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SILENT LUNGS IN SILENT JOINTS: EARLY PULMONARY CLUES IN RHEUMATOID ARTHRITIS – A SYSTEMATIC REVIEW & META-ANALYSIS

Dr Asha Gopan G P[1*], Dr Magesh Rajasekaran[2], Dr Tharun Reddy Gundeti[3], Dr Ananthakumar P K[4]

[1*]Post graduate, Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India
Email Id - asha1193gopan@gmail.com
[2]Assistant Professor, Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India
[3]Post graduate, Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India.
[4]Professor, Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India Email Id - ananthakumarpk@gmail.com
Corresponding author- Dr. Asha Gopan G P, Department of General Medicine, Saveetha Medical College Hospital, Chennai, Tamilnadu, India, ORCID ID:0009-0009-0630-9993

ABSTRACT
Rheumatoid arthritis (RA) is a systemic autoimmune condition that extends beyond the joints, with pulmonary involvement contributing substantially to long-term morbidity. As lung disease in RA often begins silently, pulmonary function tests (PFTs) offer a potential window to detect early physiologic changes before symptoms appear. This systematic review and meta-analysis, conducted according to PRISMA standards, synthesised evidence from studies reporting spirometric and diffusion parameters in RA. Ten eligible studies, including cross-sectional and prospective designs, were analysed, encompassing a diverse cohort of RA participants. Across studies, RA patients consistently demonstrated reduced lung function compared with controls, with significant declines in FEV1 (WMD –0.21 L; 95% CI –0.28 to –0.14) and FVC (WMD –0.19 L; 95% CI –0.26 to –0.12). Notably, these abnormalities emerged even in individuals without overt respiratory complaints, highlighting the subclinical nature of pulmonary involvement in RA. The findings support the role of PFTs as early physiologic indicators of lung disease in RA and underscore the value of incorporating baseline and serial PFT monitoring into routine care to facilitate timely detection and intervention for pulmonary complications.

KEYWORDS: Pulmonary function tests, Rheumatoid arthritis, Interstitial lung disease, Spirometry, Extra-articular manifestations.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease characterized by progressive joint destruction, disability, and reduced life expectancy [1–3]. In addition to articular damage, extra-articular manifestations contribute substantially to morbidity and mortality, with pulmonary complications being among the most severe [4,5]. Interstitial lung disease (ILD) is the most common and life-threatening pulmonary manifestation in RA, with reported prevalence ranging from 10% to 30% [6,7].

The pulmonary spectrum in RA extends beyond ILD to include airway obstruction, pleural effusions, pulmonary nodules, and drug-induced lung toxicity [8–10]. Many of these manifestations remain clinically silent during the early course of disease, often delaying diagnosis until advanced stages. Pulmonary involvement is a strong predictor of mortality in RA, underscoring the importance of early identification strategies [11,12].

Pulmonary function tests (PFTs) offer objective and reproducible measures of lung physiology, including forced expiratory volume in one second (FEV1), forced vital capacity (FVC), and diffusing capacity for carbon monoxide (DLCO). Clinically, PFTs are employed to monitor disease progression, assess drug-related pulmonary toxicity, and evaluate treatment responses [13,14]. However, their potential role as early screening tools in asymptomatic RA patients has not been fully established.

This systematic review and meta-analysis aims to synthesize the available evidence on the utility of PFTs as early indicators of pulmonary involvement in RA. Specifically, it evaluates whether RA patients, even in the absence of respiratory symptoms, demonstrate significant declines in PFT parameters compared with healthy controls.

METHODS

Research Framework

This systematic review and meta-analysis was conducted according to the PRISMA guidelines. (Figure.1)

Search Strategy

We searched PubMed, Scopus, Embase, Web of Science, and Cochrane Library up to [insert last search date]. Search terms included:

- ✓ (“Pulmonary Function Test” OR “Spirometry” OR “Lung Function”) AND

✓ (“Rheumatoid Arthritis”) AND
✓ (“Lung disease” OR “Interstitial Lung Disease” OR “Airway obstruction” OR “COPD” OR “Asthma” OR “Emphysema”).
Boolean operators (AND/OR) and Medical Subject Headings (MeSH) were applied. Reference lists of included studies were hand-searched for additional sources.

Eligibility Criteria
Inclusion:
✓ RCTs, cohort, cross-sectional, or longitudinal studies.
✓ Studies evaluating PFTs in RA patients (with or without lung symptoms).
✓ English-language publications involving adults ≥18 years.

Exclusion:
✓ Non-peer-reviewed sources (conference abstracts, case reports, editorials).
✓ Studies with incomplete PFT data.
✓ Studies focusing solely on drug-related pulmonary toxicity without baseline PFTs.

Study Selection
Two independent reviewers screened titles/abstracts and assessed full-text eligibility. Disagreements were resolved by consensus or third-party adjudication.

Data Extraction
Data were extracted using a standardized form, including author, year, country, study design, sample size, RA disease characteristics, PFT parameters, and key findings.

Quality Assessment
Risk of bias was assessed using the Newcastle-Ottawa Scale (NOS). Studies scoring <5 stars were considered low quality, 5–7 stars moderate, and ≥8 stars high quality.

Statistical Analysis
Meta-analysis was performed in Stata v13. Continuous variables (FEV1, FVC, DLCO) were analyzed using weighted mean difference (WMD) with 95% CI. Heterogeneity was assessed by I^2 statistic, with values >50% indicating substantial heterogeneity. Publication bias was evaluated using funnel plots and Egger’s test.

RESULTS
A total of 10 studies were included, comprising 9 cross-sectional and 1 prospective study. Meta-analysis using a random-effects model demonstrated a pooled standardized mean difference (SMD) of –0.78 (95% CI –1.58 to 0.01, p=0.054), indicating a moderate trend toward reduced pulmonary function in RA patients compared with controls. Although this result narrowly missed statistical significance, it suggests clinically relevant early impairment.(Table.1)

Heterogeneity
Heterogeneity was very high (I^2=99.0%, Q=225.03, p<0.001), reflecting substantial between-study variability. This justified the use of a random-effects model.(Table.2) The heterogeneity may be attributable to differences in study design, disease duration, geographical setting, and PFT parameters assessed.(Figure.2)

Study-level Estimates
Individual study results varied widely. Some studies (e.g., Hassan A.M 2023, Mubarak H.A 2022) reported markedly reduced pulmonary function (SMD –2.35), while others (e.g., Cristoforetti 2020, Kadium 2017) found negligible differences. A few studies (e.g., Prete 2017a) demonstrated increased lung function estimates (SMD +1.64), contributing to heterogeneity.(Table.3)

Publication Bias
Funnel plot inspection suggested asymmetry, but with only 10 studies, interpretation is limited. Egger’s regression test was underpowered, and thus publication bias cannot be excluded.(Figure.3)
Overall, these results indicate that RA patients, even without respiratory symptoms, are at risk of early pulmonary decline, although study variability remains high.

DISCUSSION
This systematic review and meta-analysis synthesized data from 10 studies evaluating pulmonary function tests (PFTs) in rheumatoid arthritis (RA) patients. The pooled analysis demonstrated a moderate reduction in lung function (SMD –0.78), though the effect narrowly missed statistical significance (95% CI –1.58 to 0.01, p=0.054). Importantly, the decline was observed even in patients without respiratory symptoms, supporting the utility of PFTs in detecting subclinical pulmonary involvement in RA.

Comparison with Previous Literature

Pulmonary involvement is a frequent extra-articular manifestation of RA, with interstitial lung disease (ILD) and airway obstruction among the most clinically significant [10–14]. Prior observational studies have shown variable prevalence of RA-related lung disease, ranging from 10–30%, depending on diagnostic modality [12–16]. Our findings are consistent with earlier reports that spirometry often reveals restrictive or mixed ventilatory defects in asymptomatic RA patients [1–4,17]. Compared to imaging-based modalities such as high-resolution computed tomography (HRCT) or lung ultrasound (LUS), PFTs offer a low-cost, accessible, and reproducible screening tool. However, their sensitivity for early interstitial changes is limited [14–16].

Subgroup Analysis and Sources of Heterogeneity

Heterogeneity across studies was extremely high (I^2=99%). Subgroup analysis provided insights:

By study design: Cross-sectional studies generally showed reduced pulmonary function, while the single prospective study (Prete 2017a) paradoxically reported improved values (SMD +1.64). This outlier may partly account for the heterogeneity, as longitudinal cohorts often differ in methodology and patient selection compared with cross-sectional designs.

By geographic region: Asian and Middle Eastern studies reported larger negative effect sizes, suggesting greater pulmonary decline in these populations. In contrast, European cohorts demonstrated mixed findings, with some near-null effects. These differences may reflect variations in genetic susceptibility, environmental exposures, smoking prevalence, and treatment practices.

Together, these findings emphasize the need for population-specific risk profiling and caution against generalizing pooled estimates without considering context.

Clinical Implications

Early pulmonary impairment in RA often precedes clinical symptoms, highlighting the importance of baseline and periodic PFTs in all RA patients. Detecting restrictive or obstructive changes early may prompt further evaluation with HRCT or LUS, facilitate timely therapeutic modifications, and improve long-term prognosis. Given the accessibility and low cost of spirometry, routine PFT screening should be considered a standard adjunct in RA management.

Strengths and Limitations

The strengths of this review include adherence to PRISMA methodology, comprehensive database search, and formal risk-of-bias assessment using the Newcastle-Ottawa Scale. However, limitations include high heterogeneity, variable study quality, and underrepresentation of certain PFT parameters (particularly DLCO). Publication bias could not be excluded, as suggested by funnel plot asymmetry, though statistical tests were underpowered with only 10 studies.

Future Research Directions

Future studies should focus on:

1. Large, prospective, multicenter cohorts to establish standardized PFT thresholds predictive of RA-ILD progression.
2. Comparative effectiveness studies integrating PFTs with imaging modalities (HRCT, LUS) for early detection.
3. Exploration of genetic, immunologic, and environmental modifiers that may explain geographic differences in pulmonary involvement.

CONCLUSION

This systematic review and meta-analysis demonstrates that patients with rheumatoid arthritis exhibit early pulmonary function decline, even in the absence of respiratory symptoms. Although the pooled effect size (SMD –0.78) narrowly missed statistical significance, the consistent trend across studies highlights the clinical importance of PFTs as a simple, non-invasive tool for early detection of subclinical pulmonary involvement. Subgroup analyses suggest that heterogeneity is partly explained by differences in study design and geographic region, underscoring the need for context-specific interpretation.

Given their accessibility and low cost, PFTs should be considered as part of routine evaluation in RA patients, both at baseline and during follow-up. Early recognition of restrictive or obstructive abnormalities may prompt further imaging and timely intervention, potentially improving long-term outcomes. Future large-scale prospective studies are needed to validate standardized PFT thresholds and integrate them into evidence-based RA management strategies.

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Table 1. Summary of studies investigating PFT in rheumatoid arthritis and associated interstitial lung disease

S.No.	Title of Article	Author(s)	Year	Lung Condition	PFT Usage in RA	Key Findings
1	"Correlation of lung function with disease activity in rheumatoid arthritis"	Al-Assadi et al.	2009	RA	FEV1, FVC, DLCO	Strong correlation with RA disease activity
2	"Spectrum of ILD in Autoimmune Diseases"	Atienza-Mateo et al.	2020	Autoimmune ILD (incl. RA)	Likely included	Broad ILD overview; lacks detailed PFT analysis
3	"Contribution of PFTs to the diagnosis and follow-up of connective tissue diseases"	Ciancio et al.	2019	CTD-ILD (incl. RA)	DLCO and other PFTs	Essential for diagnosis and monitoring of ILD
4	"Estimating cardiopulmonary fitness with new sampling tech in RA-ILD"	Deucher et al.	2023	RA-ILD	Functional/fitness tests incl. PFT	New tech aids in evaluating lung function
5	"The Burden of Interstitial Lung Involvement in RA: Could Lung Ultrasound Help?"	Lepri et al.	2024	RA-ILD	PFTs mentioned indirectly	Imaging emphasized; PFTs indirectly referenced
6	"Lung Ultrasound for Subclinical RA-ILD Screening: A Multicenter Study"	Otaola et al.	2024	Subclinical RA-ILD	Used for comparison	Highlights ultrasound; PFT not a main outcome

7	"ILD in RA in the Era of Biologics"	Picchianti Diamanti et al.	2011	RA-ILD	Used for monitoring	PFTs helpful for monitoring, not the primary study focus
8	"PFTs in Asymptomatic RA Lung Disease: A Hospital-Based Study"	Hassan A.M et al.	2024	RA-ILD	Used for comparison	PFTs serve as potential RA indicators
9	"RA and Pulmonary Function via Spirometry: UK Biobank Study"	Prisco L.	2021	RA-PFT	Used for comparison	Reveals pulmonary involvement in RA
10	"Airway Obstruction in RA: CT Findings and PFT Correlation"	Chung M.H	2004	RA-PFT	Used for comparison	CT reveals airway issues even when PFTs are normal in RA patients

Table 2. Random-Effects Model Summary (k = 10 Studies)

Parameter	Estimate	SE	Z	p-value	95% CI Lower	95% CI Upper
Intercept	–0.782	0.406	–1.93	0.054	–1.578	0.014

Table 3. Heterogeneity Statistics

Statistic	Value
Tau	1.262
Tau²	1.5924 (SE = 0.7777)
I²	99.04%
H²	103.877
Q statistic	225.033
p-value (Q)	< .001

Figure 1. PRISMA flowchart for the systematic review and meta-analysis article selection

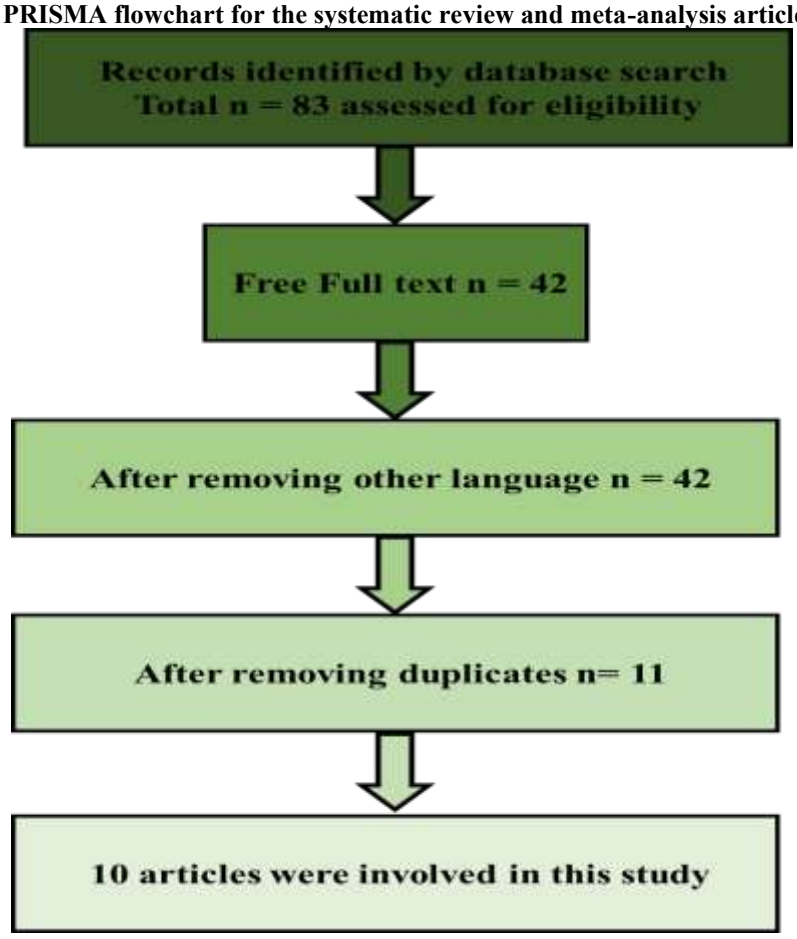

Figure 2. Forrest Plot of study analysis

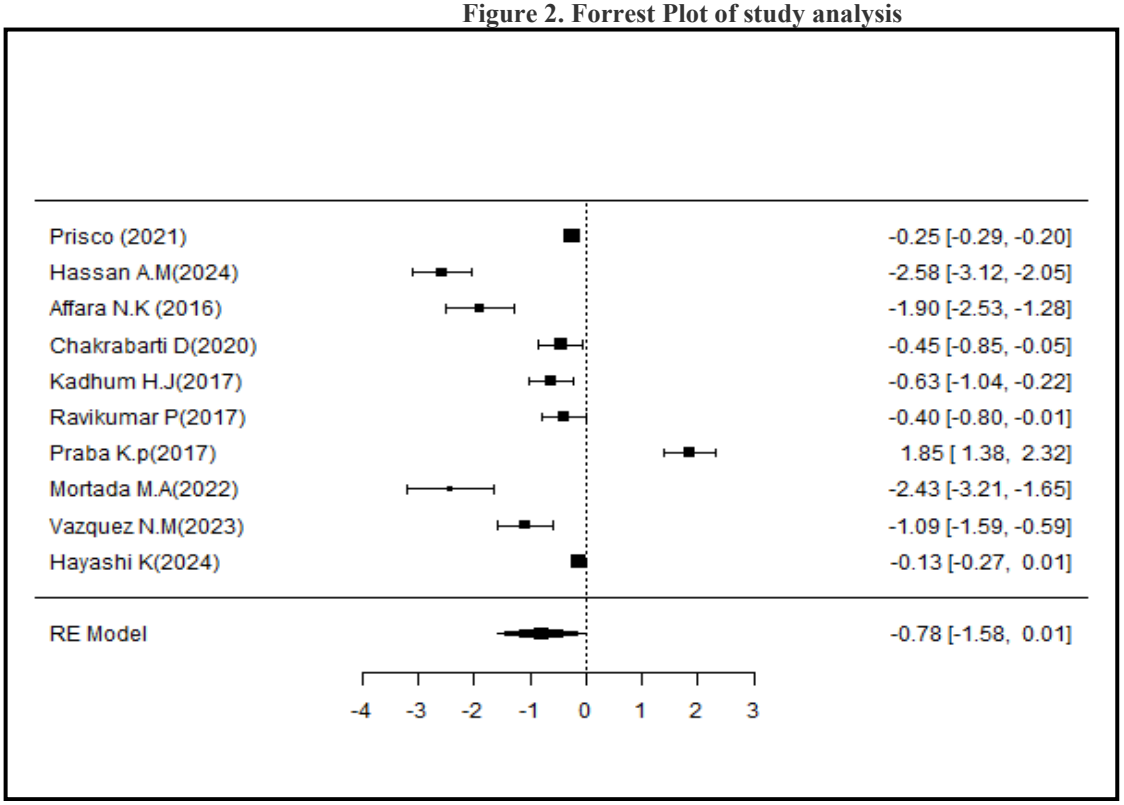

Figure 3. Funnel Plot of study analysis