CHEST RADIOGRAPH ACCURACY IN DIAGNOSING PEDIATRIC PULMONARY TUBERCULOSIS (PTB): A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

In endemic regions, tuberculosis (TB) is the major cause of morbidity and mortality among children under the age of five, accounting for a significant proportion of the global death toll among such children. Approximately 35% of pediatric TB cases are appropriately diagnosed, frequently resulting in a protracted or untreated illness. This study assessed the diagnostic value of chest radiograph examination in diagnosing pediatric pulmonary TB. The PRISMA 2020 guidelines were used to conduct this systematic review and meta-analysis of 379 articles identified in four databases. The software Meta-Disc 1.4 was used to assess the diagnostic accuracy of the pooled samples but due to insufficient data, the computed tomography (CT) and magnetic resonance imaging (MRI) examinations were removed from further investigation. Six articles containing comprehensive chest X-ray (CXR) data were analyzed with pooled sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), and diagnostic odds ratio (DOR) of 0.88 (95% confidence interval [CI]: 0.84-0.91), 0.50 (95% CI: 0.46-0.53), 3.07 (95% CI: 1.68-5.58), 0.29 (95% CI: 0.14-0.60), and 17.41 (95% CI: 3.38-89.41), respectively. The summary receiver operating characteristic (sROC) curve area under the curve (AUC) was 0.8242. In conclusion, CXR demonstrated high sensitivity, moderate specificity, excellent PLR, NLR, and DOR for diagnosing pediatric pulmonary TB.

Keywords: Chest Radiograph, Diagnostic Accuracy, Pediatric Pulmonary Tuberculosis

Introduction

In endemic regions, tuberculosis (TB) is a primary contributor to the global death toll of children under five (1). An estimated 10.6 million people had tuberculosis in 2021, increasing 4.5% from 2020 and reversing several years of steady reduction, with 1.1 million (11%) of the cases impacting children under 15 years old and as many as 196,000 HIV-negative and 20,000 HIV-positive children dying as a result (2). Merely 35% of pediatric TB cases are correctly diagnosed, possibly delaying or preventing treatment. The high infection and fatality rates in children are at least partly because 69% of infections in children under five and 40% of cases in children aged 5−14 are unreported and often misdiagnosed (3).

Many variables, including immature immune systems, a lack of characteristic TB symptoms, children's inability to expectorate sputum, and a small bacterial load (paucibacillary), make it challenging to diagnose pulmonary tuberculosis (PTB) in children (3). As a result, it is not uncommon for the diagnosis to be speculative rather than confirmed (4). The cornerstone for successful TB management on both an individual and societal scale is using better diagnostic tests for pulmonary tuberculosis in children (5, 6).

Imaging is necessary for diagnosis and monitoring, as well as judging the treatment response, and is critical to the diagnostic process, including PTB (7). Chest X-ray is the preferred modality, and the most common finding is lymphadenopathy in the mediastinum or around the hilar region (8). Nonetheless, the spectrum of radiologic abnormalities in tuberculosis is often broad and may be vague (1). Therefore, this study assessed the diagnostic value of chest radiograph examination in diagnosing pediatric PTB.

Materials and Methods

Search strategy

The review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines (9). Before conducting the literature search, the entire review panel approved the study's protocol and to avoid unnecessary delay and allow the data-gathering procedure to begin immediately, the search method was not registered on the International Prospective Registry of Systematic Reviews (PROSPERO).

Four databases, including PubMed (Medline via PubMed), Scopus, Google Scholar, and JSTOR, were searched for articles published from 2013 through 2023 that assessed the accuracy of radiology examination in diagnosing pediatric TB using the keyword combinations listed in Table 1.

Table 1: Search strategy

Databases	Keywords
PubMed	("TB" OR "pulmonary TB" OR "miliary TB") AND ("children" OR "adolescent" OR "infant" OR "pediatric") AND ("radiology" OR "imaging" OR "chest X-ray" OR "computed tomography" OR "ultrasound") AND ("diagnosis accuracy" OR "sensitivity" OR "specificity")
Google Scholar	"TB", "pulmonary TB", "children", "pediatric", "radiology", "imaging", "chest X-ray", "computed tomography", "ultrasound". "accuracy"
Scopus	("TB" OR "pulmonary TB") AND ("children" OR "pediatric") AND ("radiology" OR "imaging" OR "chest X-ray" OR "computed tomography" OR "ultrasound") AND ("accuracy")
JSTOR	("pulmonary TB") AND ("pediatric") AND ("radiology") AND ("accuracy")

Study selection

Quantitative studies in English that analyzed the value of radiography in diagnosing childhood tuberculosis were included and only full-text, peer-reviewed articles (excluding preprints) were considered to avoid any potential discrepancies. The following articles were excluded: case-control studies, case studies, clinical trials, protocols, conference abstracts, news articles, editorials, posters, presentations, and literature reviews. Titles and abstracts were separately screened by two reviewers (DA and IAL), and duplicates were removed before a roundtable discussion to settle any remaining differences in the screening of titles and abstracts, as well as the evaluation of the entire texts. There were 42 duplicates among the 379 items initially retrieved, of which, 25 papers were selected for full-text and reference assessment. Finally, nine studies that met all of the criteria for data synthesis were included in this review and meta-analysis (Figure 1).

Data extraction

Three authors collected data from each trial independently (DA, YF, IAL) including authors, year, country, study design, study populations, and primary findings.

Risk of bias analysis

The quality of the study's methodology was assessed using the Modified Newcastle Ottawa Quality Assessment Scale (NOS) for Cross-Sectional Studies (10) which considers the quality of selection (representative sample, sample size, proportionality of non-respondents), comparability (management of confounding factors), and outcome (assessment of outcome and follow-up or statistical test) (11). Each article was scored on the NOS by two researchers (DA and IAL) before the results were compared. Discrepancies were discussed and resolved by consensus. A moderator (YF) was also present to evaluate the articles in question as part of the quality control process to ultimately decide whether the manuscript would be included. Overall, the methodologic integrity of the included papers was rated as either low (7-10), moderate (5-6), or high risk of bias (0-4) (12). The risk of bias assessment was visualized using the Risk-of-bias VISualization (robvis) software (13).

Statistical analysis

The diagnostic sensitivity, specificity, positive likelihood ratio (PLR), negative likelihood ratio (NLR), diagnostic odds ratio (DOR), and 95% confidence intervals (CI) were calculated using Meta-Disc1.4 software (14).

Results

Characteristics of the included studies

The main features of the nine included studies published from 2017 to 2022 are summarized in Table 2. The studies were all cross-sectional with the study samples ranging from 40 to 541. Most children had been diagnosed with pulmonary TB, with chest X-rays (CXR) being the most imaging technique used (6, 8, 15–20). Most studies describe the radiological findings in children with pulmonary TB, and several also compared the results across imaging modalities (16, 18, 21).

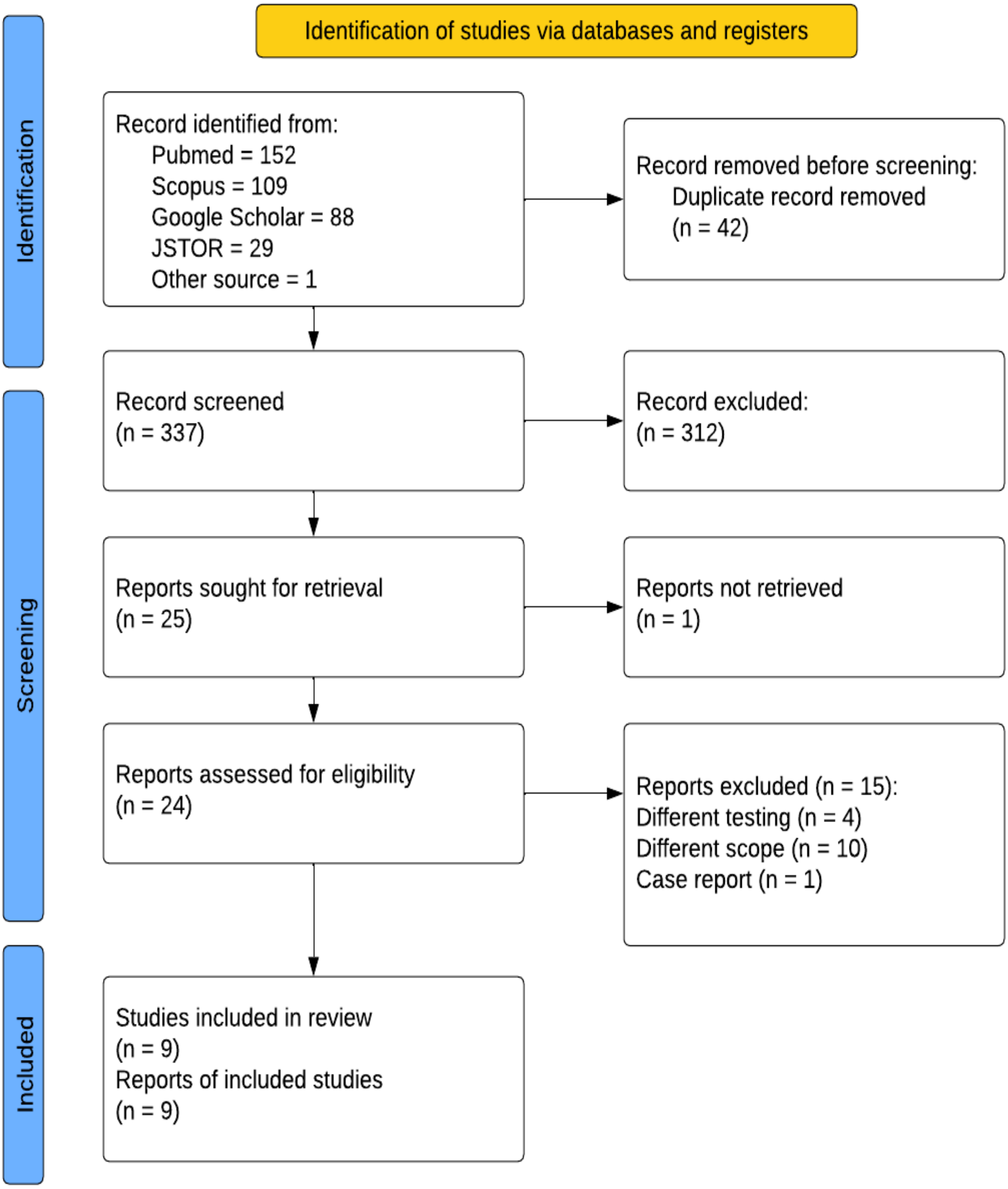

Figure 1: PRISMA 2020 flow diagram of literature search

Table 2: Summary and key radiologic findings of included studies

Author (year)	Country	Methods	Study populations	Primary aim	Radiologic findings
Buonsenso et al. (2021) (16)	Italy	Cross-sectional	41 patients aged <16 years with active TB	Explain the CT findings of PTB in children, with special attention to the involvement of the airways and lymphadenopathy	• Out of 41 patients, only 7 CXRs were normal (17.1%), while all CT scans showed abnormalities • CXR was negative for pulmonary TB in 19 of 37 cases (46.3%), while CT was negative in 11 of 37 patients (29.7%) • 15 of the 37 patients reviewed by CXR (36.6% of the total) were identified as probable TB, whereas 26 of the 37 patients examined using CT (70.3%) were categorized as probable TB • Consolidation regions were discovered in 27 cases (73%), with a higher prevalence in children under 5 years old • Nodules were reported in 13 cases (35.1%) of other parenchymal abnormalities • Lymphadenopathy was identified in 33 children (out of 37 who had a CT scan), with numerous spots in most cases
Yang et al. (2021) (21)	China	Cross-sectional	100 patients aged ≤ 14 years who received surgical intervention with empyema as the indication	Examine the similarities and differences between empyema caused by non-tuberculous CAP (non-tuberculosis empyema, NTE) and empyema caused by tuberculosis (TE) in pediatric patients who require surgical intervention	• Pleural thickness, consolidation, and atelectasis were the most prevalent CT findings in both patient populations • TE showed low sensitivity (33.3, 14.8, and 29.6%) but good specificity (93.2, 98.6, and 98.5%) for enlarged lymph nodes, calcification of lymph nodes, and pleural nodules
Rossoni et al. (2022) (6)	Brazil	Cross-sectional	A total of 186 children under the age of 14 years evaluated for TB	Analyze the usefulness of individual versus combination tests to diagnose pediatric TB at a central location serving as a reference	• 21 children were classified in the TB group, while 165 children were classified in the non-TB group • The sensitivity of the altered chest X-ray (aCXR) was 85.7%, with a specificity of 91.1% • The PPV and NPV for aCXR were 99.8% and 33.7%, respectively, in other healthcare settings (5% of prevalence), while they were 99.2% and 54.4% in the research site (11% of prevalence)
Myo et al. (2018) (17)	Myanmar	Cross-sectional	231 children under the age of 13 who have a PTB suspicion	Test the efficacy of Xpert in diagnosing PTB in children using gastric lavage aspirates from (GLAs)	• All 38 children diagnosed with tuberculosis (100%) displayed typical X-ray abnormalities in the chest area for TB • Chest X-ray features indicative of tuberculosis were seen in 74 of 83 (90.2%) youngsters who were not confirmed to have TB • Chest X-ray results suggestive of tuberculosis were seen in 77 of 110 (70%) youngsters who were not expected to develop TB

Table 2: Summary and key radiologic findings of included studies (continued)

Author (year)	Country	Methods	Study populations	Primary aim	Radiologic findings
Rossoni et al. (2022) (6)	India	Cross-sectional	40 children aged 5 to 15 with a clinical suspicion of pulmonary TB referred to the radiodiagnostics and imaging division for a chest CT scan	Determine the role of lung MRI in diagnosing thoracic tuberculosis in young patients	• Compared to the CT scan findings (as the gold standard): • Pleural effusion, lymphadenopathy, and cavitation were detected with 100% sensitivity, specificity, PPV, and NPV by MRI • Nodule detection sensitivity and specificity of MRI are 88.2% and 95.7%, respectively. Overall, the test has an NPV of 91.7% and a PPV of 93.8% • Both the MRI sensitivity and specificity for detecting consolidation were 100% with 96.3% PPV and 100% NPV • MRI has a sensitivity of 87.5% for detecting bronchiectasis and a specificity of 100%, with a 100% PPV and a 97% NPV. • The sensitivity of a chest X-ray for detecting pulmonary TB was only 49.4%, but it had a high specificity of 93.5%, 80.8% PPV, and 77.1% NPV
Palmer et al. (2022) (15)	South Africa	Cross-sectional	541 children younger than 13 years old with probable TB	Find radiographic characteristics of the chest that correlate highly with TB cases confirmed by a bacteriological test	• There were abnormalities on chest radiographs in 225 of 236 cases (95%) • Abnormal chest radiograph results were present in 373 of 512 readings (73%), all of whom were unlikely to have tuberculosis. • With a 65% specificity and 55% sensitivity, alveolar opacification was a moderately effective diagnostic tool • The sensitivity of enlarged perihilar lymph nodes was 28%, whereas the specificity was 95%. • There was a sensitivity of 24% and a specificity of 98% for enlarged paratracheal lymph nodes • The sensitivity of bronchial deviation/compression was 29%, whereas the specificity was 98% • In the case of cavities, the sensitivity was 8% and the specificity was 98% • The sensitivity for expanding pneumonia was 5%, whereas the specificity was 99% • The sensitivity of pleural effusion was 9% and its specificity was 96%
Walters et al. (2017) (19)	South Africa	Cross-sectional	379 patients younger than 13 years old with probable TB	Analyze Xpert's performance on stool samples in comparison to bacteriologic confirmation using respiratory specimens and a clinical gold standard	• Among the 73 individuals having a CXR finding suggestive of tuberculosis, 51 (or 71.8% of the total) were confirmed with PTB • 47 out of 185 patients (25.7%) who have CXR suggestive of TB were unconfirmed with PTB • 7 of 121 (6%) patients with a CXR consistent with tuberculosis were found not to have the disease

Table 2: Summary and key radiologic findings of included studies (continued)

Author (year)	Country	Methods	Study populations	Primary aim	Radiologic findings
Osorio et al. (2020) (20)	Mozambique	Cross-sectional	45 children under the age of 5 with severe acute malnutrition (SAM)	Determine the incidence of PTB among severely undernourished children, and test the efficacy of the urine lipoarabinomannan antigen assay for detecting tuberculosis (TB-LAM)	• In 16 of 17 (94%) and 1 of 28 (4.9%) patients with and without TB, respectively, chest X-ray findings compatible with TB were identified
Heuvelings et al. (2019) (8)	South Africa	Cross-sectional	159 children up to 13 years of age with possible cases of PTB	Contrast the results of a chest ultrasound with a chest X-ray in children suspected of having PTB.	• CXR abnormalities were verified in 22 of 26 patients (61%) with confirmed TB, 37 of 73 patients (51%) with unconfirmed TB, and 30 of 50 patients (60%) who were unlikely to have PTB

Study quality

Based on the risk-of-bias analysis, five studies were of moderate quality (5-6), with a low (7-10) and high (0-4) risk-of-bias in two studies (Figure 2 and Table 3).

Meta-analysis results of diagnostic accuracy of radiology examination in pediatric pulmonary TB

There was insufficient data for a meta-analysis of the diagnostic accuracy of CT and MRI examinations, therefore,

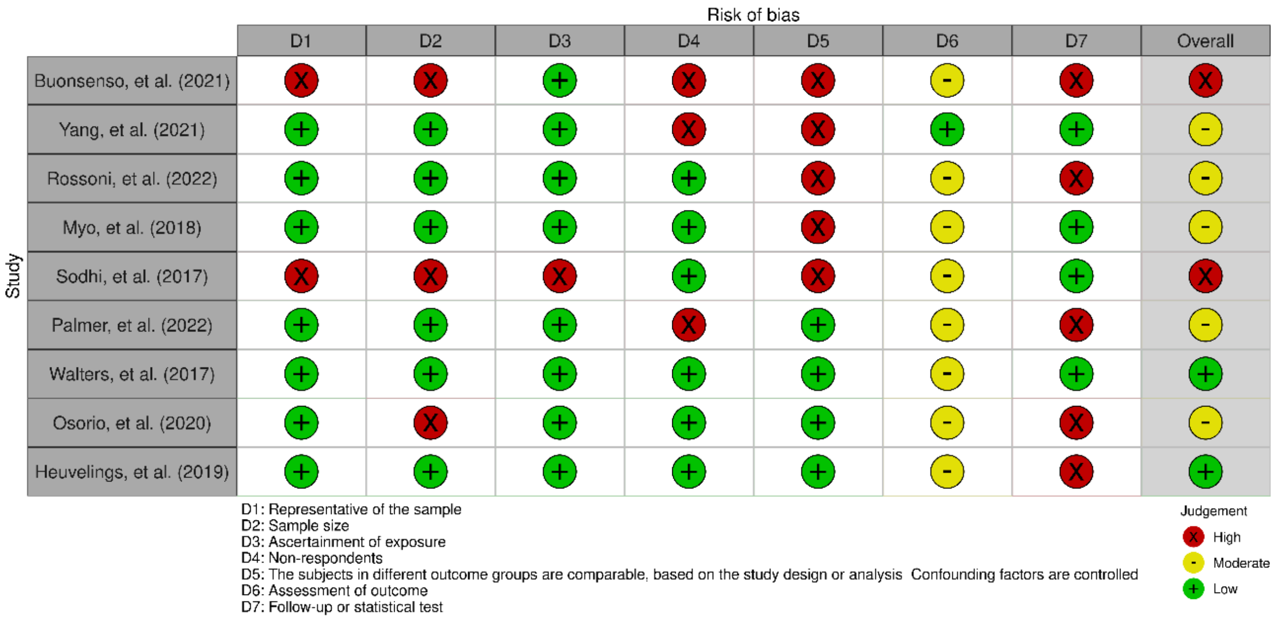

Figure 2: Modified Newcastle Ottawa Quality Assessment Scale (NOS) results for the cross-sectional studies assessed in this review

Table 3: NOS risk-of-bias scoring

Study	Selection (D1-D4)	Comparability (D5)	Outcome (D6-D7)	Total score
Bounsenso et al. (2021)	2	0	1	3
Yang et al. (2021)	3	0	2	5
Rossoni et al. (2022)	4	0	1	5
Myo et al. (2018)	4	0	1	5
Sodhi et al. (2017)	1	0	2	3
Palmer et al. (2022)	3	2	1	6
Walters et al. (2017)	4	2	2	8
Osorio et al. (2020)	3	2	1	6
Heuvelings et al. (2019)	4	2	1	7

NOS = Modified Newcastle Ottawa Quality Assessment Scale

only a meta-analysis of the diagnostic accuracy of CXR was performed. CXR examination was mentioned in 6 out of 9 articles. The positive and negative likelihood ratios (PLR and NLR) were 3.07 (95% CI: 1.68–5.58) and 0.29 (95% CI: 0.14–0.60), respectively, when considering the pooled data from all sample types and the overall DOR was 17.41 (95% CI: 3.37–89.90) (Figure 3). The Q* index (0.7574) and the area under the sROC curve (0.8242) were high, with high heterogeneity for sensitivity (91.6%) and specificity (99%), as measured by their respective I^2 statistics (Figure 4).

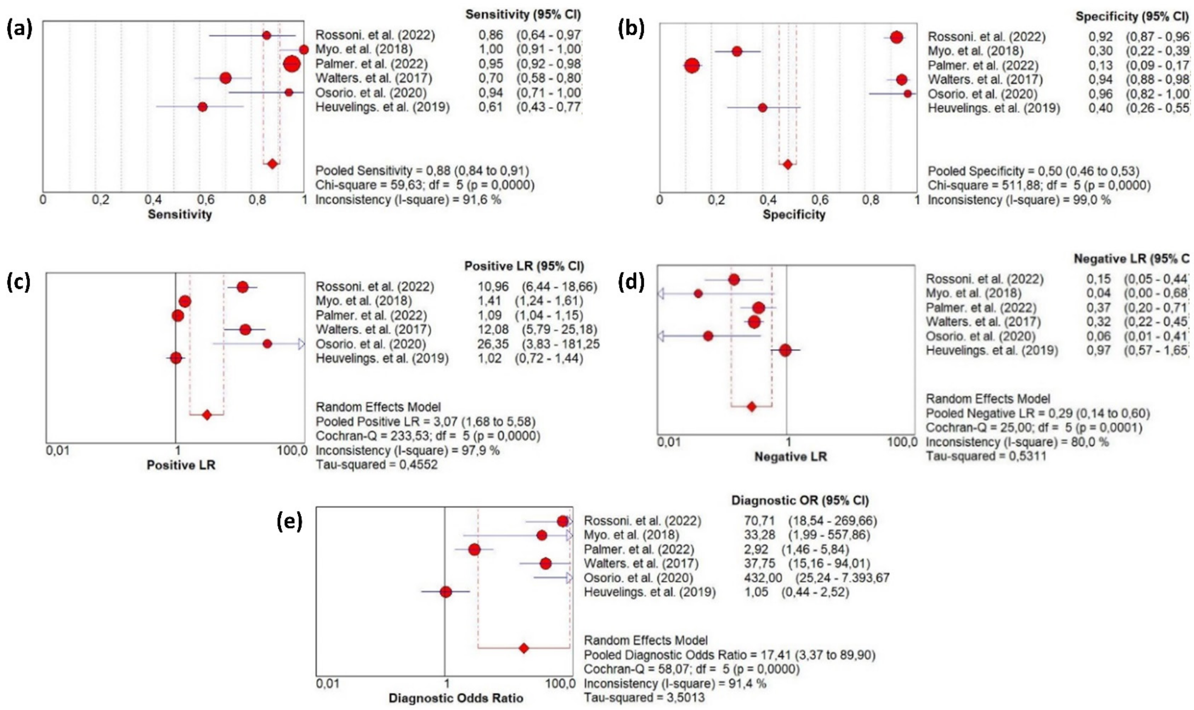

Figure 3: Forest plots of (a) sensitivity, (b) specificity, (c) positive likelihood ratio, (d) negative likelihood ratio, and (e) diagnostic odds ratio of chest X-ray for the diagnosis of pediatric pulmonary TB

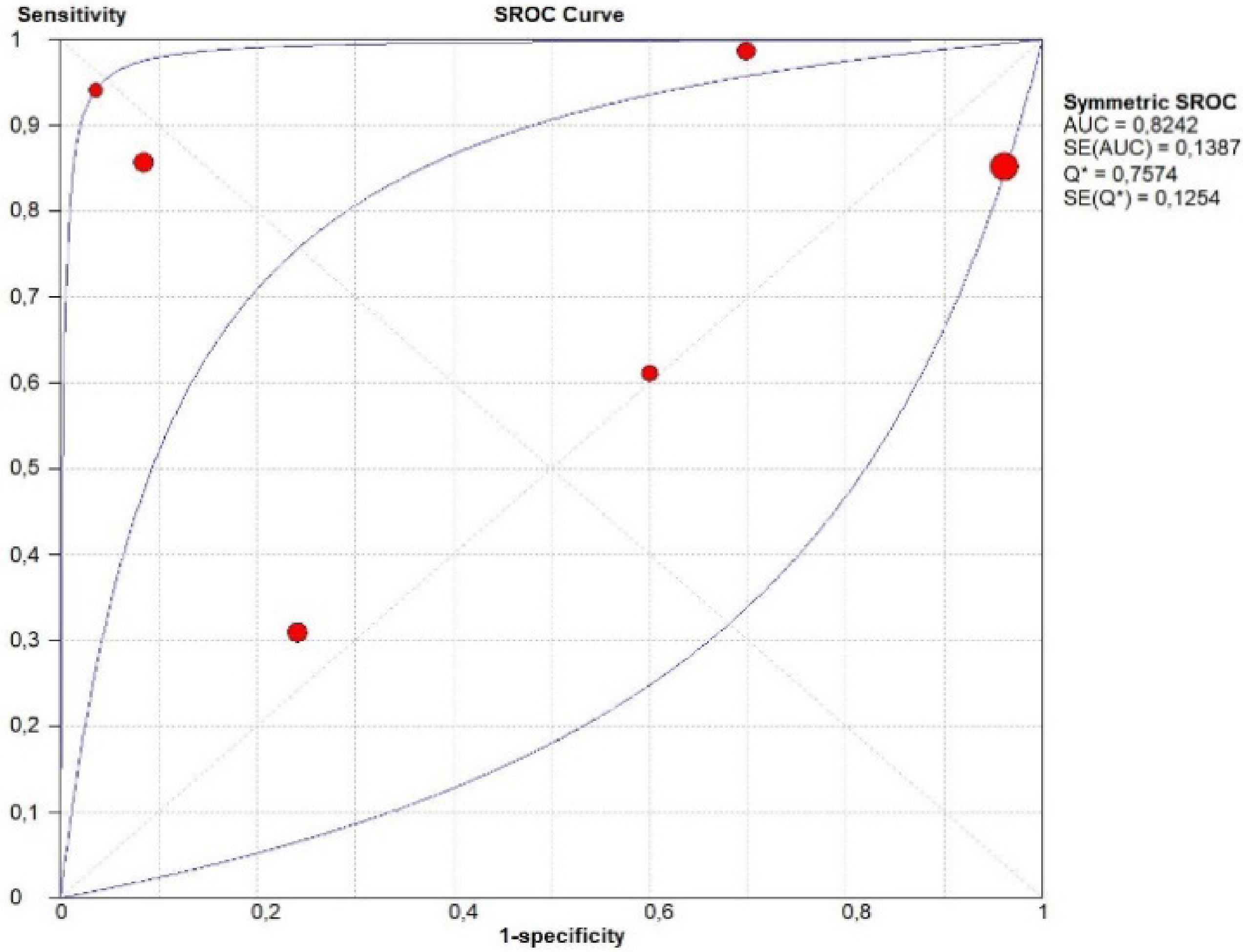

Figure 4: Summary receiver operating characteristic curve of chest X-ray for the diagnosis of pediatric pulmonary TB

Discussion

The purpose of this study was to evaluate the performance of chest radiograph tests in diagnosing pulmonary tuberculosis in children. While comparing CT with X-ray for the detection of TB, Buonsenso et al. (16) discovered that CT was more effective. Consequently, while chest radiography is still employed for the first evaluation, CT can increase diagnostic accuracy in children with suspected TB. Some key radiological findings are consolidation, nodules, and lymphadenopathy (16). Pediatric patients with tuberculous vs. non-tuberculous empyema were compared in Yang et al.'s study (21) and a CT scan was used as the evaluation tool for the radiological examination. It was discovered that various abnormalities, including lymph node enlargement, lymph node calcification, and pleural nodules, were detected in TE with high specificity but low sensitivity in the tuberculous empyema group. In contrast, Sodhi et al. (18) evaluated the diagnostic efficacy of MRI and chest radiograph compared to CT scans as the gold standard for imaging findings. Thus, MRI should be encouraged wherever there are sufficient resources, as it outperformed chest radiography and is on par with CT in detecting radiological abnormalities. Due to limited data, the CT scan and MRI findings were not statistically analyzed in the meta-analysis.

In pediatric pulmonary TB, radiologic findings, notably CXR, are vague. Six articles were included in this meta-analysis on the diagnostic accuracy of chest X-rays for this condition, with high sensitivity, so there is a less likely to be false negatives. At the same time, the intermediate specificity implies a moderate possibility of false positives, necessitating additional testing for some individuals. The PLR of > 1.0 in this study indicates that the test result is more likely to occur in those with disease than in those without disease (22). The NLR scale ranges from 1 to 0, and the closer the LR is to 0, the less likely the disease is if the test results are negative (23). However, the PLR and NLR are less helpful in establishing or excluding a diagnosis since the value did not exceed > 10 in PLR and was not lower than 0.1 in NLR (22). These findings may be because the studies used to define test performance are of poor quality or entail verification bias. Differences between a test's characterization population and the group to which it is applied may render the LR inapplicable (24). In other words, if the way the disease is defined changes, none of the derived metrics will apply in another clinical situation

(25). Finally, the study's high DOR suggests a more effective screening tool (26). The AUC was between 0.8 and 0.9, indicating excellent performance in distinguishing between individuals with and without the disease (27), and the Q* index demonstrates that the likelihood of a false positive result is the same for both disease cases and non-cases (28).

The most robust (and commonly accepted) reference standard for TB was microbiologically confirmed TB, which was used in the estimates of sensitivity and specificity as well as the multivariable regression model. Confirmed, unconfirmed, and unlikely intrathoracic TB are widely acknowledged as the clinical reference standards (29). A CR consistent with TB, as stated in the research conducted by Palmer et al. (15), is a crucial criterion for the case definition of PTB. Comparing the CR features with another reference, such as the clinical reference standard of unconfirmed TB, will flaw the method, so following the research, we decided not to use the standard.

Palmer et al. (15) stated that some individual CR traits with high specificity for and highly related to proven intrathoracic TB exhibit substantial inter-reader agreement. Mediastinal lymph node enlargement, compression of the bronchial tree, pleural effusion, and cavities on CR significantly support the diagnosis of a child with probable intrathoracic TB in a high-TB burden situation. Alveolar consolidation, commonly observed in pediatric intrathoracic TB, usually presents with other CR characteristics and does not distinguish confirmed pediatric TB from unlikely TB cases. Compared with the oldest age group, some characteristics, such as mediastinal lymph node enlargement, compression of the bronchial tree, and expansile pneumonia, are more sensitive features for intrathoracic TB than in the youngest age group. In contrast, pleural effusion and cavitary are the opposite, possibly due to the age-related fluctuation in the prevalence of specific CR traits.

The current study is an update of a systematic review of imaging modalities for pediatric pulmonary tuberculosis published by Tonne et al. (30) and includes a meta-analysis. Our new meta-analysis includes studies by Yang et al. (21) Rossoni et al. (6), Myo et al. (17), Palmer et al. (15), Walters et al. (19), and Osorio et al. (20), with a total of 1,513 participants as opposed to 1,244 in the prior study. This systematic review uses more recent data because nine included papers were published in 2017−2022, while the previous study used data from 1997−2021. In conclusion, this research improves upon and supplements the systematic review and meta-analysis of radiological examinations to diagnose pediatric PTB.

There are several caveats to this study. First, the study was limited in our ability to ensure that all relevant publications were included in the analysis because we only searched four databases. While the study's sample size was more extensive than in similar studies, only six of the included publications were eligible for meta-analysis, meaning further work is needed to improve the diagnostic accuracy of the tool.

Conclusion

According to the aforementioned meta-analysis, radiological examinations, especially CXR, have high sensitivity and moderate specificity, indicating that they are a reliable approach. The extensive clinical use of radiology examination in the future will be supported by additional experimental and clinical research in various scenarios.

Competing interests

The authors declare that they have no competing interests.

Financial support

There is no financial support received for the study.

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