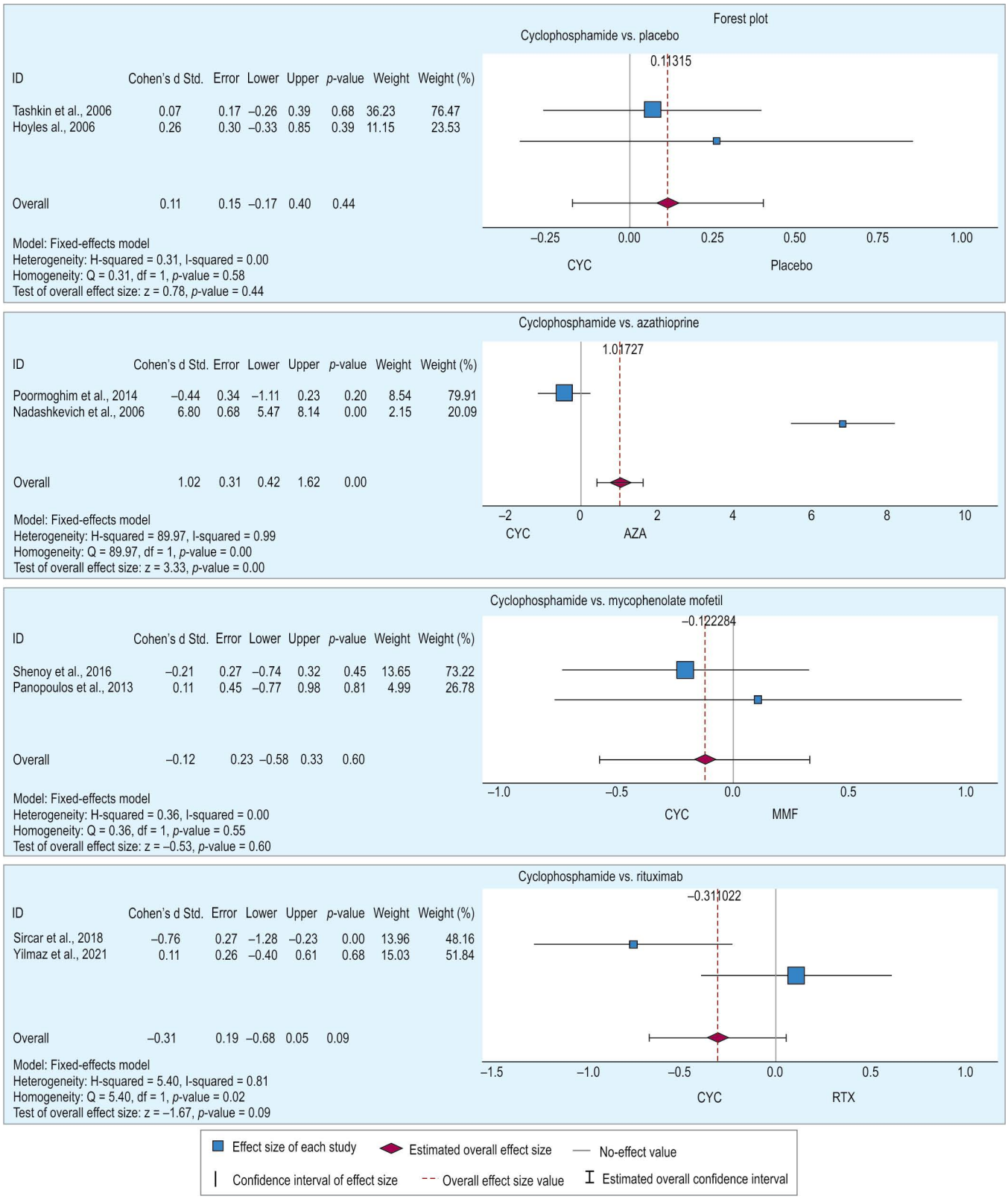



**Fig. 2:** Forest plot demonstrating the pooled data on FVC outcome for CYC compared to placebo, AZA, MMF, and RTX

in SSc-ILD patients. Conversely, RTX had the lowest *P*-score of 0.3410, indicating a less central or influential role within the network and a lesser impact on FVC outcomes compared to other treatments. MMF and placebo had moderate *P*-scores (0.4371 and 0.4364, respectively), reflecting a moderate level of network connectivity or influence on FVC outcomes (Fig. 4 and Table 3).

### *Diffusing Capacity of the Lung for Carbon Monoxide Outcomes*

The network analysis of DLCO outcomes in patients with SSc-ILD revealed that AZA had the highest *P*-score of 0.5707, indicating that it

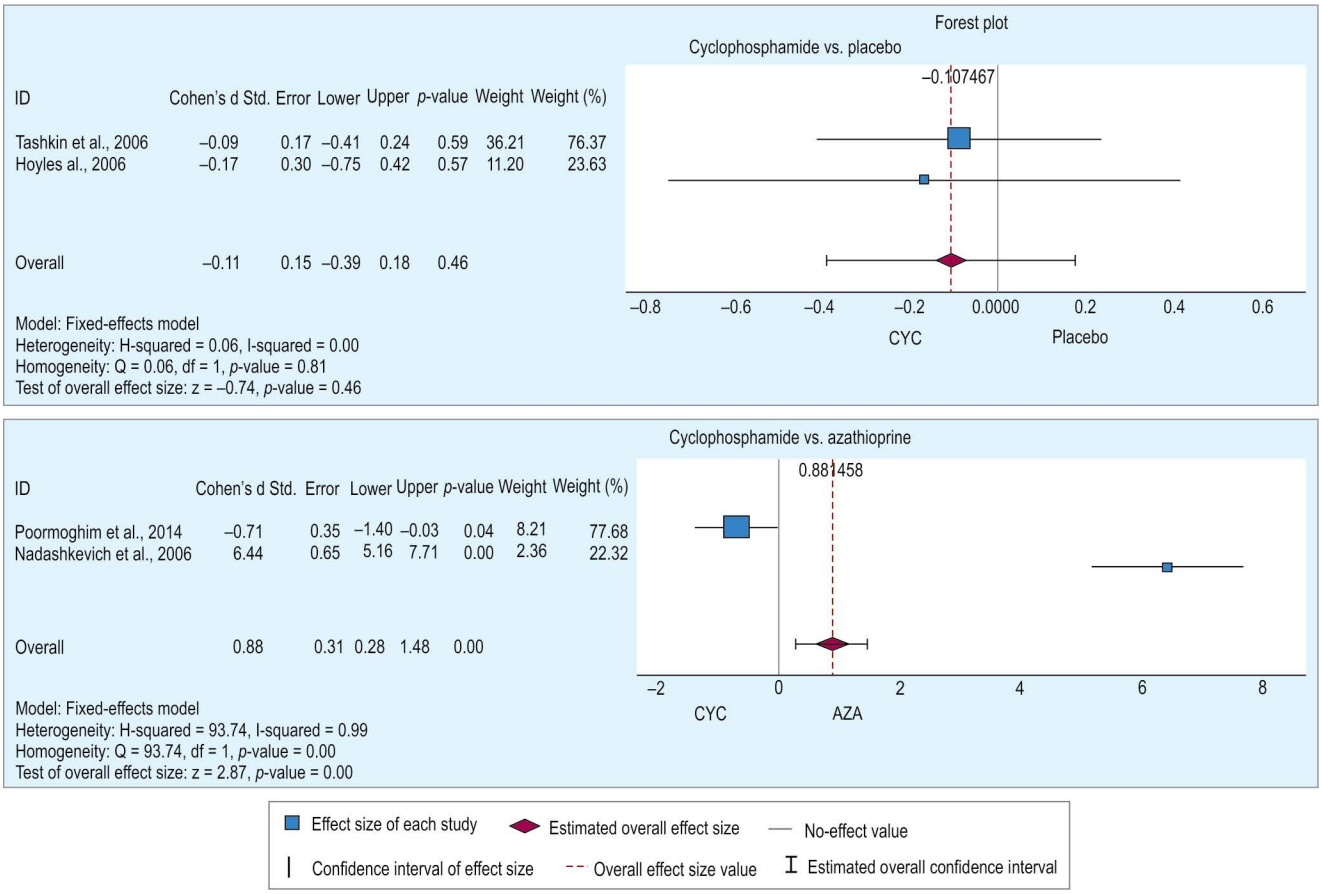
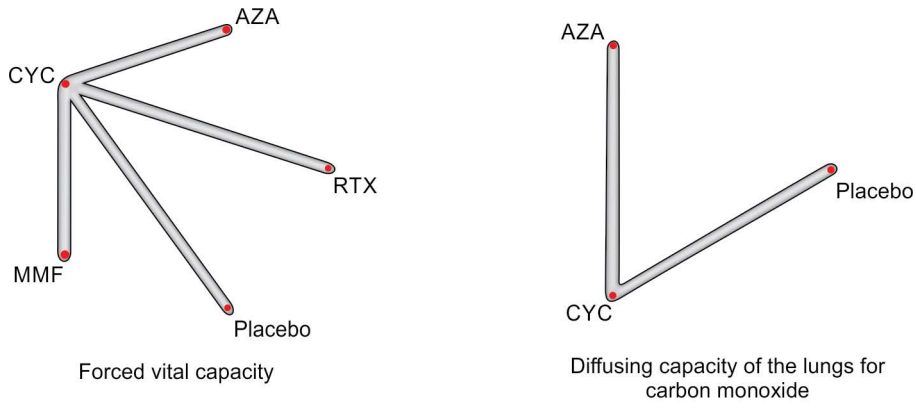



**Fig. 3:** Forest plot demonstrating the pooled data on DLCO for CYC compared to placebo and AZA




CYC: Cyclophosphamide, AZA: Azathioprine, RTX: Rituximab, MMF: Mycophenolate mofetil

**Fig. 4:** Network diagram of treatment interactions

is the most central or influential treatment in the network. This suggests a more substantial impact on maintaining or improving DLCO in SSc-ILD patients compared to other treatments. The placebo ranked second with a *P*-score of 0.5180, suggesting a moderate level of network connectivity or influence on DLCO outcomes. This finding implies that other factors, apart from the evaluated treatments, may significantly affect DLCO in SSc-ILD patients. In contrast, CYC had a lower *P*-score of 0.4113, positioning it as less central or influential within the network. The impact of CYC on DLCO outcomes appeared less pronounced compared to AZA and placebo (Fig. 4 and Table 3).

The *P*-scores remained consistent between the common and random models for all treatments. This suggests that the observed network structure did not significantly deviate from what would be expected in a random network, indicating that other factors or mechanisms not accounted for in this analysis would have influenced the relationships between treatments and FVC and DLCO outcomes.

## Sensitivity Analysis

### *Difference between the Basic and Outcome Characteristics*

The sensitivity analysis revealed significant patterns across the included studies. Age distribution ranged from 34.67 ± 8.13 to 83.5 ± 14.25 years, with most studies focusing on middle-aged participants, except for Hoyles et al., which included notably older subjects.[34] Sample sizes varied considerably, ranging from small studies with 10–30 participants per arm to larger trials with over 70 subjects per arm.[1,29,31] Most studies maintained balanced treatment arms.

The methodological quality varied, with four studies classified as RCTs and four as observational studies.[1,28–34] Treatment regimens also showed notable variations, particularly for CYC, which was administered either orally (1–2 mg/kg/day) or intravenously (500–1200 mg/m$^2$ monthly) for durations ranging from 6 to 24 months. Comparator drugs included AZA (1.5–2.5 mg/kg/day), MMF (500–3000 mg/day), RTX (500–2000 mg IV), and placebo in two studies. Follow-up rates were generally robust across studies (Table 1).

**Table 2:** Outcome characteristics of the included studies

| *Author and year* | *Drugs used* | *FVC (% of predicted) (Mean ± SD)* | | *TLC (% of predicted) (Mean ± SD)* | | *DLCO (% of predicted) (Mean ± SD)* | | *Mahler dyspnea index score* | |
|---|---|---|---|---|---|---|---|---|---|
| | | *Baseline* | *Posttreatment* | *Baseline* | *Posttreatment* | *Baseline* | *Posttreatment* | *Baseline* | *Posttreatment* |
| Nadashkevich et al., 2006[28] | CYC | 90.3 ± 1.9 | 93.6 ± 1.7 | NR | NR | 83.5 ± 1.6 | 83.5 ± 1.6 | NR | NR |
| | AZA | 91.7 ± 2 | 80.6 ± 2.1 | NR | NR | 84.8 ± 1.4 | 73.2 ± 1.6 | NR | NR |
| Poormoghim et al., 2014[29] | CYC | 59.5 ± 10.7 | 63.1 ± 16.2 | NR | NR | 67.7 ± 27.5 | 60 ± 22.9 | NR | NR |
| | AZA | 62.8 ± 9.8 | 71.1 ± 20.9 | NR | NR | 61.4 ± 25.8 | 76.7 ± 24 | NR | NR |
| Shenoy et al., 2016[30] | CYC | 48.74 ± 15.67 | 53.09 ± 14.93 | NR | NR | NR | NR | NR | NR |
| | MMF | 53.44 ± 13.69 | 55.99 ± 13.47 | NR | NR | NR | NR | NR | NR |
| Panopoulos et al., 2013[31] | CYC | 77.3 ± 12.5 | 82.5 ± 12.9 | NR | NR | NR | NR | NR | NR |
| | MMF | 79 ± 12.5 | 81.2 ± 11.4 | NR | NR | NR | NR | NR | NR |
| Sircar et al., 2018[32] | CYC | 59.25 ± 12.96 | 58.06 ± 11.23 | NR | NR | NR | NR | NR | NR |
| | RTX | 61.3 ± 11.28 | 67.52 ± 13.59 | NR | NR | NR | NR | NR | NR |
| Yılmaz et al., 2021[33] | CYC | 70 ± 18.3 | 72.7 ± 21.6 | NR | NR | NR | NR | NR | NR |
| | RTX | 67 ± 14.6 | 70.4 ± 15.2 | NR | NR | NR | NR | NR | NR |
| Tashkin et al., 2006[1] | CYC | 67.6 ± 13.33 | 66.6 ± 15.1 | 70.4 ± 17.94 | 70.5 ± 15.99 | 47.2 ± 13.67 | 42.8 ± 15.1 | 5.6 ± 1.95 | 1.4 ± 2.04 |
| | PBO | 68.3 ± 13.33 | 65.6 ± 14.22 | 67.9 ± 16.12 | 64.7 ± 16.88 | 47.9 ± 14.42 | 44.3 ± 18.66 | 5.6 ± 3.73 | −1.5 ± 3.82 |
| Hoyles et al., 2006[34] | CYC | 80.1 ± 10.3 | 82.5 ± 11.3 | 81.8 ± 10.1 | 80.2 ± 9.8 | 52.9 ± 11.5 | 49.6 ± 10.7 | 7.7 ± 3 | 8.75 ± 3.5 |
| | PBO | 81 ± 18.8 | 78 ± 21.6 | 76.8 ± 16.9 | 74.4 ± 16.7 | 55 ± 12.9 | 51.8 ± 14.9 | 7.2 ± 4.5 | 7.8 ± 3 |

AZA, azathioprine; CYC, cyclophosphamide; DLCO, diffusing capacity for carbon monoxide; FVC, forced vital capacity; MMF, mycophenolate mofetil; NR, not reported; PBO, placebo; RTX, rituximab; TLC, total lung capacity

**Table 3:** Network analysis *P*-scores for FVC and DLCO outcomes in SSc-ILD patients

| *Treatment* | *FVC* | | *DLCO* | |
|---|---|---|---|---|
| | *P-score (common)* | *P-score (random)* | *P-score (common)* | *P-score (random)* |
| CYC | 0.6559 | 0.6559 | 0.4113 | 0.4113 |
| AZA | 0.6296 | 0.6296 | 0.5707 | 0.5707 |
| MMF | 0.4371 | 0.4371 | – | – |
| Placebo | 0.4364 | 0.4364 | 0.5180 | 0.5180 |
| RTX | 0.3410 | 0.3410 | – | – |

AZA, azathioprine; CYC, cyclophosphamide; MMF, mycophenolate mofetil; RTX, rituximab

The comprehensive sensitivity analysis of baseline measurements revealed notable variations in pulmonary function parameters across studies. Baseline DLCO measurements showed the highest variability, while TLC measurements were the most consistent. FVC measurements exhibited moderate variability (Table 2).

### *Difference between Meta-analytic Models (Fixed-effect vs Random-effects)*

Cyclophosphamide vs placebo study: There was no change in the confidence interval or weight in the CYC vs placebo study for FVC, DLCO, and TLC (Figs 2 and 3 and Supplementary Figs 1 to 5). The stability of the confidence intervals and weights indicates that the meta-analysis results are robust. Both studies were consistent, contributing similarly to the pooled effect size, which is highly reliable with no heterogeneity. This consistency allows the results to be interpreted with confidence.

However, for the Dyspnea Index score, there was a difference between the confidence intervals (−0.30 to 0.88 for the fixed-effect model vs 0.03–1.30 for the random-effect model) and weights (74.53, 25.47 for the fixed-effect model vs 56.86, 43.14 for the random-effect model) (Supplementary Figs 2 and 6). This difference suggests potential heterogeneity between the studies, rendering the meta-analysis less robust.

*Cyclophosphamide vs mycophenolate mofetil study:* In the case of FVC, there was no change in the confidence interval or weight in the CYC vs MMF study (Fig. 2 and Supplementary Fig. 3). This stability demonstrates that the meta-analysis results are robust, with consistent studies and a highly reliable pooled effect size. The absence of heterogeneity suggests that both studies contributed similarly to the overall result, allowing for confident interpretation.

*Cyclophosphamide vs azathioprine study:* For FVC, there was a notable difference between the two models, with the confidence interval ranging from 0.42 to 1.62 in the fixed-effect model compared to −3.94 to 10.26 in the random-effect model. The weights also differed significantly (79.91, 20.09 for the fixed-effect model vs 50.30, 49.70 for the random-effect model) (Fig. 2 and Supplementary Fig. 3).

Similarly, for DLCO, a marked difference was observed in the confidence intervals (0.28–1.48 for the fixed-effect model vs −4.17 to 9.85 for the random-effect model) and weights (77.68, 22.32 for the fixed-effect model vs 50.33, 49.67 for the random-effect model) (Fig. 3 and Supplementary Fig. 4). These discrepancies suggest potential heterogeneity between the studies, indicating that the meta-analysis is not robust.

*Cyclophosphamide vs rituximab study:* In the case of FVC, there was a difference in the confidence intervals (0.68–0.05 for the fixed-effect model vs −1.17 to 0.52 for the random-effect model) and weights (48.16, 51.84 for the fixed-effect model vs 49.66, 50.34 for the random-effect model) (Fig. 2 and Supplementary Fig. 3). This variation indicates potential heterogeneity between the studies, suggesting that the meta-analysis is not robust.

## Discussion

Systemic sclerosis-associated ILD has a variable clinical course. Most patients experience a slow decline in lung function, but some progress rapidly after disease onset, with progression defined by an increase in the extent of pulmonary fibrosis on HRCT or by a decline in PFTs.[36]

Many therapies have been investigated for SSc-ILD, including immunosuppressive therapies, antifibrotic agents, immunomodulators, monoclonal antibodies, hematopoietic stem cell transplant (HSCT), and lung transplant. Since there were no approved drug treatments available until the approval of the tyrosine kinase inhibitor nintedanib in 2019, patients with SSc-ILD had a high unmet medical need.[37] CYC is frequently recommended as a treatment for SSc-ILD. A meta-analysis by Nannini et al. suggested that patients with SSc-ILD who are treated with CYC may experience a modest increase in the FVC and the DLCO after 12 months of therapy.[38]

The current comparison of CYC with AZA revealed a significant difference in FVC and DLCO predicted, favoring AZA. This finding is consistent with the research conducted by Dheda et al., which corroborated the efficacy of AZA in preserving lung function among patients with SSc-ILD. AZA was also effective in three patients who relapsed after previous CYC therapy.[39] When assessing the efficacy of CYC compared to MMF in preserving lung function among patients with SSc-ILD, the current analysis revealed no significant difference in the FVC predicted. Despite this lack of statistical significance, the present fixed-effect analysis leaned slightly toward favoring CYC. A systematic review by Ma et al. also suggested no significant difference in FVC improvement between MMF and CYC. These findings suggest a comparable efficacy between the two agents in mitigating the decline in lung function associated with SSc-ILD.[40]

In the current study, a comparison between CYC and RTX demonstrated a mild but statistically insignificant difference in FVC. Despite the lack of statistical significance, the analysis slightly favored CYC over RTX. This finding aligns with the research conducted by Daoussis et al., which indicated marginal differences in FVC predicted following treatment with RTX.[41] The mild and statistically insignificant difference observed in FVC between CYC and RTX may be attributed to various factors, including sample size, patient characteristics, and the heterogeneity of SSc-ILD. While the current analysis leaned toward favoring CYC, it is essential to interpret these findings cautiously, considering the nuanced nature of treatment responses in complex diseases like SSc-ILD. Comparison between CYC and placebo in the current analysis did not show significant differences in FVC, DLCO, and TLC. However, the fixed-effect analysis indicated a tendency toward favoring CYC in both FVC and TLC predicted outcomes. This observation aligns with the study conducted by Tashkin et al.[42]

The lack of significant differences in FVC, DLCO, and TLC between CYC and placebo underscores the need for a cautious interpretation of treatment effects in the context of SSc-ILD. While the present analysis suggests a preference for CYC in FVC and TLC outcomes, further research is necessary to confirm and elucidate the clinical implications of these findings. Upon comparing CYC with AZA, a significant difference in DLCO predicted was observed and confirmed by the fixed-effect analysis, favoring AZA. Similarly, Raghu et al. observed a statistically significant improvement in lung parameters following AZA treatment.[43] A significant difference in the Dyspnea Index score was found, and the analysis favored CYC. CYC notably reduced breathlessness among patients with SSc-ILD. The findings are consistent with literature suggesting improvements in the Dyspnea Index score with CYC compared to placebo. Khanna et al. reported a significant decrease in the Dyspnea Index score with CYC.[44]

The network analysis findings highlight the potential benefits of CYC and AZA in preserving lung function, as measured by FVC and DLCO, in patients with SSc-ILD. The impact of CYC on maintaining or improving FVC in patients with SSc-ILD was found to be more significant than other treatments. This conclusion is supported by the SLS II trial study conducted by Tashkin et al., which demonstrated the efficacy of CYC in enhancing lung function in patients with progressive SSc-ILD, resulting in improved FVC.[45] Additionally, a systematic review and meta-analysis by Nannini et al. suggested that patients with SSc-ILD treated with CYC may experience a modest increase in FVC and DLCO after 12 months of therapy.[38]

In contrast, for DLCO outcomes, AZA exhibited the highest network connectivity, implying a more substantial effect on maintaining or improving DLCO compared to other treatments. Huapaya et al. reported that long-term treatment with AZA was associated with improved DLCO.[46] Placebo exhibited the second-highest *P*-score for DLCO outcomes and moderate network influence on FVC, suggesting that factors other than the evaluated treatments may play a role in influencing DLCO in SSc-ILD patients. In contrast, CYC had a relatively lower *P*-score for DLCO outcomes, indicating a lesser impact on DLCO compared to AZA and placebo. While CYC has been shown to preserve FVC in SSc-ILD patients, its effects on DLCO may be more variable.

The moderate *P*-scores for MMF in the present network analysis reflect the mixed findings from studies evaluating their effects on FVC in SSc-ILD. While Janardana et al. reported stabilization or improvement in FVC with MMF, Naidu et al. showed no significant improvement in lung function in SSc-ILD, including FVC.[47,48] On the contrary, a low *P*-score was observed for RTX in comparison to CYC in the present network analysis. An RCT study by Maher et al. did not find the superiority of RTX over CYC for FVC improvement, and the improvement was numerically higher in CYC compared to RTX.[49]

It is important to note that the lack of significant deviation from a random network structure in the analysis suggests that other factors or mechanisms may influence FVC outcomes in SSc-ILD beyond the treatments evaluated. These could include disease severity, duration, and progression, as well as individual patient characteristics and comorbidities. Overall, the network analysis results, supported by existing literature, highlight the potential efficacy of CYC and AZA in preserving or improving lung function, as measured by FVC and DLCO, in SSc-ILD patients.

The current meta-analysis study holds significant relevance as it provides a comprehensive assessment of the efficacy of CYC in managing SSc-ILD. By synthesizing data from RCTs to observational studies, the study offers valuable insights into the potential benefits of CYC in preserving lung function, as measured by FVC and DLCO, in comparison to other immunosuppressants, such as AZA, MMF, RTX, and placebo. CYC was found to have a more significant impact on maintaining or improving FVC, while AZA exhibited a substantial effect on maintaining or improving DLCO. These results could guide clinical decision-making and potentially improve outcomes for patients with SSc-ILD by informing treatment selection based on specific lung function parameters. Furthermore, the study identifies areas of uncertainty and the need for further research, such as the influence of placebo on DLCO outcomes and the lack of significant deviation from a random network structure, which suggests that other factors or mechanisms may influence lung function outcomes beyond the evaluated treatments. This direction for future investigations could aid in refining treatment approaches and addressing existing knowledge gaps.

### Limitations

One of the major limitations of the study is its relatively small pool of included studies and participants, possibly limiting the generalizability of findings. Moreover, the diversity among the included studies, notably in treatment approaches and patient demographics, might introduce bias and compromise result reliability. Additionally, combining retrospective observational studies with RCTs could introduce inherent biases and confounding variables, impacting the outcomes. Despite comprehensive searches across multiple databases, the possibility of publication bias cannot be entirely eliminated. In addition, reliance on fixed-effect analysis may inadequately address the observed study heterogeneity, potentially affecting the accuracy of pooled estimates. Due to the lack of significant differences favoring CYC and the influence of factors beyond the evaluated therapies, larger studies with standardized measures are necessary to determine the best treatment approach. The meta-analysis is limited by significant methodological heterogeneity across included studies, including variations in study designs, diverse age distributions, and varying sample sizes. Treatment protocols showed considerable variation in CYC administration and duration, along with different comparator drugs and dosages. Statistical analyses revealed inconsistencies between fixed-effect and random-effects models (CYC vs AZA and RTX), suggesting potential heterogeneity and limited robustness of some findings. Further research is crucial to refine treatment strategies, clarify the comparative benefits of CYC, and address remaining questions about its effectiveness and safety in managing this complex, debilitating condition.

## Conclusion

While CYC has been identified as a key treatment for SSc-ILD, the present analysis suggests that its effectiveness compared to other immunosuppressants needs careful consideration. The study findings indicate that CYC may help maintain FVC but does not decisively prove its superiority over other treatments for most lung function parameters. CYC remains a viable option for SSc-ILD, especially when there is no compelling evidence for alternatives. However, its use should involve considering potential risks along with individual patient characteristics and preferences.

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## Supplementary Material

Supplementary files are available with the author. Please contact the author for the supplementary content.

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