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Chest radiography in interstitial lung disease: Accuracy and radiological features from a systematic review and meta-analysis

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Abstract. *Background:* This systematic review aims to summarize and evaluate the diagnostic performance of chest X-ray (CXR) compared with high-resolution computed tomography (HRCT) for detecting interstitial lung disease (ILD). *Research question:* what is the diagnostic accuracy and radiological finding of CXR in ILD, using HRCT as a gold standard. *Study Design and Method:* We systematically searched electronic databases to find studies evaluating the diagnostic accuracy of CXR and HRCT for detecting ILD. We used StataMP/17 and R statistical software for the quantitative analysis. Values like pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, diagnostic odds ratio with their 95% confidence interval, and the SROC curve was performed. *Results:* We included a total of 18 studies involving 1917 patients. Compared to HRCT, CXR had sensitivity of 0.62 (95% CI: 0.47–0.74), specificity of 0.90 (95% CI: 0.85 – 0.93), positive likelihood ratio of 5.9 (95% CI 4.5–7.7), negative likelihood ratio of 0.43 (95% CI 0.31, 0.59), diagnostic odds ratio of 14 (95% CI 9 - 21), and area under the ROC curve of 0.88 (95% CI 0.85–0.91). Deek's plot showed no publication bias (p= 0.44). CXR had lower sensitivity compared with HRCT in detecting specific radiologic findings. Subgroup analysis revealed that a patient sample surpassing 100 indicated significantly higher specificity. *Conclusion:* Chest radiography exhibits moderate sensitivity and high specificity for detecting ILD when HRCT is regarded as the gold standard test. Although CXR is recommended as an initial diagnostic tool, it should not be solely relied upon for a definitive diagnosis, as it might miss some cases.

Key words: Chest x-ray, Interstitial lung diseases, Diagnostic imaging, Radiographic image interpretation, Meta-analysis

Introduction

Interstitial lung diseases (ILDs) comprise a large group of over 200 pulmonary diseases. It involves inflammation and/or fibrosis of the alveolar interstitium. ILDs may be idiopathic due to autoimmune disease related to environmental or occupational exposure, secondary to certain types of drugs, or because of an old lung infection (1). Idiopathic pulmonary fibrosis is the most prevalent form of pulmonary fibrosis (2). According to the 2019 Global Burden of Disease study, an estimated 654,841 individuals in the US were diagnosed with ILD, with a prevalence of approximately 179.7 per 100,000 in males and 218.9/100,000 in females (3). Challenges mainly revolve around the early diagnosis of ILDs (4–6). Due to the insidious progression of symptoms and their lack of specificity,

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patients may endure prolonged periods without diagnosis or treatment (7). Moreover, variations among people in life expectancy necessitate quick and accurate assessment. Although ILD can worsen over time, results can be greatly improved with prompt intervention and proper management (4). High-resolution computed tomography (HRCT) has emerged as a definitive diagnostic tool for ILDs (7–9). It is also valuable for monitoring disease progression and predicting mortality (10). However, HRCT requires substantial radiological expertise to accurately classify ILD subtypes (11). Additionally, HRCT is associated with higher costs, limited accessibility in resource-limited settings, and significant radiation exposure, particularly in pregnant patients (12). Consequently, HRCT is considered less suitable as an initial diagnostic tool, especially in resource-constrained setting. CXR is a widely used imaging tool and it is often the initial radiography for assessing many pulmonary symptoms (13) because of its advantages such as low cost, widespread availability, minimal radiation exposure, and non-invasiveness (14). Recent studies have explored the diagnostic accuracy of CXR in ILD (14–17). However, the sensitivity and specificity reported in these studies vary widely, and there is no agreement on its diagnostic effectiveness. Moreover, the exact accuracy of CXR in diagnosing ILD has not been evaluated in a meta-analysis. This systematic review and meta-analysis aim to review and analyze all the publications reporting CXR as an index test to characterize the radiological findings in ILD using HRCT as a reference test. In addition, to measure the pooled sensitivity, specificity, and diagnostic performance of CXR in ILDs to resolve the question regarding could the CXR serve as an alternative or initial diagnostic test for ILDs.

Methods

The present quantitative/meta-analysis was performed in accordance with the Cochrane Collaboration and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statements (18). Our protocol was registered on PROSPERO "CRD42024540955".

Literature search

We searched the electronic databases of PubMed, Embase, Web of Science, and the Cochrane Library for eligible studies from inception throughout March 2024. We used the following keywords: chest x-ray or chest radiography and diffuse parenchymal lung disease or interstitial lung disease. A Google Scholar alert was set, and an independent manual search and references list of the identified articles were also reviewed to identify any other possible articles. Our search was limited to English studies only and according to the inclusion criteria. A detailed search strategy can be found in the Table S1.

Eligibility criteria and study selection

We used Endnote (Clarivate Analytics, PA, USA) to eliminate duplicated references, and then we screened the remaining articles in two stages. At first, two reviewers independently evaluated the titles and abstracts of the publications. After that, we assessed the full text of the selected articles to ensure that they met the meta-analysis criteria. Any disagreements were resolved through a consensus review process. Included studies have to be 1- Clinical cohort studies or diagnostic test studies that utilized CT scan as the gold standard imaging modality for ILD and CXR as index test. 2- The study population was restricted to ILD patients. 3- All studies that directly or indirectly contain original data such as true positive (TP), false positive (FP), false negative (FN), and true negative values (TN) were included in the analysis, while studies with incomplete data (i.e., data that could not form a 2 x 2 contingency table) or data that were combined from more than one reader were excluded. 4- Studies that were not sufficient for accuracy analysis but included data about differences in radiological findings between CXR and HRCT were analyzed to study the differences between CXR and CT in detecting these findings. We excluded studies that were not available in English language, abstracts, reviews, case reports, incomplete original data, different imaging modalities and non-human or cadaveric studies.

Data extraction and quality assessment

Two investigators extracted data from the studies and any discrepancies were deliberated, resolved, and subsequently reviewed by a third investigator. From the studies that included, relevant data, such as study year of publication, study duration, country,

inclusion criteria, image interpreter with years of experience, and conclusions, were extracted. Additionally, baseline characteristics, including age, sample size, number of males, and symptoms or disease duration, were also extracted. For the results section, a 2×2 table, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), prevalence, and sample size were extracted. Moreover, Radiological Findings on both CXR and CT were extracted. Two authors conducted a quality assessment for diagnostic studies using the Quality Assessment of Diagnostic Accuracy 2 (QUADAS-2) tool (19). This involved assessing the included studies across four domains for bias assessment (patient selection, index test, reference standard, and flow and timing) and three domains for applicability assessment (patient selection, index test, and reference standard). In addition, the Newcastle-Ottawa Scale (NOS) (20) was used to assess observational non-diagnostic studies which we included for radiological findings analysis.

Data synthesis and heterogeneity assessment

We used StataMP 17 (Stata Corporation, College Station, TX) Meta package v6.5 in R statistical software for our quantitative analysis. We created two-by-two tables for each study that provided the value of TP, TN, FN, and FP. This process encompassed studies that directly reported these data and those where we could calculate them from the reported specificity and sensitivity values. Then, we calculated the sensitivity, specificity, and summary receiver operating characteristic (SROC) curve with the corresponding area under the curve (AUC), diagnostic odds ratio (DOR), and positive and negative likelihood ratios (LR+, LR-). We evaluated the threshold effect by examining the 95% confidence interval (CI). In diagnostic studies, significant heterogeneity often exists (21). To address this, we employed the Cochran Q test to determine the presence of heterogeneity, considering a P value of less than 0.1 as significant. The extent of variability attributable to actual differences rather than chance was assessed using the I^2 statistic. Variability was deemed moderate at an I^2 value above 50% and significant at an I^2 value above 75%, prompting further sensitivity analyses. We used Deek's funnel plot to detect publication bias, where a P value under 0.10 indicated significant asymmetry and suggested bias. We also conducted additional analyses, including meta-regression for the following covariates (reader experience, sample size, image interpreter, and publication year), subgroup analyses based on gender, and sensitivity analyses for the radiological findings.

Results

Literature search and characteristics

The electronic databases search yielded 2230 records; of which 197 were duplicates and were excluded by endnote. A total of 1953 studies were excluded after reviewing the titles and abstracts. The remaining 80 studies were selected for full-text evaluation and 65 studies were excluded. As shown in Figure 1, 12 studies with 1641 patients were included in the diagnostic accuracy meta-analysis. Additionally, six studies including 276 that had incomplete data (2*2 table) but reported the differences in radiological features between CXR and HRCT were included in a different sensitivity analysis to conclude these differences in a larger scale (23–28). Finally, a total of 18 studies were included in this review involving 1917 patients from a wide variety of regions. The included studies were published between 1987 and 2024 and reader experience ranged from fellowship trainees to more than 10 years of experience. The summary and baseline characteristics of the included studies are shown in Table 1 and Table 2 respectively.

Quality assessment of included studies

Of the 18 included studies, 12 were diagnostic accuracy studies evaluated using the QUADAS-2 tool. Five studies showed a low risk of bias across all domains. The recruitment of patients with ILD was not consecutive in two studies, which led to a high risk of patient selection. And five studies were unclear due to missing information in some domains, see Figure 2 for more details. The remaining six observational non-diagnostic accuracy studies were evaluated using the Newcastle-Ottawa Scale (NOS), with three studies achieving good quality scores and the remaining three scoring fair (Table S2).

Diagnostic performance

Twelve studies provided data on TP, TN, FP, and FN and were eligible for inclusion in the

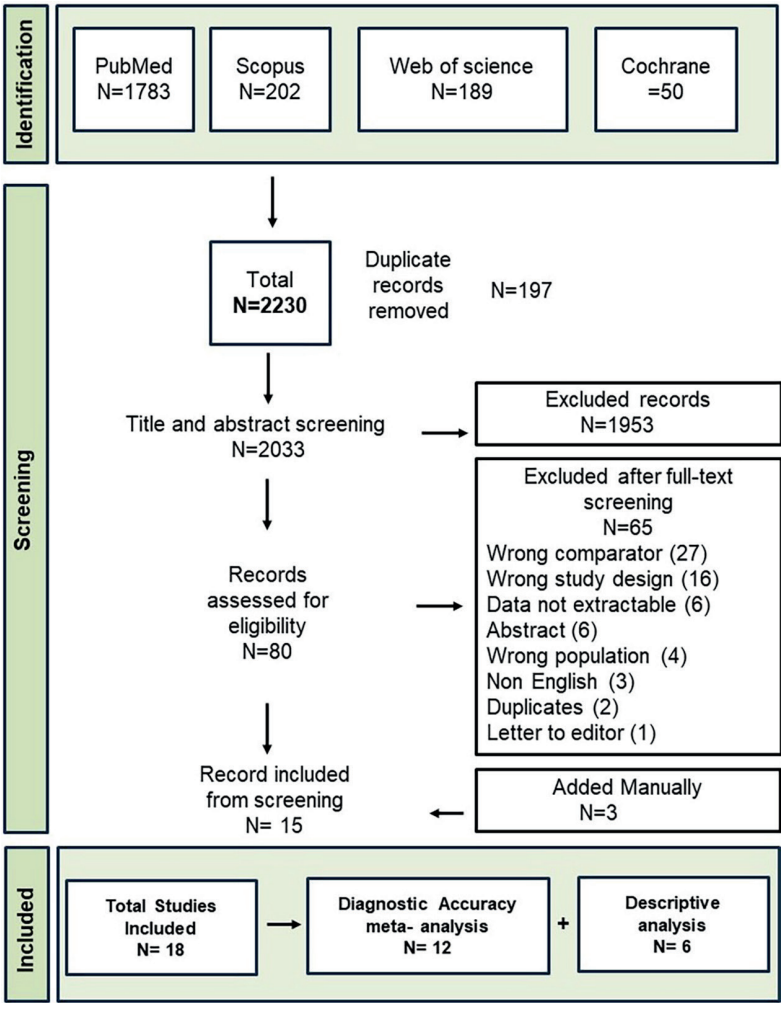

Figure 1. PRISMA flow diagram for study selection.

meta-analysis (14–17,29–36). The overall sensitivity and specificity of CXR in diagnosing ILD were 0.62 (95% CI: 0.47, 0.74) and 0.90 (95% CI: 0.85, 0.93), respectively (Figure 3). LR+ was 5.9 [95% CI 4.5, 7.7], LR- was 0.43 [95% CI: 0.31, 0.59], and the DOR of the CXR was 14 [95% CI: 9, 21]. SROC curve shows that the AUC is 0.88 [95% CI: 0.85, 0.91]. The sensitivity and specificity summarized were eliminated one by one to check the stability of the synthetic results. It demonstrated the low variation in the total effect of the different indicators, suggesting excellent dependability of the results and good stability of the included literature (Figure 4). Given the considerable heterogeneity among the studies (Chi-square P < 0.0001, I2 = 98%), a random-effects model was employed. Additionally, we conducted further meta-regression and subgroup analyses and categorized the potential sources of heterogeneity into the following groups: image interpreter, study design, radiologist experience, sample size, and publication year.

Meta regression analysis

Meta-regression analysis revealed no statistically significant difference in sensitivity between consultant radiologists and radiologist/pneumologists (p = 0.80) however specificity was significantly higher in radiologist/pneumologists group (p = 0.05). Additionally, studies with a prospective design exhibited significantly lower specificity than those with retrospective or cross-sectional designs (p = 0.01). Studies with

Table 1. Summary of the included studies in our systematic review

Study ID	Country	Study Design	Inclusion Criteria	Image Interpreter	Number of Interpreters	Reader Experience	Study Duration	Conclusion
Studies included in the diagnostic accuracy analysis								
Sadiq 2024 (17)	Pakistan	Cross-sectional validational study	Individuals aged 20-70 years with dyspnea on physical examination, cough lasting 3-6 weeks on medical history, fatigue lasting 4-6 weeks, and weight loss (=4.5 kilograms or 5% of normal body weight = 3 months without knowing the reason).	Radiologist	2	> 10 years	One year and two months	CXR offers high diagnostic accuracy and is cost-effective and readily available in low-resource settings. It can serve as an alternative to the expensive HRCT for diagnosing ILD. Cases with a high suspicion can undergo HRCT for confirmation.
Anwar 2024 (29)	Pakistan	Cross-sectional validation study	Individuals aged 20-70 years sent to Radiology to assess the presence of ILD, with dyspnea on physical examination, cough lasting 3-6 weeks on medical history, fatigue lasting 4-6 weeks, and weight loss (=4.5 kilograms or 5% of normal body weight = 3 months without knowing the reason), and only CXR performed within the last three months of the HRCT.	Consultant radiologists	NA	> 5 years	Dec 2020 - Nov 2022	CXR is the ideal initial investigation for diagnosing (ILD) with an accuracy of 78.6% compared to HRCT.
Santos-Moreno 2024 (15)	Colombia	Prospective Cohort	Adults aged ≥ 18 years with a diagnosis of RA according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) criteria and respiratory signs and symptoms that might suggest the presence of ILD in RA	Pneumologist	1	NA	Oct 2020 – Oct 2021	LUS is a useful tool for detecting ILD in RA and, when combined with DLCO. However, these tests do not substitute HRCT, which is necessary to confirm the diagnosis, quantify the extent, and the progression of ILD.
Ghodrati 2022 (16)	USA	Retrospective Cohort	Adult patients with a multidisciplinary diagnosis of fibrotic ILD, including idiopathic pulmonary fibrosis, connective tissue disease-associated ILD, chronic hypersensitivity pneumonitis, and unclassifiable ILD were identified using the UC-Davis ILD registry. Also, patients with incident ILD underwent CXR up to 12 months before the first HRCT confirming ILD.	Chest radiologist and pulmonologist	2	NA	2014 -2021	CXR may overlook a significant number of patients with fibrotic ILD, but the likelihood of ILD increases if features are detected. A chest radiograph indicating ILD features should prompt further investigation with HRCT.

Table 1 *continues*

Table 1. Summary of the included studies in our systematic review (*continued*)

Study ID	Country	Study Design	Inclusion Criteria	Image Interpreter	Number of Interpreters	Reader Experience	Study Duration	Conclusion
Akram 2022 (14)	Pakistan	Prospective Validation Cohort Study	Adult patients aged 30–60 years were presented with progressive exertional dyspnea.	Consultant Radiologist	1	5 years	Jun - Dec 2019	CXR is a simple, non-invasive, and economical alternative to HRCT, however, its specificity and diagnostic accuracy are questionable. While CXR is recommended as a first-line investigation, it should not be solely relied upon for a definitive diagnosis, as it can miss the diagnosis.
Kruamak 2019 (30)	Egypt	Prospective Cohort	Male and female individuals who underwent chest DTS for a 5-year interval.	Radiologists	2	Radiologists in cardiothoracic fellowship training	Jan 2009–Dec 2014	DTS enhances diagnostic performance and confidence in diagnosing ILD compared to conventional CXR. With its high diagnostic accuracy, DTS can be considered as an optional diagnostic technique for these patients.
Negm 2018 (31)	Italy	Prospective Cohort	Patients who were admitted in the Respiratory Care Unit between September 2015 to September 2017.	N/A	NA	N/A	Sep 2015 - Sep 2017	LUS is a noninvasive and promising bedside tool offers better diagnostic performance than CXR for diagnosing most common respiratory pathologies.
Vizioli 2017 (32)	Pakistan	Cross-sectional validational study	A suspected new diagnosis of ILD (dyspnea on exertion, chronic cough, or restrictive pulmonary function tests), being asymptomatic with risk factors for ILD (professional exposure, smoking habit, history of connective tissue disease, immunodeficiency, and drugs), or a medical history of ILD.	Radiologists	2 for CXR, 2 for CT	Several years	Apr 2014 - Mar 2015	LUS shows promise as a sensitive tool for detecting ILD. CXR and LUS exhibit different yet complementary features, suggesting that their combined use could decrease reliance on HRCT.
Afzal 2017	USA	Prospective Cohort	Patients referred for HRCT scan with clinical suspicion of ILD between the ages of 20-50 years of both genders.	Consultant Radiologist	2	10 years	Oct 2013 – Apr 2014	CXR serves as a simple, non-invasive, economical, and available alternative to HRCT, with an acceptable diagnostic accuracy of 81% in diagnosing ILD.

Dawson 2001 (34)	UK	Cross Sectional	Patients with definite RA, as defined by the American Rheumatism Association 1987 revised criteria,13 and enrolled irrespective of chest symptoms or signs.	NA	2	NA	NA	HRCT evidence of FA was present in 19% of outpatients with RA. Abnormalities on chest examination or on full pulmonary function tests, even without restrictive changes or CXR abnormalities, should prompt physicians to request a chest HRCT scan when investigating dyspnea in RA patients.
Schaefer 1991 (35)	USA	Retrospective Cohort	Patients who underwent CT of the chest for clinical indications.	Radiologist	6	NA	NA	The results primarily pertain to high-frequency edge enhancement of interstitial lesions. We advocate for the evaluation of post-processing algorithms based on task-specific criteria. An algorithm that performs well in detecting one type of lesion may not be suitable for another.
Friedman 1987 (36)	USA	Retrospective Cohort	Men suspected of having an occupational lung disease (asbestosis) made up the study group	Radiologist	2	NA	NA	HRCT often boosts the radiologist's confidence in the final diagnosis, particularly in cases featuring prominent subpleural fat, nonspecific increased parenchymal markings, or extensive plaques that obscure the underlying lungs.
Studies included in the descriptive analysis of the radiological findings								
Ardeshna 2024 (23)	India	Prospective Cohort	ILD patients who need follow up radiological investigations, patients presenting with associated conditions and with symptoms such as RA, patients with history of industrial / certain drug exposure, evaluation of diffuse pulmonary disease discovered on CXR, CT, patients with clinically suspected pulmonary disorders with normal or equivocal CXR. evaluation of suspected small and/or large airway disease., and quantification of the extent of diffuse lung disease.	NA	NA	NA	15 months	CXR is a modality for preliminary diagnosis and screening of patients and HRCT proves to be a ultimate modality for near to accurate diagnosis of the pathology.

Table 1 *continues*

Table 1. Summary of the included studies in our systematic review (*continued*)

Study ID	Country	Study Design	Inclusion Criteria	Image Interpreter	Number of Interpreters	Reader Experience	Study Duration	Conclusion
Adarsh 2023 (24)	India	Cross-sectional validational study	Patients referred for CXR and HRCT investigations with lesions in the lung, previously diagnosed cases of ILD requiring follow up radiological investigations and Patients with clinically suspected pulmonary disorders who presented with normal chest x-rays.	NA	NA	NA	Mar 2019 -Mar 2020	Clinical indicators and respiratory symptoms are frequently mistaken for those of more pulmonary disorders, which delays diagnosis. So, HRCT is crucial for the diagnosis, treatment, and follow-up of diffuse lung diseases cases.
Patel 2020 (25)	India	Cross-sectional validational study	Patients aged 20-80 presented with dyspnea and CXR findings like reticular opacities, unequivocal CXR, Honeycombing, poorly demarcated pleural-parenchymal borders along the hemi diaphragm and heart, distortion of lung architecture and changes of tractional bronchiectasis, GGO, already diagnosed case of ILD.	NA	NA	NA	Jan 2018-June 2019	CXR is the primary radiological tool for the diagnosis. HRCT is the best imaging modality and crucial in the diagnosis of ILD.
Agrawal 2019 (26)	India	Cross-sectional validational study	Patients suspected of having ILD on CXR. Patients with clinically suspected ILD with normal or equivocal radiographs.	NA	NA	NA	Jan 2018-Aug 2018	HRCT of the lung in cases of the suspected ILD forms an accurate tool for early identification and in conjunction with the clinical findings can obviate the need of lung biopsy in diagnosis of ILD's.
Siddhant 2016 (27)	India	Prospective Validation Cohort Study	Patients referred to Department of Radiology with clinically suspected ILD.	NA	NA	NA	Sep2015-Sep 2016	HRCT seems to be the investigation of choice in evaluating patients of ILD. CXR is relatively insensitive and all patients with a clinical suspicion of ILD should benefit from chest HRCT.

Rentia 2015 (28)	India	Cross-sectional validational study	Patients referred to the Radiology Department for X - thorax investigations, a lesion, were included in this study. Diagnosed cases of such ILD which need follow up radiological investigations. Patients presented conditions and with symptoms such as rheumatoid arthritis. Patients with known history of industrial /certain drug exposures. Evaluation of diffuse pulmonary disease discovered on CXR, CT, Evaluation of the lungs in patients with clinically suspected pulmonary disorders with normal or equivocal chest radiographs. Evaluation of suspected small and/or large airway disease. Quantification of the extent of diffuse lung disease for evaluating effectiveness of treatment.	NA	NA	NA	May 2014-Apr 2015	CXR is a primary modality used to screen patients with lung pathologies, being cheap, easy to perform and requires less radiation. HRCT is the modality of choice for diagnosis of interstitial lung diseases.

Abbreviations: HRCT: High-resolution computed tomography, ILD: Interstitial Lung Disease, RA: Rheumatoid Arthritis, LUS: Lung Ultrasound, DTS: Digital tomosynthesis, US: Ultrasound, CT: Computed Tomography, DPLD: diffuse parenchymal lung disease.

Table 2. Baseline characteristics of the included studies

Study ID	Sample Size	Age, Years Mean (SD)	Male Number (%)	Symptoms or disease duration (Y), Mean (SD)
Sadiq 2024	160	46.91 (10.16)	116 (72.5)	0.132 (0.326)
Anwar 2024	75	59 (8.3)	49 (65.3)	NA[a]
Santos-Moreno 2024	192	65 (13)	41 (21.3)	16.8 (11.1)
Ghodrati 2022	180	69.7 (11.4)	108 (60.0)	NA
Akram 2022	60	47.18 (6.90)	40 (66.7)	9.66 (1.7)
Kruamak 2019	78	53.05 (19-83)[b]	60 (61.2)	NA
Negm 2018	256	56.22 (14.45)	152 (59.3)	NA
Vizioli 2017	104	65 (13)	56 (53.8)	NA
Afzal 2017	137	40.21 (4.2)	79 (57.6)	NA
Dawson 2001	150	58.84 (10.3)	50 (33.3)	12.7 (8) years
Schaefer 1991	65	58.9 (2.6)	40 (61.5)	NA
Friedman 1987	60	58	60 (100)	NA
Descriptive studies of the radiological findings				
Ardeshna 2024	48	40-79	28 (58.33)	NA
Adarsh 2023	50	NA	21 (46.73)	NA
Patel 2020	60	46.73	27 (45)	NA
Agrawal 2019	40	30-74	26 (65)	NA
Siddhant 2016	30	24-74	18 (60)	NA
Rentia 2015	48	39-80	28 (58.33)	NA

Abbreviations: *NA: not applicable, Y: years, b: the data are presented as mean (Range)

sample sizes exceeding 100 patients showed significantly higher specificity than those with smaller sample sizes (p = 0.03). There was also no significant variation in sensitivity and specificity between radiologists with over five years of experience and those with less than five years of experience (Table S3).

Diagnostic accuracy according to gender, age, and publication year

Regarding diagnostic accuracy by gender, two studies compared the sensitivity and specificity of CXR between males and females and were included in this analysis. The pooled results indicated that females and males had comparable sensitivity (75% for females vs. 74% for males) and specificity (74% for females vs. 79% for males) (Table S3). There were two studies that compared the diagnostic accuracy results between two different age groups. Subgroup analysis for age could not be conducted due to variations in age subgroups between these studies; therefore, we review the results of them individually. Akram et al. (14) found that patients older than 47 had higher sensitivity than patients aged 46 or less (57.9 % vs. 44.4 %). However, Sadiq et al. (17) found that patients aged 46 or more had comparable sensitivity with patients aged less than 46 (86.9 % vs. 88%). Moreover, both studies found that the older patients had lower specificity than the younger age groups. Sadiq et al reported 79.4% specificity for patients who aged 46 or more compared to 87% for younger ages. Akram et al. Reported 0 specificity for patients older than 47 compared to 25% for the younger age group. Further subgroup analysis categorized by publication year revealed no significant difference in the sensitivity of CXR for diagnosing ILD between older studies (conducted from 1987 to 2001) and newer studies (conducted from 2017 to 2024). In contrast, a significant difference in specificity was observed, with the more recent studies

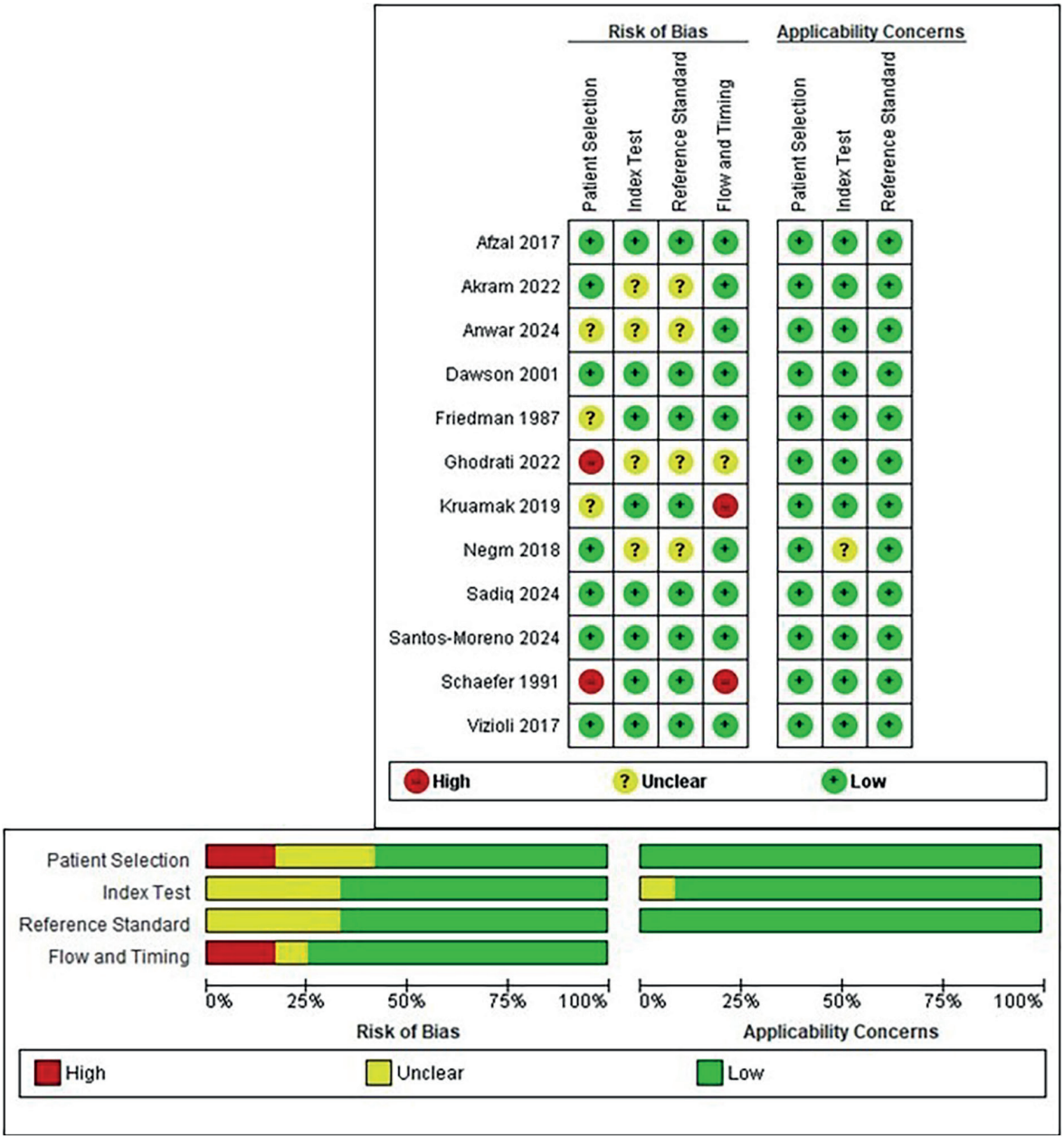

Figure 2. Risk of bias assessment of the included studies.

demonstrating higher specificity for diagnosing ILD compared to the earlier subgroup.

Diagnostic accuracy of lung ultrasound (LUS)

Two of the included studies (15,32) compared the accuracy of LUS in the diagnosis of ILD with CXR while HRCT was considered the gold standard. Our analysis of these studies revealed a pooled estimate for sensitivity of LUS was 0.97 [95% CI 0.93 - 0.99], indicating higher sensitivity than CXR. However, the specificity was 0.28 [95% CI 0.2 – 0.38], lower than CXR's (Table S3).

Publication bias and clinical applicability

We performed Deek's funnel plot with a p value of 0.44, indicating no significant asymmetry

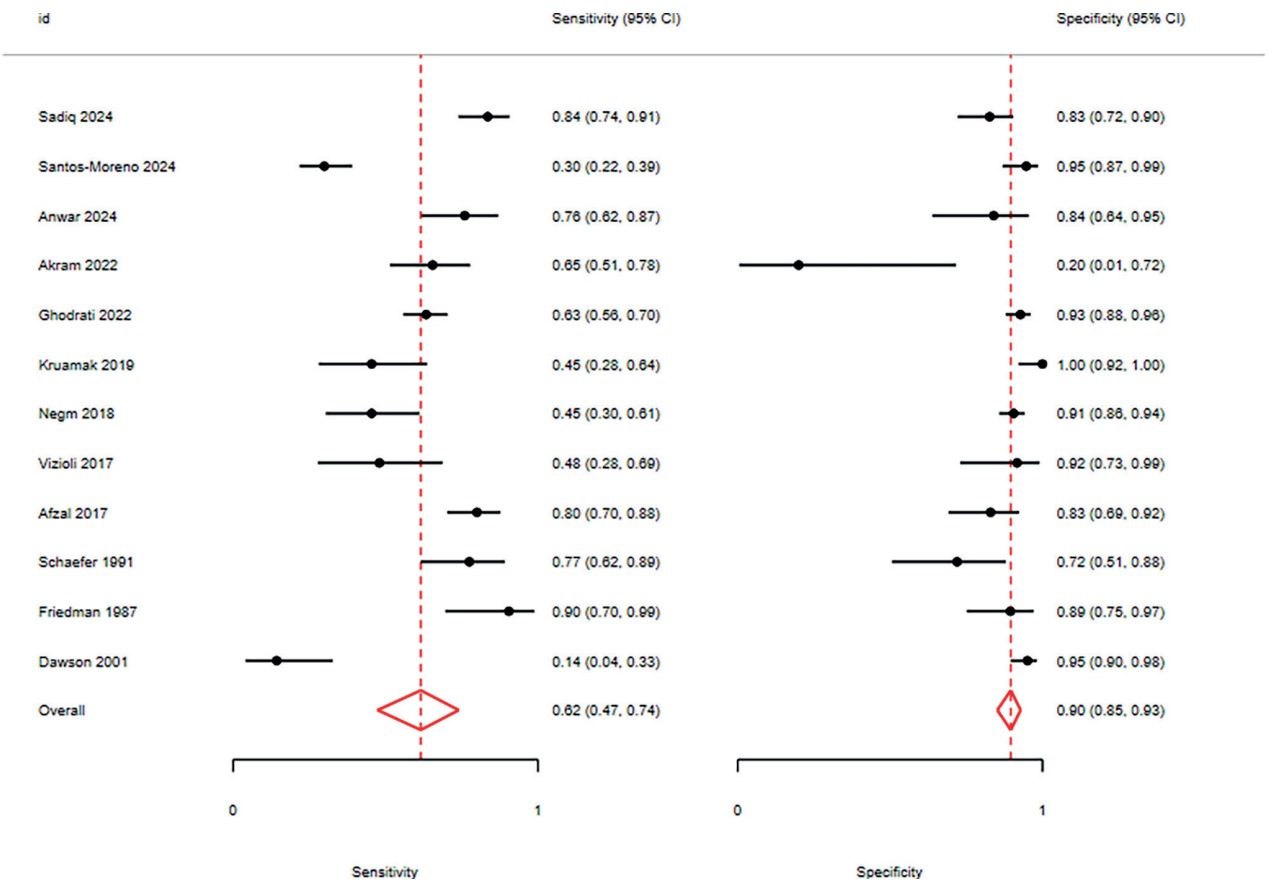

Figure 3. Forest plot showing CXR pooled sensitivity and specificity for ILD

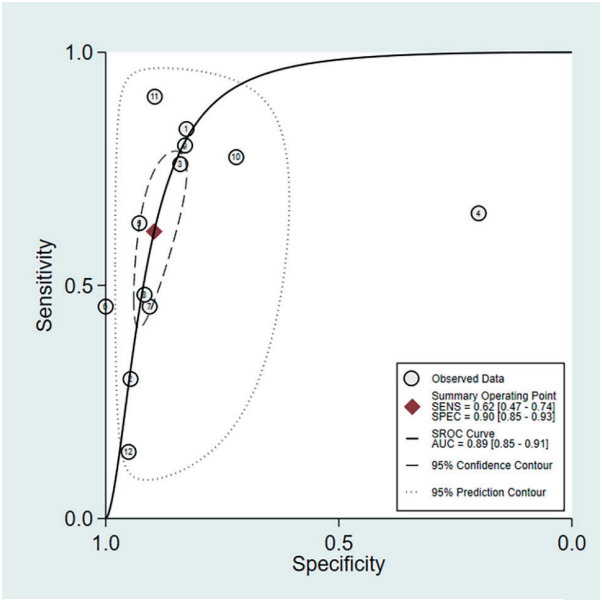

Figure 4. Summary Roc curve of CXR in the diagnosis of ILD

or publication bias (Figure 5). From the Fagan diagram, the post-test probability is 66%, which is 50% higher than the pre-test probability. The combined positive likelihood ratio is less than 10, and the combined negative likelihood ratio in the diagnosis of ILD is more than 0.1, indicating that CXR is effective in the diagnosis (Figure 6).

Sensitivity of chest X-ray for detecting different radiographic findings associated with ILD

The meta-analysis revealed that chest x-rays had moderate sensitivities for detecting reticular opacity (68.9% [95% CI: 66.9% to 70.9%]), nodular opacity (65.3% [95% CI: 58.8% to 71.2%]), consolidation (67.4% [95% CI: 65.6% to 69.1%]), traction bronchiectasis (65.4% [95% CI: 63.4% to 67.3%]), honeycomb appearance (63% [95% CI: 61% to 65%], septal thickening (59% [95% CI: 56% to 63.3%]),

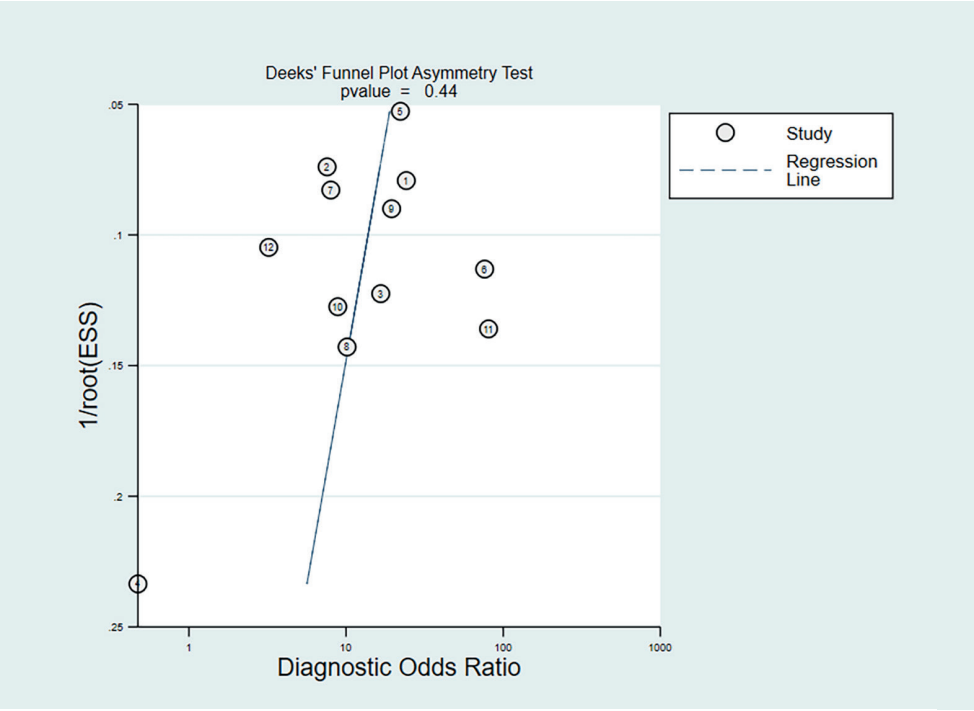

Figure 5. Deeks' funnel plot showing no publication bias.

ground glass opacity (66.7% [95% CI: 61.8% to 71.3%]), and lymphadenopathy (61.4% [95% CI: 54.9% to 67.5%]), however, there was notable variability in sensitivity estimates across studies, indicating the influence of factors such as study populations and methodologies. Heterogeneity was particularly pronounced for nodular opacity (I2 = 96.9%), ground glass opacity (I2 = 81.0%), lymphadenopathy (I2 = 92.1%), and septal thickening (I2 = 76.8%). Due to the limited data available from the included studies and the small number of studies for each radiographic finding, a comprehensive exploration of the sources of heterogeneity through subgroup analysis and meta-regression was not feasible. The variability observed in sensitivity estimates across studies underscores the need for further research with larger sample sizes and more detailed data. to better understand and address sources of heterogeneity in the sensitivity of CXRs for detecting radiographic findings in ILD (Figure S1 and S2).

Discussion

HRCT is the cornerstone of the diagnosis of ILD. However, new approaches have been developed in the diagnosis and image analysis. CXR has been deemed to have a high diagnostic value, CXR is less expensive, less radiation, commonly used and readily available in medical settings, and still the first line in patients with respiratory symptoms (13,14,17). Recently, a lot of questions followed by up to 8 studies published in previous three years, measuring CXR as a diagnostic test for ILDs (14–17,23–25,29). This systematic review and meta-analysis is mandatory to pole all published studies to provide significant evidence regarding CXR in ILDs. Our meta-analysis included 18 studies, with a total of 1917 patients, and the pooled data showed that CXR in comparison to HRCT in patients with ILD has moderate sensitivity 62% and high specificity 90%. Also, the AUC of 88% indicates an acceptable overall accuracy. Furthermore, CXR had moderate sensitivities for detecting reticular opacity, nodular opacity, consolidation, traction bronchiectasis, honeycomb appearance, septal thickening, ground glass opacity, and lymphadenopathy. This means that X-rays cannot correctly identify true negative patients. A meta-analysis of 543 patients from Winkler et al. (37) comparing CXR to HRCT in Intensive care unit patients demonstrated the same findings as our

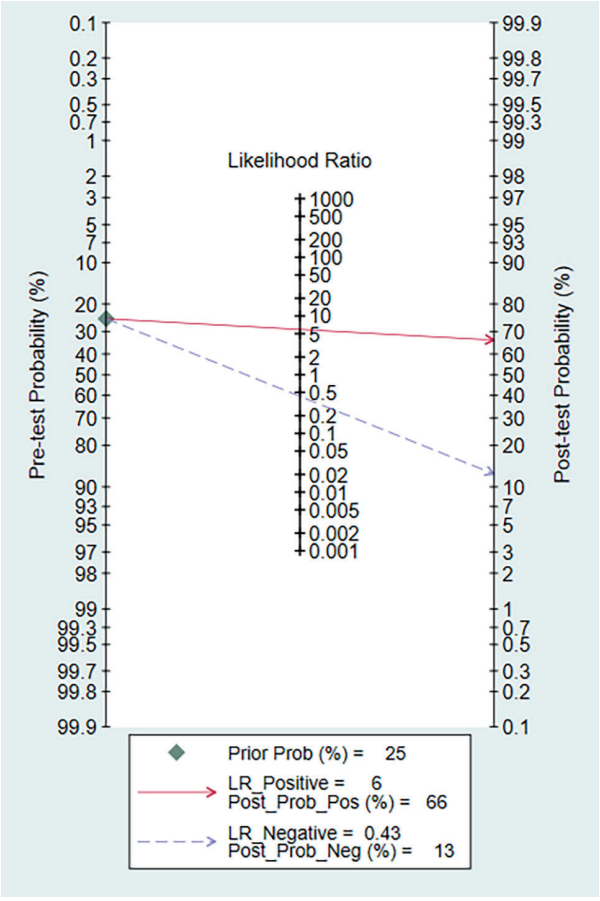

Figure 6. Fagan diagram analysis for CXR in the diagnosis of ILD

results. Of course, ILD severity and disease staging requires a highly sensitive method and HRCT can evaluate patient prognosis and the disease progression. However, CXR could be the initial indicator for ILD patients. The pooled CXR diagnostic accuracy of 12 studies in our study was 88%, 80% in Afzal et al. (33) and 61.66% in Akram et al. (14) proving that a normal CXR does not eliminate the presence of ILD. A study by Ardeshna et al. (23) reported that CXR demonstrated a normal field in a case of tuberous sclerosis while HRCT demonstrated a ground glass opacity and intra-parenchymal cysts with septal thickening. Also, Patel et al. (25) reported that CXR demonstrated a normal field in three patients while HRCT showed focal findings including septal thickening. Moreover, Agrawal et al. (26) reported that CXR was normal in six patients while reticular changes were observed in HRCT for the same patients. These previous findings could be proven by a study by Adarsh et al (24) that HRCT was able to show septal thickening in 45 patients with a percentage of 90%, however, CXR showed 10 patients with septal thickening with a percentage of 20%. Sadiq et al. discovered that CXR accuracy declines in older patients, with a specificity of 79.4% for those aged 46 and above, compared to 87% for younger individuals. This decrease in specificity is linked to the difficulties in interpreting CXRs due to age-related changes and comorbidities, which further complicate the imaging process in the elderly (40). This finding highlights the importance of careful assessment and the possible need for additional imaging techniques to ensure accurate diagnosis in this demographic. Akram et al (14). reported a specificity of zero for chest X-ray (CXR) in patients over 47 years old. However, this result is due to the small number of healthy patients in this subgroup, which included only one healthy individual, while the remaining 19 cases had ILD. Consequently, CXR failed to identify this single healthy control, resulting in a specificity of 0. Depending on these findings and given the lack of CXR sensitivity we could not depend on CXR as a definitive diagnosis or an alternative to HRCT for ILD. However, it could be the initial diagnostic technique. Subgroup analysis based on publication year revealed a significantly higher specificity in studies published after 2001 (2017–2024). This improvement can be attributed to enhanced radiologist training, advancements in imaging techniques and quality, and development of standardized protocols. These factors have led to better visualization of anatomical structures and pathologies, resulting in more accurate interpretations of chest radiographs. Collectively, these advancements have significantly improved the diagnostic capability and quality of CXRs. Additionally, Advancements in HRCT technology have transitioned from older protocols that used noncontiguous thin-section images at 10-20mm intervals, limiting diagnostic accuracy for ILD. The introduction of multi detector CT (MDCT) enabled continuous, thin-section imaging of the entire chest in one breath-hold, greatly improving precision. Modern MDCT scanners offer high-resolution imaging with lower radiation doses, enhanced by advanced detector technology and iterative noise reduction, significantly increasing the accuracy of ILD detection. This underscores the improved capabilities of HRCT for diagnosing ILD . The diagnosis of ILD now relies on a multidisciplinary approach, including clinical and

radiographic assessments, with HRCT becoming the preferred diagnostic tool. It has largely replaced invasive histopathological procedures, enabling early detection, assessment of disease severity, and prognosis. HRCT was used as the reference standard in this study to ensure consistent and reliable results. Further subgroup analysis comparing LUS with CXR in patients with ILD demonstrated that LUS had a significantly higher pooled sensitivity (97%) than CXR. This finding aligns with the results of Song et al. (46), who reported a sensitivity of 91.5%, and Radic et al. (47) who found a sensitivity of 93% in patients with ILD and systemic sclerosis. The enhanced sensitivity of LUS is attributed to its superior ability to detect critical indicators, such as B-lines and pleural abnormalities (48). However, the specificity of LUS was notably lower (28%) in our analysis, although Song et al. and Radic et al. reported higher specificities of 81.3% and 61%, respectively. This discrepancy in specificity may stem from the limited number of studies included in our subgroup analysis. However, LUS only assesses the lung surface, limiting its diagnostic scope compared with other imaging modalities. Despite this limitation, LUS can be a highly useful adjunct method for monitoring patients with connective tissue disease-associated ILD (CTD-ILD) during both initial treatment and follow-up. The heterogeneity in the results of our meta-analysis can be attributed to several factors. Variations in demographic characteristics, such as age and underlying health conditions, likely contribute to differences in the study outcomes. Additionally, the duration and severity of the disease among patients can significantly affect the results, as a longer disease duration and more severe cases may present differently on imaging. Differences in the experience and expertise of radiologists and image interpreters also play a crucial role, as more experienced professionals may be better at identifying subtle abnormalities. These factors collectively contributed to the heterogeneity observed in our meta-analysis.

Strengths and limitations

To our knowledge, this is the first systematic review and meta-analysis to measure the diagnostic accuracy of CXR in patients with ILD, with a focus on one reference test (HRCT) to minimize bias. A notable strength is the inclusion of five studies from the past three years, ensuring that the analysis is up to date with recent findings. The study quality was rigorously evaluated using the QUADAS tool, and most included studies were of high quality. The included studies had sample sizes ranging from 60 to 256 patients, culminating in a pooled analysis of 1641 patients, thereby increasing the statistical power and precision of the diagnostic accuracy findings compared to individual studies. Despite its strengths, this meta-analysis has several limitations. This review included only English-language studies, potentially omitting relevant data from non-English publications, which may have influenced the comprehensiveness of the findings. Despite subgroup analyses and regression to address heterogeneity, it remains a limitation. Furthermore, most of the included studies were cross-sectional, which may have affected the generalizability of the results. For future research, we recommend taking into consideration the application of deep learning in CXR, comparing different diagnostic tests within the same patient cohort and presenting results in 2×2 tables for clearer comparisons. Conducting large, multicenter studies would enhance the generalizability of the findings. Researchers should also compare true positive and false negative populations and investigate whether false positive and false negative results occur in the same or different patients. Additionally, including the duration of respiratory symptoms in suspected ILD patients would provide more context for the diagnostic accuracy. Finally, since some studies included pulmonologists as image interpreters, future studies should compare the diagnostic accuracy of pulmonologists versus radiologists to better understand the impact of the interpreter's expertise on diagnostic outcomes.

Conclusion

In conclusion, our meta-analysis indicates that chest radiography (CXR) exhibits moderate sensitivity but high specificity for detecting ILD when HRCT is the gold standard. While CXR is recommended as an initial diagnostic tool, it should not be solely relied upon for a definitive diagnosis due to its potential to miss some cases. the need for further application of deep learning for confirmatory tests for accurate diagnosis and image analysis.

Conflicts of Interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership,

equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Authors' Contribution: All authors took part in the conception of the study, and all authors approved the manuscript for publication and agree to be accountable for the work's integrity.

Availability of Data and Materials: All data generated or analyzed during this study are included in this published article or in the data repositories listed in References.

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ANNEX

Table S1. Search queries for the systematic review.

Databases	Search Strategy	Number
PUBMED	(Chest X-ray OR Chest Radiograph OR chest radiography OR CXR OR plain radiography OR Chest Film) AND (ROC curve OR Sensitivity and specificity OR Diagnostic accuracy OR Diagnostic value OR Accuracy OR receiver operating characteristic OR diagnostic efficiency) AND (Diffuse Parenchymal Lung Disease OR Interstitial Lung Diseases OR Diffuse Parenchymal Lung Diseases OR Interstitial Lung Disease OR Lung Disease, Interstitial OR Pneumonia, Interstitial OR Interstitial Pneumonia OR Interstitial Pneumonias OR Pneumonias, Interstitial OR Pneumonitis, Interstitial OR Interstitial Pneumonitides OR Interstitial Pneumonitis OR Pneumonitides, Interstitial OR Pulmonary Fibrosis OR Fibrosis, Pulmonary OR Idiopathic Diffuse Interstitial Pulmonary Fibrosis OR Pulmonary Fibroses OR Fibroses, Pulmonary OR Alveolitis, Fibrosing OR Alveolitides, Fibrosing OR Fibrosing Alveolitides OR Fibrosing Alveolitis)	**1783**
SCOPUS	("Chest X-ray" OR "Chest Radiograph" OR "chest radiography" OR "CXR" OR "plain radiography" OR "Chest Film") AND ("ROC curve" OR "Sensitivity" and "specificity" OR "Diagnostic accuracy" OR "Diagnostic value" OR "Accuracy" OR "receiver operating characteristic" OR "diagnostic efficiency") AND ("Diffuse Parenchymal Lung Disease" OR "Interstitial Lung Diseases" OR "Diffuse Parenchymal Lung Diseases" OR "Interstitial Lung Disease" OR "Lung Disease, Interstitial" OR "Pneumonia, Interstitial" OR "Interstitial Pneumonia" OR "Interstitial Pneumonias" OR "Pneumonias, Interstitial" OR "Pneumonitis, Interstitial" OR "Interstitial Pneumonitides" OR "Interstitial Pneumonitis" OR "Pneumonitides, Interstitial" OR "Pulmonary Fibrosis" OR "Fibrosis, Pulmonary" OR "Idiopathic Diffuse Interstitial Pulmonary Fibrosis" OR "Pulmonary Fibroses" OR "Fibroses, Pulmonary" OR "Alveolitis, Fibrosing" OR "Alveolitides, Fibrosing" OR "Fibrosing Alveolitides" OR "Fibrosing Alveolitis")	**202**
WOS	("Chest X-ray" OR "Chest Radiograph" OR "chest radiography" OR "CXR" OR "plain radiography" OR "Chest Film") AND ("ROC curve" OR "Sensitivity" and "specificity" OR "Diagnostic accuracy" OR "Diagnostic value" OR "Accuracy" OR "receiver operating characteristic" OR "diagnostic efficiency") AND ("Diffuse Parenchymal Lung Disease" OR "Interstitial Lung Diseases" OR "Diffuse Parenchymal Lung Diseases" OR "Interstitial Lung Disease" OR "Lung Disease, Interstitial" OR "Pneumonia, Interstitial" OR "Interstitial Pneumonia" OR "Interstitial Pneumonias" OR "Pneumonias, Interstitial" OR "Pneumonitis, Interstitial" OR "Interstitial Pneumonitides" OR "Interstitial Pneumonitis" OR "Pneumonitides, Interstitial" OR "Pulmonary Fibrosis" OR "Fibrosis, Pulmonary" OR "Idiopathic Diffuse Interstitial Pulmonary Fibrosis" OR "Pulmonary Fibroses" OR "Fibroses, Pulmonary" OR "Alveolitis, Fibrosing" OR "Alveolitides, Fibrosing" OR "Fibrosing Alveolitides" OR "Fibrosing Alveolitis")	**189**
COCHRANE	(Chest X-ray OR Chest Radiograph OR chest radiography OR CXR OR plain radiography OR Chest Film) AND (ROC curve OR Sensitivity and specificity OR Diagnostic accuracy OR Diagnostic value OR Accuracy OR receiver operating characteristic OR diagnostic efficiency) AND (Diffuse Parenchymal Lung Disease OR Interstitial Lung Diseases OR Diffuse Parenchymal Lung Diseases OR Interstitial Lung Disease OR Lung Disease, Interstitial OR Pneumonia, Interstitial OR Interstitial Pneumonia OR Interstitial Pneumonias OR Pneumonias, Interstitial OR Pneumonitis, Interstitial OR Interstitial Pneumonitides OR Interstitial Pneumonitis OR Pneumonitides, Interstitial OR Pulmonary Fibrosis OR Fibrosis, Pulmonary OR Idiopathic Diffuse Interstitial Pulmonary Fibrosis OR Pulmonary Fibroses OR Fibroses, Pulmonary OR Alveolitis, Fibrosing OR Alveolitides, Fibrosing OR Fibrosing Alveolitides OR Fibrosing Alveolitis)	**50**

Table S2. Methodological quality assessment of the included 5 observational studies, based on the NOS for assessing the quality of observational studies.

	Selection				Comparability	Exposure			
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at the start of the study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow-up of cohorts	Total score
Ardeshna 2024		★		★	★★		★		5
Adarsh 2023	★	★	★	★	★★		★		7
Patel 2020	★	★	★	★	★★	★	★		8
Agrawal 2019			★	★	★★		★		5
Siddhant 2016	★	★	★	★	★★	★	★		8
Rentia 2015		★	★		★★				4

Table S3. Meta regression and subgroup analysis

Meta-regression and Subgroups	No. of studies	Sensitivity	*P* value	Specificity	*P* value
Image Interpreter					
Consultant radiologist	3	0.75 [0.58 - 0.91]	0.80	0.76 [0.54 - 0.99]	0.05
Radiologist/ pneumologist	5	0.61 [0.45 - 0.77]		0.92 [0.85 - 0.98]	
Study design					
Prospective	5	0.55 [0.34 - 0.75]	0.59	0.89 [0.83 - 0.95]	0.00
Retrospective/ cross-sectional	7	0.66 [0.50 - 0.82]		0.90 [0.85 - 0.95]	
Radiologist's experience					
> 5 years	3	0.80 [0.74 - 0.87]	0.34	0.84 [0.62 - 1.00]	0.91
≤ 5 years	3	0.54 [0.42 - 0.66]		0.89 [0.69 - 1.00]	
Sample size					
>100	6	0.55 [0.36 - 0.74]	0.25	0.91 [0.87 - 0.95]	0.03
<100	6	0.68 [0.51 - 0.85]		0.87 [0.80 - 0.94]	
Publication Year					
After 2001	9	0.61 [0.46 - 0.77]	0.85	0.90 [0.86 - 0.94]	0.04
Before 2001	3	0.61 [0.33 - 0.90]		0.88 [0.80 - 0.97]	
Females Males Lung ultrasound	2 2 2	0.75 [0.62 - 0.84] 0.74 [0.64 – 0.83] 0.97 [0.93 – 0.99]		0.74 [0.50 - 0.89] 0.79 [0.62 – 0.90] 0.28 [0.2 – 0.38]	

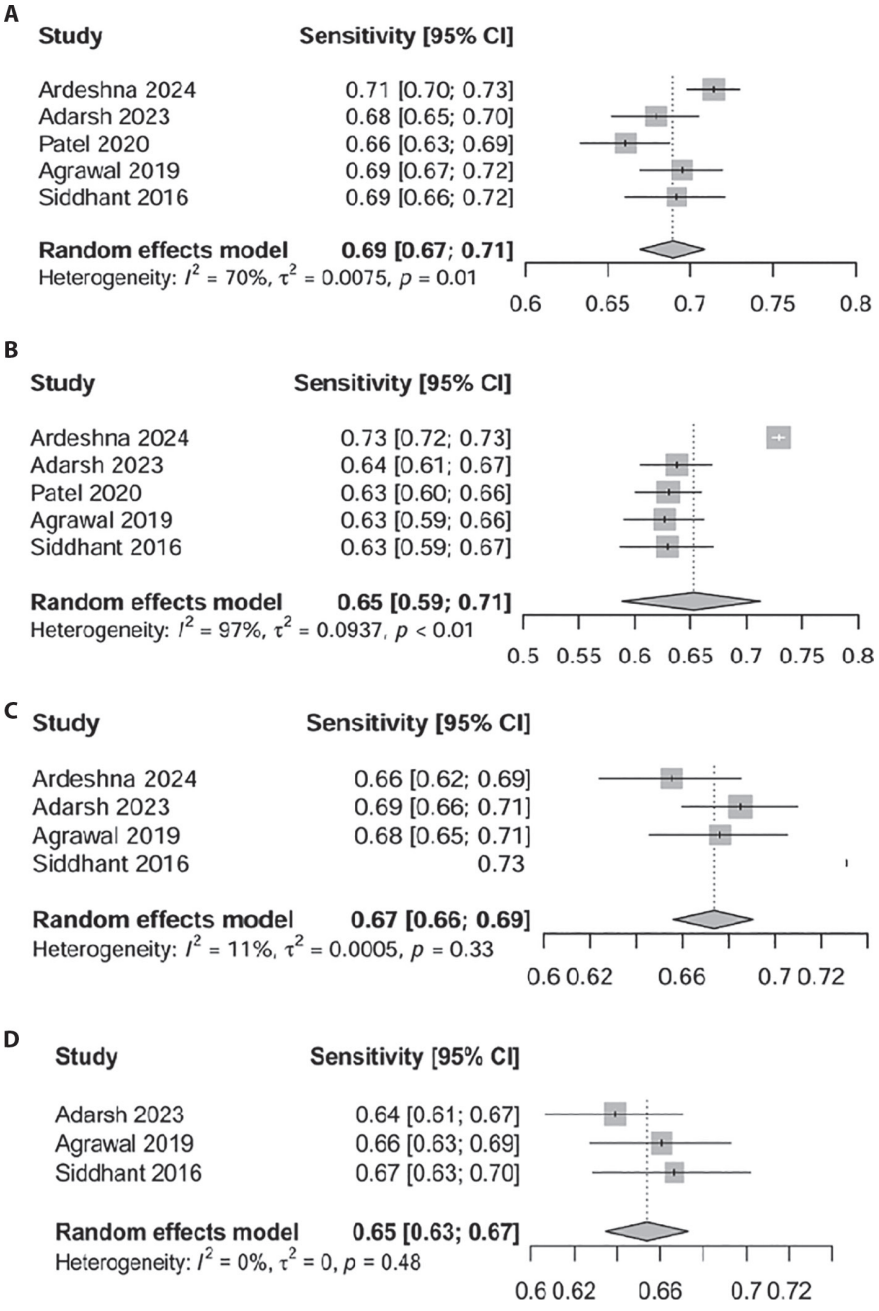

Figure S1. Forest Plot for the Sensitivity analysis of CXR for detecting different radiographic findings associated with ILD **a)** Reticular opacity, **b)** Nodular opacity, **c)** Consolidation **d)** Traction bronchiectasis

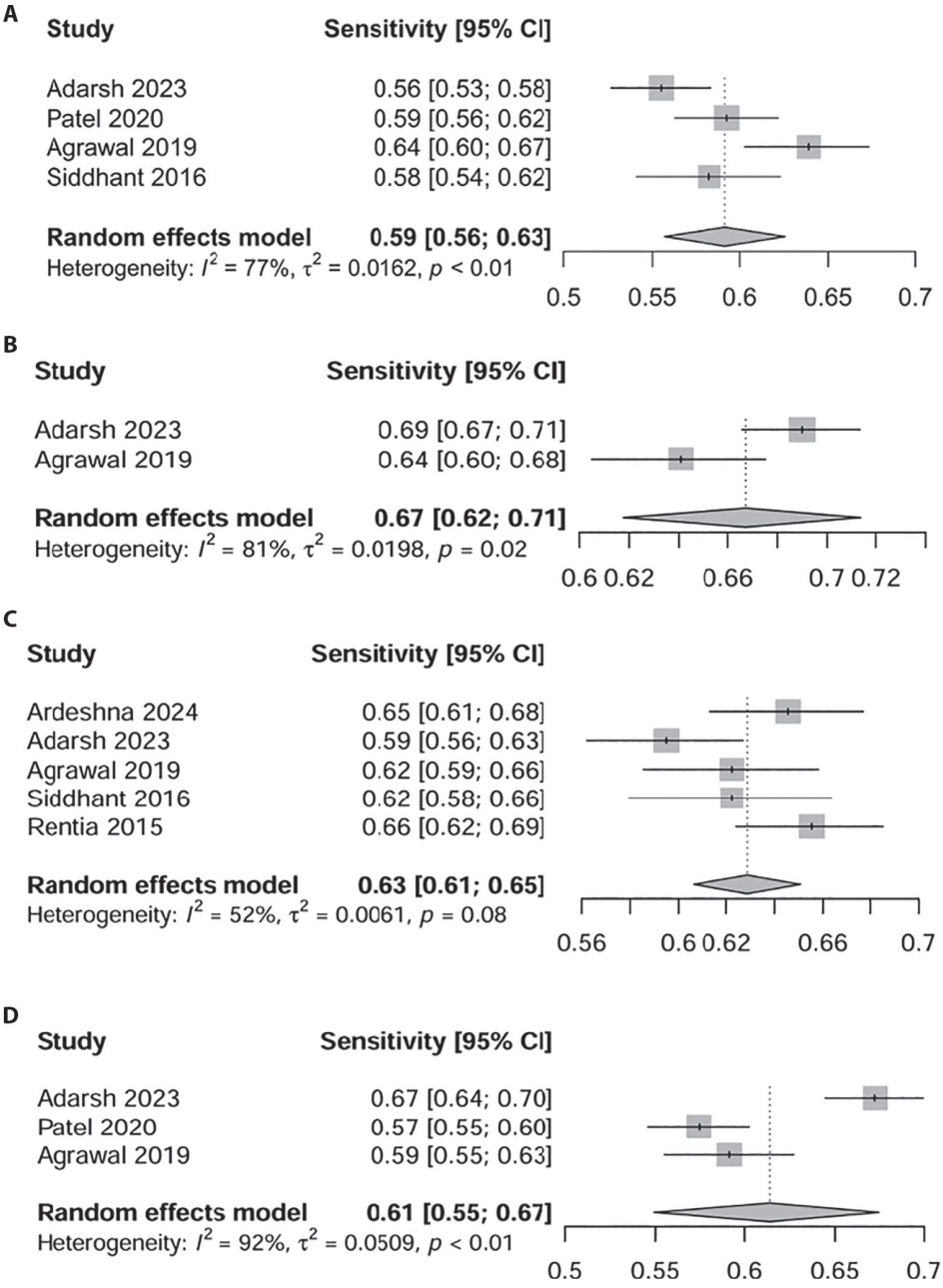

Figure S2. Sensitivity analysis of CXR for detecting different radiographic findings associated with ILD **a)** Septal thickening, **b)** Ground glass opacity, **c)** honeycomb appearance, **d)** Lymphadenopathy