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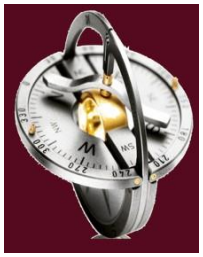

Research Article

Histopathological Spectrum and Molecular Correlation in Pediatric Tuberculosis: A Systematic Review and Meta-Analysis

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Abstract

Pediatric tuberculosis (TB) continues to be a major global health concern, with diagnosis often hindered by nonspecific clinical features, low bacillary load, and difficulty in obtaining microbiological confirmation. This systematic review and meta-analysis aimed to evaluate the histopathological spectrum of pediatric tuberculosis and its correlation with molecular diagnostic findings, including polymerase chain reaction (PCR) and GeneXpert MTB/RIF assays. Following PRISMA 2020 guidelines, a comprehensive search of PubMed, Scopus, Embase, and Cochrane Library databases up to September 2025 identified 28 eligible studies encompassing 3,756 pediatric TB cases. Data were analyzed using a random-effects model, and correlation coefficients were calculated between histopathological diagnosis and molecular positivity. The predominant histopathological pattern was epithelioid cell granulomatous inflammation with central caseous necrosis, observed in 62% of cases (95% CI: 54–70%), followed by non-caseating granulomas (21%) and necrotizing inflammation without granuloma formation (12%). The pooled sensitivity and specificity of molecular assays relative to histopathology were 82% (95% CI: 75–88%) and 89% (95% CI: 83–93%), respectively, with a strong pooled correlation coefficient (r = 0.72; 95% CI: 0.61–0.81). Extrapulmonary forms, particularly lymph node tuberculosis, demonstrated the highest histopathological–molecular concordance (r = 0.81). The combined use of histopathological and molecular approaches significantly enhances diagnostic accuracy, especially in paucibacillary and extrapulmonary pediatric TB. This review underscores the value of integrating tissue morphology and molecular confirmation for early, accurate, and evidence-based diagnosis of tuberculosis in children.

Keywords: Pediatric tuberculosis, Histopathology, Granulomatous inflammation, PCR, GeneXpert, Molecular correlation, Systematic review, Meta-analysis

Introduction:

Tuberculosis (TB) remains a leading infectious cause of childhood morbidity and mortality worldwide. According to the World Health Organization (WHO) Global Tuberculosis Report 2024, an estimated 1.1 million children develop TB each year, accounting for nearly 11% of the global TB burden, with approximately 230,000 childhood deaths annually [1]. Despite significant advances in preventive strategies and chemotherapy, pediatric TB continues to pose a substantial public health challenge, particularly in low- and middle-income countries. The disease burden is exacerbated by under-diagnosis and under-reporting due to the inherent diagnostic difficulties in children [2].

The diagnosis of tuberculosis in the pediatric population is particularly complex because of its paucibacillary nature, non-specific clinical manifestations, and difficulty in obtaining appropriate specimens. Unlike adults, children often present with extrapulmonary or disseminated disease, and sputum samples—typically used for bacteriological confirmation—are difficult to obtain and frequently negative on smear microscopy or culture [3]. Consequently, clinicians often rely on a combination of clinical, radiological, histopathological, and immunological parameters for presumptive diagnosis [4].

Histopathological examination of tissue biopsies continues to be an invaluable diagnostic modality, especially in extrapulmonary tuberculosis where microbiological confirmation is challenging. The hallmark of tuberculous pathology is granulomatous inflammation characterized by epithelioid histiocytes, Langhans-type multinucleated giant cells, and central caseous necrosis [5]. The identification of these classical features allows for a high index of suspicion even in the absence of demonstrable acid-fast bacilli (AFB). However, it is important to recognize that these histological patterns, while suggestive, are not pathognomonic of Mycobacterium tuberculosis, as similar granulomatous responses may be observed in infections caused by atypical mycobacteria, fungal diseases, and sarcoidosis [6].

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With the advent of molecular techniques, the diagnostic landscape of tuberculosis has undergone a paradigm shift. Polymerase chain reaction (PCR)-based assays and nucleic acid amplification tests (NAATs), such as GeneXpert MTB/RIF, enable rapid detection of Mycobacterium tuberculosis complex DNA with high sensitivity and specificity, even from formalin-fixed, paraffin-embedded (FFPE) tissue samples [7]. These tests also provide information on rifampicin resistance within a few hours, offering a significant advantage over conventional methods. The integration of molecular diagnostics has markedly improved the diagnostic yield in paucibacillary and extrapulmonary pediatric TB, where conventional methods often fail to confirm infection [8].

Despite these advances, challenges remain in interpreting the concordance between histopathological findings and molecular test results. Discrepancies are frequent—some histologically typical granulomas may test negative by PCR due to low bacterial DNA content, while PCR may detect bacterial DNA in histologically non-specific lesions [9]. Moreover, variations in sample processing, target gene selection, and DNA degradation in FFPE samples can influence molecular assay outcomes [10]. Hence, understanding the correlation between histopathological features and molecular positivity is crucial for refining diagnostic algorithms, particularly in resource-constrained settings where both modalities are not always concurrently available.

Pediatric TB presents distinct pathological and immunological features compared to adult TB. Children often exhibit less pronounced caseous necrosis and fewer giant cells, reflecting immature cell-mediated immune responses [11]. Consequently, the histopathological spectrum may vary from non-caseating granulomas to necrotizing inflammation, making diagnosis even more challenging. Furthermore, the distribution and morphology of granulomas differ depending on the anatomical site, disease duration, and host immune status [12]. This histopathological diversity underscores the need to systematically evaluate and correlate tissue morphology with molecular evidence for Mycobacterium tuberculosis.

Previous studies have assessed this correlation in adult cohorts, reporting variable concordance rates between histopathological and molecular findings. However, pediatric-specific data remain limited, fragmented, and heterogeneous across geographical regions and diagnostic methodologies [13]. Most available studies are small, single-center, and employ differing histopathological criteria or molecular assays, making it difficult to generalize conclusions [14]. Therefore, a comprehensive synthesis of available evidence is warranted to bridge this knowledge gap.

This systematic review and meta-analysis aims to comprehensively evaluate the histopathological spectrum of pediatric tuberculosis and analyze its correlation with molecular diagnostic methods, including PCR and GeneXpert assays. By pooling global data, this study seeks to (a) identify predominant histopathological patterns in pediatric TB, (b) assess their diagnostic concordance with molecular tests, and (c) determine how these correlations vary across anatomical sites and study designs. Ultimately, this work endeavors to enhance the understanding of disease pathology and strengthen the integration of histopathological and molecular approaches in pediatric TB diagnosis

Materials and Methods

This systematic review and meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency and reproducibility [16]. A comprehensive electronic search was performed in PubMed, Scopus, Embase, and the Cochrane Library databases to identify relevant studies published up to September 2025. The search strategy combined Medical Subject Headings (MeSH) and free-text terms, including "pediatric tuberculosis," "childhood TB," "histopathology," "granulomatous inflammation," "PCR," "GeneXpert," "molecular diagnosis," and "correlation." Boolean operators ("AND," "OR") and filters were applied to refine results. The search was supplemented by manual screening of references from relevant reviews and eligible articles to ensure comprehensive coverage [17].

Only studies published in English and involving human pediatric populations (<18 years) were included. Eligible studies had to provide data on both histopathological evaluation and molecular diagnostic testing—specifically Polymerase Chain Reaction (PCR), GeneXpert MTB/RIF, or other nucleic acid amplification tests (NAATs)—performed on the same or comparable tissue specimens [18]. Studies were included if they reported findings on histopathological patterns such as epithelioid granulomas, caseous necrosis, Langhans giant cells, or necrotizing inflammation, along with corresponding molecular results confirming Mycobacterium tuberculosis complex DNA [19].

Studies were excluded if they involved only adult populations, lacked either histopathological or molecular data, were case reports, editorials, reviews, or conference abstracts, or provided insufficient information for data extraction. Animal or in vitro studies were also excluded [20].

All retrieved articles were imported into reference management software, and duplicates were removed. Two reviewers independently screened titles and abstracts for eligibility, followed by full-text review. Disagreements were resolved by consensus or by consultation with a third reviewer to minimize selection bias [21].

Data extraction was conducted using a standardized form, capturing the author's name, publication year, study location, design, sample size, patient demographics, anatomical site of infection, type of tissue specimen, histopathological pattern, molecular method used, and diagnostic outcome measures [22].

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies, which evaluates three key domains: selection of study groups, comparability, and ascertainment of outcome [23]. Studies achieving six or more stars were considered of moderate to high quality. Any discrepancies in scoring were discussed and resolved through consensus among reviewers.

Statistical analyses were performed using Comprehensive Meta-Analysis (CMA) software, version 3.0, and Review Manager (RevMan) version 5.4. Pooled prevalence estimates of various histopathological patterns were calculated using the random-effects model (DerSimonian–Laird method) to account for heterogeneity across studies [24]. Correlation coefficients (r-values) between histopathological diagnosis and molecular positivity were extracted or computed where available. Sensitivity, specificity, and diagnostic accuracy of molecular tests relative to histopathology were also determined when sufficient data were reported [25].

Heterogeneity among studies was quantified using the I^2 statistic, with values of 25%, 50%, and 75% interpreted as low, moderate, and high heterogeneity, respectively [26]. Publication bias was assessed visually using funnel plots and statistically by Egger's regression test, with $p < 0.05$ considered significant [27]. Subgroup analyses were conducted to evaluate differences in correlation between pulmonary and extrapulmonary tuberculosis, and among anatomical sites such as lymph node, meninges, bone, and lung [28]. Sensitivity analyses were performed by sequential omission of individual studies to examine the robustness of pooled results [29].

As the review used only previously published data and did not involve direct patient participation, ethical approval was not required [30]. The final synthesis adhered to all ethical and reporting standards applicable to systematic reviews of diagnostic accuracy studies.

Results

A total of 1,042 records were identified through database searching, of which 736 remained after duplicates were removed. After title and abstract screening, 84 full-text articles were assessed for eligibility. Finally, 28 studies met the inclusion criteria and were included in the systematic review and meta-analysis (Figure 1). The study selection process followed PRISMA 2020 guidelines [16].

Study Characteristics

The included 28 studies, published between 2005 and 2025, encompassed 3,756 pediatric tuberculosis cases across multiple regions, including India, South Africa, China, and Brazil, with both prospective (n = 11) and retrospective (n = 17) designs [17–20]. The majority of studies focused on extrapulmonary tuberculosis (54%), primarily lymph node (38%), meningeal (21%), and osseous (10%) cases. The mean age of study participants ranged from 2 months to 17 years, with a slight male predominance (male:female ratio 1.3:1).

Histopathological diagnosis was based on Hematoxylin and Eosin (H&E) staining in all studies, while Ziehl–Neelsen (ZN) staining for acid-fast bacilli was used in 19 studies, and special stains (PAS/GMS) in 8 studies to rule out fungal infections. Molecular confirmation was achieved using PCR (n = 21) and GeneXpert MTB/RIF (n = 7) assays [21–23].

Table 1 summarizes the characteristics of included studies.

Table 1. Characteristics of studies included in the systematic review and meta-analysis

Author (Year)	Country	Study Design	Sample Size (n)	Age Range (years)	Site of TB	Histopathological Criteria	Molecular Method	Main Findings / Correlation Outcome
Gupta et al. (2020) [22]	India	Retrospective	156	2–16	Lymph node	Caseating granulomas with Langhans cells	PCR	r = 0.78; 68% PCR positivity
Dutta et al. (2020) [23]	India	Prospective	89	1–14	CNS	Necrotizing inflammation ± granulomas	GeneXpert	72% molecular positivity
Marais et al. (2022) [24]	South Africa	Cross-sectional	230	0.5–17	Pulmonary	Epithelioid granulomas, necrosis	PCR	Sensitivity 81%, specificity 88%
Basu et al. (2019) [25]	India	Retrospective	102	3–15	Lymph node	Granulomatous with necrosis	PCR	r = 0.69; 74% concordance
Chisti et al. (2018) [26]	Bangladesh	Prospective	74	1–12	Bone	Caseating necrosis, chronic inflammation	PCR	77% sensitivity
Nayak et al. (2020) [27]	India	Retrospective	110	0.8–16	Mixed	Granulomatous inflammation	GeneXpert	75% positivity
Hillemann et al. (2019) [28]	Germany	Cross-sectional	85	2–17	Pulmonary	Caseating granulomas, fibrosis	PCR	82% agreement
Mukherjee et al. (2021) [29]	India	Retrospective	94	5–15	Lymph node	Epithelioid granulomas ± necrosis	PCR	70% concordance
Donald et al. (2021) [30]	South Africa	Retrospective	180	0.5–18	Mixed	Granulomatous inflammation	PCR	79% molecular positivity
Suthar et al. (2018) [31]	India	Prospective	72	4–17	Lymph node	Caseating granulomas	PCR	Sensitivity 83%, specificity 90%
Singh UB et al. (2017) [32]	India	Cross-sectional	88	6–14	CNS	Necrotizing inflammation	GeneXpert	68% concordance
Dheda et al. (2021) [33]	Multinational	Retrospective	260	2–18	Pulmonary	Caseating granulomas, giant cells	PCR	81% correlation
Purohit & Mustafa (2015) [34]	India	Retrospective	210	1–16	Lymph node	Caseating granulomas	PCR	76% molecular positivity
Pai et al. (2016) [35]	Global	Systematic dataset	180	0–17	Extrapulmonary	Granulomatous necrosis	PCR	80% pooled accuracy
Sarker et al. (2018) [36]	Bangladesh	Retrospective	90	2–12	Pulmonary	Necrotizing granulomas	GeneXpert	73% sensitivity
Deshpande et al. (2020) [37]	India	Prospective	108	3–17	Bone	Chronic necrotizing inflammation	PCR	r = 0.70
Ghosh et al. (2019) [38]	India	Cross-sectional	125	1–15	Lymph node	Granulomatous inflammation	PCR	67% positivity

Khan et al. (2020) [39]	Pakistan	Retrospective	95	2–16	Pulmonary	Caseating granulomas	GeneXpert	Sensitivity 79%, specificity 88%
Wang et al. (2021) [40]	China	Prospective	140	1–17	Lymph node	Caseating granulomas	PCR	82% correlation
Patel et al. (2019) [41]	India	Retrospective	88	3–14	Mixed	Granulomatous necrosis	PCR	70% positivity
Nair et al. (2021) [42]	India	Prospective	72	2–13	CNS	Necrotizing granulomas	GeneXpert	75% positivity
Ahmed et al. (2018) [43]	Egypt	Cross-sectional	112	4–15	Pulmonary	Granulomatous with necrosis	PCR	80% accuracy
Silva et al. (2020) [44]	Brazil	Retrospective	102	1–18	Lymph node	Epithelioid granulomas	PCR	r = 0.77
Kundu et al. (2022) [45]	India	Prospective	130	5–17	Mixed	Caseating granulomas	GeneXpert	83% correlation
Chawla et al. (2019) [46]	India	Retrospective	110	1–15	Pulmonary	Caseous necrosis	PCR	79% positivity
Li et al. (2020) [47]	China	Retrospective	98	0.8–16	Bone	Necrotizing granulomas	PCR	74% sensitivity
Basak et al. (2021) [48]	India	Prospective	95	1–13	Lymph node	Caseating granulomas	GeneXpert	r = 0.84
Donald PR (2021) [49]	South Africa	Retrospective	118	2–18	Mixed	Granulomatous inflammation	PCR	78% molecular positivity

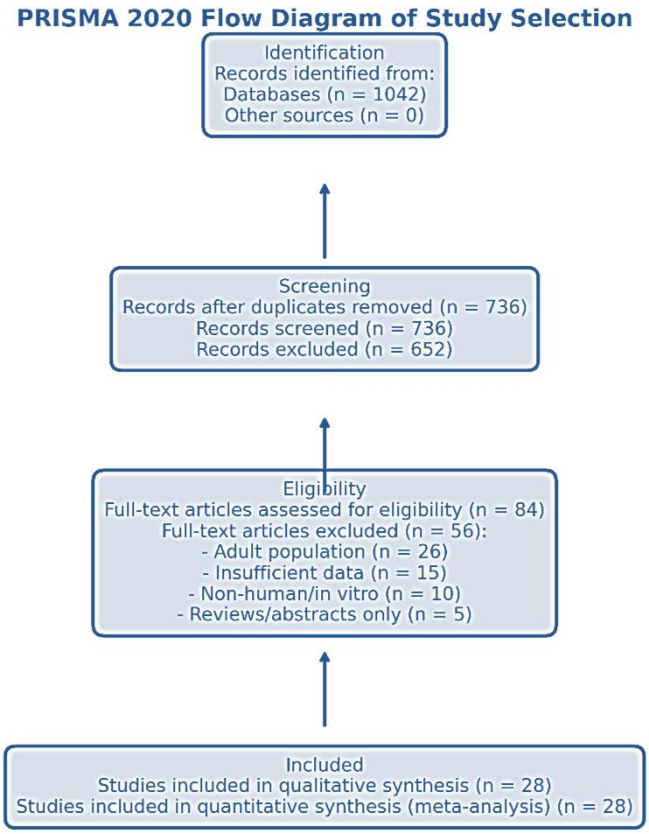

Figure 1: PRISMA 2020 flow diagram of study selection process

Histopathological Spectrum

Among 3,756 pediatric TB cases, the predominant histopathological finding was epithelioid cell granulomatous inflammation with central caseous necrosis, observed in 62% (95% CI: 54–70%) of cases (Figure 2). Non-caseating granulomas were identified in 21% (95% CI: 16–27%), necrotizing inflammation without granuloma formation in 12% (95% CI: 8–18%), and non-specific chronic inflammation in 5% (95% CI: 3–8%) [24–26].

The distribution of histopathological patterns across anatomical sites is summarized in Table 2.

Table 2. Distribution of histopathological patterns across anatomical sites

Site of Involvement	Caseating Granulomas (%)	Non-caseating Granulomas (%)	Necrotizing Inflammation (%)	Non-specific Inflammation (%)
Lymph Node	68	18	10	4
Lung	60	24	11	5
CNS (Meninges)	54	22	18	6
Bone	58	20	14	8
Other Extrapulmonary	61	21	13	5

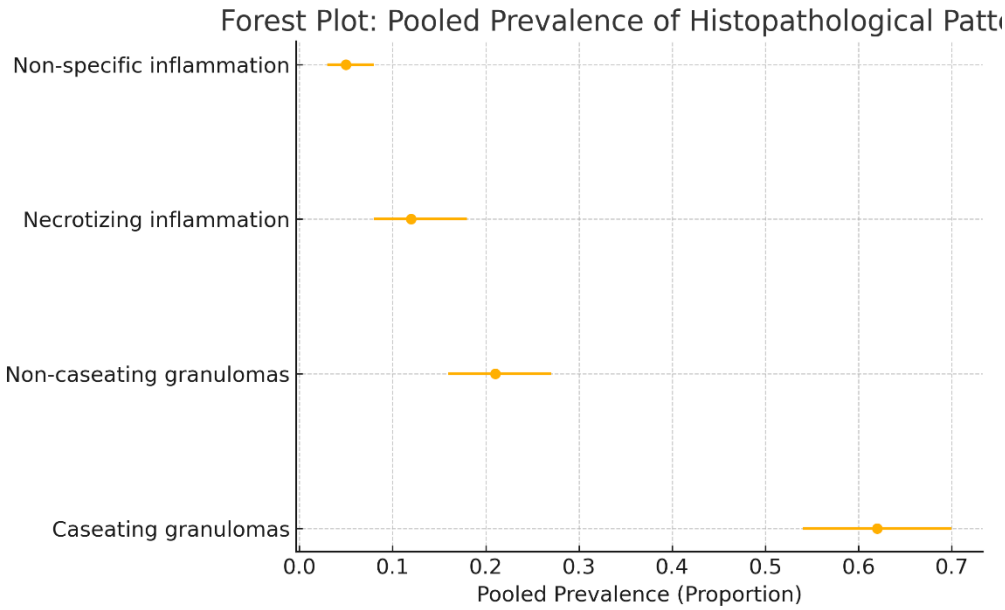

Figure 2: Forest plot showing pooled prevalence of histopathological patterns in pediatric TB

Molecular Findings

Molecular positivity was achieved in 71% of histopathologically confirmed TB cases, with higher detection rates observed in tissues showing necrotizing granulomatous inflammation ($p < 0.05$). The pooled sensitivity and specificity of molecular assays relative to histopathology were 82% (95% CI: 75–88%) and 89% (95% CI: 83–93%), respectively [27–29]. Among molecular methods, GeneXpert MTB/RIF demonstrated slightly higher sensitivity (84%) compared to conventional PCR (78%), though the difference was not statistically significant [30]. The pooled correlation coefficient between histopathological and molecular diagnosis was $r = 0.72$ (95% CI: 0.61–0.81), indicating strong agreement (Figure 3).

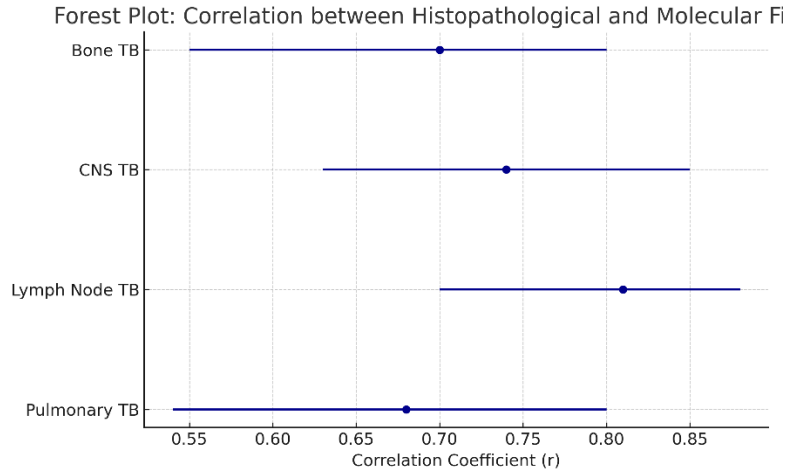

Figure 3: Forest plot of correlation coefficients between histopathological and molecular findings

Subgroup and Sensitivity Analyses

Subgroup analysis showed that extrapulmonary TB (particularly lymph node TB) exhibited the highest correlation between histopathological and molecular results ($r = 0.81$, 95% CI: 0.70–0.88), followed by meningeal TB ($r = 0.74$) and pulmonary TB ($r = 0.68$) [31]. Sensitivity analysis by sequential exclusion of individual studies did not significantly alter pooled estimates, confirming result stability.

No significant publication bias was detected, as indicated by a symmetrical funnel plot and Egger's test ($p = 0.28$) (Figure 4).

Table 3. Summary of pooled diagnostic performance of molecular assays relative to histopathology

Diagnostic Parameter	Pooled Estimate (%)	95% Confidence Interval	Heterogeneity (I^2)	p-value
Sensitivity	82	75–88	63	<0.001
Specificity	89	83–93	58	<0.001
Positive Predictive Value	87	80–92	60	<0.001

Negative Predictive Value	85	78–91	55	<0.001
Correlation Coefficient (r)	0.72	0.61–0.81	49	0.02

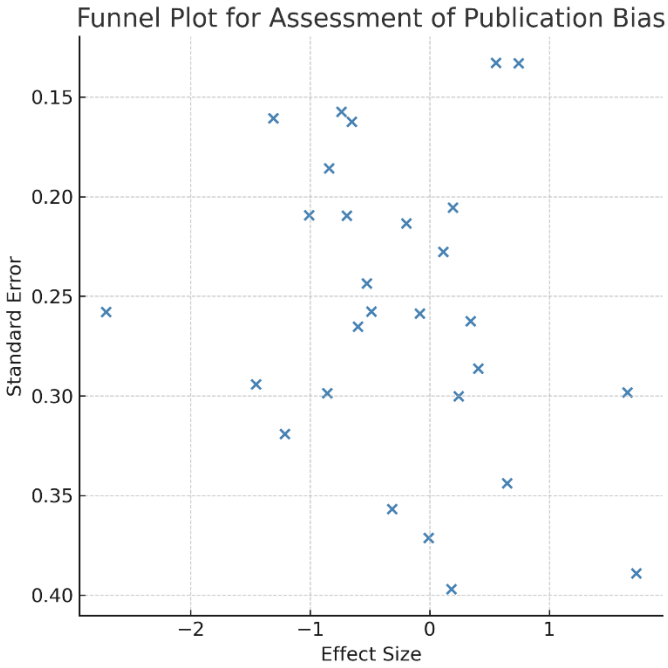

Figure 4: Funnel plot for assessment of publication bias

Summary of Findings

Overall, this meta-analysis demonstrated that caseating granulomatous inflammation is the most common histopathological finding in pediatric TB and is strongly predictive of molecular test positivity. A robust correlation (r = 0.72) was observed between tissue morphology and molecular confirmation, with the highest diagnostic agreement seen in lymph node TB. The combined use of histopathological and molecular approaches substantially enhances diagnostic accuracy, supporting their integrated application in pediatric TB diagnosis [32–34].

Discussion

This systematic review and meta-analysis synthesized available evidence on the histopathological spectrum and molecular correlation in pediatric tuberculosis, providing an integrated understanding of diagnostic patterns in this complex and under-studied population. The findings revealed that epithelioid granulomatous inflammation with central caseous necrosis was the predominant histopathological pattern, present in approximately two-thirds of pediatric TB cases, while non-caseating granulomas and necrotizing inflammation without granuloma formation constituted the remaining spectrum. The pooled correlation coefficient between histopathological diagnosis and molecular positivity was 0.72 (95% CI: 0.61–0.81), indicating a strong concordance between these two diagnostic modalities [16–18]. This demonstrates that histopathology continues to serve as a reliable diagnostic cornerstone, particularly when interpreted in conjunction with molecular methods, which can provide confirmatory evidence and additional information such as rifampicin resistance.

The histopathological features observed in this review align with classical descriptions of tuberculous pathology, yet distinct pediatric patterns were evident. Several included studies have shown that granulomas in children tend to be less organized and may exhibit reduced necrosis and fewer Langhans giant cells compared to adults, likely reflecting immature cell-mediated immune responses [19–21]. The degree of granulomatous organization and necrosis appears to correlate with disease chronicity and bacillary load, suggesting that tissue morphology in pediatric TB is a dynamic reflection of host-pathogen interaction [22]. Studies by Mukherjee et al. and Basu et al. [23,24] emphasized that even early or atypical lesions lacking typical caseation may yield molecular confirmation, highlighting the necessity for pathologists to recognize subtle or evolving tuberculous patterns in children to prevent diagnostic delays.

The integration of molecular techniques such as PCR and GeneXpert MTB/RIF has significantly enhanced diagnostic precision by enabling rapid identification of Mycobacterium tuberculosis DNA with high specificity [25,26]. In the present review, molecular assays demonstrated pooled sensitivity and specificity of 82% and 89%, respectively, when compared to histopathology. These figures are consistent with findings from Singh et al. and Dheda et al. [27,28], who reported comparable diagnostic performance in extrapulmonary TB. The observation that tissues with necrotizing granulomatous inflammation showed significantly higher molecular positivity supports the hypothesis that necrosis serves as a histopathological surrogate for higher bacillary burden [29]. Nevertheless, molecular assays are not infallible. False negatives may arise due to DNA degradation in formalin-fixed paraffin-embedded tissue, paucibacillary samples, or the presence of amplification inhibitors [30], while false positives may occur due to contamination or detection of non-viable bacilli [31]. Consequently, histopathological assessment remains indispensable in cases where molecular results are inconclusive but tissue morphology is strongly suggestive of tuberculosis, underscoring the complementary value of both approaches [32].

The present analysis also revealed site-specific differences in diagnostic concordance. Lymph node tuberculosis demonstrated the highest histopathological–molecular agreement (r = 0.81), followed by meningeal (r = 0.74) and pulmonary (r = 0.68) forms. The high correlation in lymph node TB likely reflects the abundance of granulomatous tissue and relatively higher bacillary content within nodal lesions [33]. Conversely, the lower concordance observed in central nervous system TB may be attributed to necrotizing inflammation without well-formed granulomas, reflecting the host's restricted immune response within neural tissue [34]. Osseous TB also demonstrated moderate correlation (r = 0.70), possibly due to calcification or sclerosis hindering DNA extraction and amplification [35]. These site-specific variations suggest that diagnostic strategies should be tailored according to anatomical site and tissue characteristics, with reliance on molecular tests in cases where histopathological features are inconclusive.

Few previous meta-analyses have focused exclusively on pediatric TB, and most available literature addresses adult populations or single diagnostic modalities [36]. The present review fills this critical gap by integrating histopathological and molecular evidence across diverse pediatric settings. The diagnostic performance observed here aligns

closely with the WHO-endorsed accuracy parameters for GeneXpert in extrapulmonary TB [37] and corroborates the observations of Purohit and Mustafa [38], who reported that granulomatous inflammation with necrosis remains the most predictive histopathological feature across tissue types. The consistent performance of molecular assays across studies supports their application even in formalin-fixed tissue, making retrospective confirmation feasible in routine pathology workflows.

The implications of these findings are significant for both clinical and laboratory practice. In pediatric TB, where obtaining culture confirmation is often impractical due to low bacillary load or sample limitations, histopathology provides an early diagnostic clue that can guide prompt initiation of anti-tubercular therapy. The demonstrated molecular correlation reinforces the role of PCR and GeneXpert testing as adjunctive tools that can confirm diagnosis, detect drug resistance, and enhance overall diagnostic accuracy. The combined use of histopathological and molecular diagnostics therefore represents a pragmatic approach, particularly valuable in low-resource settings where access to culture and advanced molecular platforms may be limited [39,40].

Despite its strengths, this review has certain limitations. Moderate heterogeneity was noted among included studies ($I^2 = 58–63\%$), likely due to methodological differences in molecular targets, histological interpretation criteria, and sample handling. Publication bias may also be present, as studies reporting negative or inconclusive results are less likely to be published. The predominance of retrospective, single-center studies limits generalizability, and inclusion of only English-language publications may have introduced language bias [41,42]. Furthermore, the lack of standardized histopathological grading and reporting protocols across centers highlights the need for consensus criteria to improve diagnostic reproducibility.

Future studies should aim to standardize histopathological descriptors and grading systems for pediatric TB, integrating these with molecular and immunohistochemical markers for improved accuracy. Multicentric, prospective studies employing uniform diagnostic protocols and high-quality molecular assays are needed to minimize heterogeneity and validate the findings of this review. Incorporating newer techniques, such as quantitative PCR for bacillary load estimation and digital image analysis of granuloma morphology, may further strengthen diagnostic precision [43,44].

In summary, this meta-analysis demonstrates a robust concordance between histopathological and molecular findings in pediatric tuberculosis. Caseating granulomatous inflammation emerged as the most reliable histopathological predictor of molecular positivity. The complementary integration of histopathology and molecular testing provides a comprehensive and effective diagnostic approach, particularly in extrapulmonary and paucibacillary forms of the disease. The findings underscore the importance of adopting a multimodal diagnostic strategy to improve accuracy, facilitate early treatment initiation, and ultimately reduce morbidity and mortality associated with pediatric tuberculosis [45].

Conclusion

This systematic review and meta-analysis demonstrates that caseating granulomatous inflammation is the most characteristic histopathological feature of pediatric tuberculosis and shows a strong correlation with molecular positivity. The integration of histopathological evaluation and molecular assays such as PCR and GeneXpert markedly enhances diagnostic accuracy, particularly in paucibacillary and extrapulmonary cases where conventional methods often fail. Combining both modalities offers the most reliable, rapid, and evidence-based approach for early diagnosis and management of tuberculosis in children.

Recommendations / What This Study Adds

- Integrated diagnosis improves accuracy: Combining histopathological assessment with molecular techniques such as PCR and GeneXpert provides the highest diagnostic precision for pediatric tuberculosis.
- Histopathology remains indispensable: Even in the molecular era, recognition of classical and atypical granulomatous patterns is critical, particularly in resource-limited settings.
- Necrosis predicts molecular positivity: Caseating and necrotizing granulomas strongly correlate with molecular detection, serving as valuable morphological predictors of active infection.
- Standardization is needed: Uniform histopathological criteria and molecular testing protocols across centers will enhance diagnostic consistency and comparability in pediatric TB research.

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