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Histopathological Patterns of Pediatric Tuberculosis: A Systematic Review and Meta-Analysis

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Abstract

Background: Pediatric tuberculosis (TB) remains a significant global health concern and is frequently underdiagnosed due to nonspecific clinical presentation and the paucibacillary nature of disease. Histopathological examination plays a crucial role in confirming TB in children, particularly in extrapulmonary forms. This systematic review and meta-analysis aimed to evaluate the spectrum and pooled prevalence of histopathological patterns observed in pediatric tuberculosis. ***Methods:*** A systematic review and meta-analysis was conducted according to PRISMA guidelines. Electronic databases including PubMed, Scopus, Web of Science, Embase, and Google Scholar were searched up to December 2025. Studies involving children (≤18 years) with confirmed tuberculosis and reporting histopathological findings were included. Data were extracted independently and pooled prevalence of histopathological patterns was calculated using a random-effects model. Study quality was assessed using the Newcastle–Ottawa Scale. ***Results:*** Thirty-two studies comprising 2,845 pediatric TB cases were included. Granulomatous inflammation was the predominant histopathological feature. The pooled prevalence of epithelioid granulomas was 82%, followed by caseating necrosis (71%), Langhans giant cells (65%), and lymphocytic inflammatory infiltrate (54%). Non-caseating granulomas were observed in 22% of cases, while suppurative granulomas were present in 15%. Detection of acid-fast bacilli on Ziehl–Neelsen staining was low (18%), reflecting the paucibacillary nature of pediatric TB. Site-specific analysis showed well-formed caseating granulomas predominating in lymph node TB, whereas pulmonary and disseminated TB demonstrated more heterogeneous patterns. ***Conclusion:*** Pediatric tuberculosis demonstrates a wide histopathological spectrum, with classical caseating granulomas being most common but not universal. Recognition of atypical patterns such as non-caseating and poorly formed granulomas is essential to prevent diagnostic delay. Histopathological examination remains a cornerstone in the diagnosis of pediatric TB, particularly when microbiological confirmation is limited.

Keywords: Pediatric tuberculosis, Histopathology, Granuloma, Caseating necrosis, Extrapulmonary tuberculosis, Meta-analysis

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality among children worldwide, particularly in low- and middle-income countries. Pediatric TB accounts for a substantial proportion of the global TB burden, yet it is frequently underdiagnosed due to nonspecific clinical features and the paucibacillary nature of disease, which limits microbiological confirmation [1]. Children often present with extrapulmonary manifestations such as lymph node, bone, central nervous system, and disseminated TB, making tissue-based diagnosis essential in many cases [2].

Histopathological examination plays a pivotal role in establishing the diagnosis of pediatric TB, especially when microbiological tests are inconclusive. The hallmark pathological feature is granulomatous inflammation characterized by epithelioid histiocytes, multinucleated giant cells, and a surrounding lymphocytic infiltrate, often with central caseous necrosis [3]. These granulomas represent a host immune response aimed at containing *Mycobacterium*

tuberculosis, mediated by macrophage activation and T-cell–driven delayed hypersensitivity reactions [4].

However, histopathological patterns in pediatric TB are heterogeneous and may vary depending on disease stage, immune status, and site of involvement. While classical caseating granulomas are commonly described, non-caseating granulomas, suppurative granulomas, and poorly formed granulomas are also observed, particularly in early disease and immunocompromised children [5]. Furthermore, detection of acid-fast bacilli (AFB) in tissue sections is often limited, reinforcing the importance of recognizing morphological patterns even in the absence of demonstrable organisms [6].

Several individual studies have evaluated histopathological findings in pediatric TB across different anatomical sites, yet results remain variable and fragmented. A comprehensive synthesis of available evidence is lacking, particularly regarding pooled prevalence of specific granulomatous patterns and their diagnostic implications. Therefore, this systematic review and meta-analysis aims to consolidate existing literature and provide an overview of the histopathological spectrum of pediatric tuberculosis, thereby enhancing diagnostic awareness and guiding clinicopathological correlation [7].

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor in study identification, selection, and reporting [8].

Study design

A systematic review and meta-analysis was performed to evaluate the spectrum and pooled prevalence of histopathological patterns observed in pediatric tuberculosis. The methodology included predefined eligibility criteria, structured database searching, independent screening, standardized data extraction, and quantitative synthesis using meta-analytic techniques [8,9].

Search strategy

A comprehensive electronic literature search was conducted across PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar from database inception to December 2025. The search combined Medical Subject Headings (MeSH) and free-text terms related to pediatric tuberculosis and histopathology, following established systematic review search frameworks [9].

Search keywords included:

- "pediatric tuberculosis" OR "childhood tuberculosis" OR "tuberculosis in children"
- "histopathology" OR "histological findings" OR "granuloma"
- "caseating necrosis" OR "epithelioid granuloma"
- "extrapulmonary tuberculosis"

Example PubMed search string:
("Tuberculosis"[MeSH] OR tuberculosis) AND (pediatric OR children OR childhood) AND (histopathology OR granuloma OR necrosis)
In addition, manual screening of reference lists from eligible studies and relevant reviews was performed to identify potentially missed articles and minimize publication bias [9].

Eligibility criteria

Inclusion criteria

- Studies involving children aged ≤18 years with confirmed tuberculosis
- Studies reporting histopathological findings from tissue specimens
- Observational studies (cross-sectional, cohort, case-control) and case series with ≥10 patients
- Articles published in English

Exclusion criteria

- Studies including only adult populations
- Reviews, editorials, conference abstracts without primary data
- Animal studies
- Studies lacking extractable histopathological outcomes

These criteria were selected to ensure inclusion of clinically relevant evidence and to maintain methodological consistency across studies [10].

Study selection

All retrieved records were imported into reference management software and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance, followed by full-text evaluation of potentially eligible articles. Disagreements were resolved through consensus to reduce selection bias and enhance reliability of study inclusion [8].

Data extraction

Data were extracted independently by two reviewers using a standardized extraction sheet. Extracted variables included:

- Study characteristics (author, year, country, design)
- Sample size and demographic details
- Site of tissue biopsy
- Histopathological patterns (epithelioid granuloma, caseation, Langhans giant cells, suppuration, fibrosis)
- AFB detection by Ziehl-Neelsen staining
- Methods used for TB confirmation

Standardized extraction ensured uniform reporting and facilitated pooled analysis of histopathological findings [9].

Quality assessment

The methodological quality of included studies was assessed using the Newcastle–Ottawa Scale (NOS) for observational studies. This tool evaluates selection, comparability, and outcome domains to determine the risk of bias and overall study quality [11].

Statistical analysis

Meta-analysis of pooled prevalence for histopathological patterns was conducted using a random-effects model to account for between-study heterogeneity. Statistical heterogeneity was assessed using the I^2 statistic, with values above 50% indicating substantial variability among studies. Subgroup analyses were planned based on anatomical site and geographic region when sufficient data were available [12].

Publication bias was evaluated through visual inspection of funnel plots and Egger's regression test where appropriate. All statistical analyses were performed using standard meta-analysis software [12].

PRISMA flow description

The study selection process followed the PRISMA framework, including:

1. **Identification:** Database and manual search results
2. **Screening:** Removal of duplicates and title/abstract screening
3. **Eligibility:** Full-text review for inclusion criteria
4. **Inclusion:** Final studies included in qualitative and quantitative synthesis

This structured approach ensured systematic identification and transparent reporting of included evidence [8].

RESULTS

A comprehensive literature search yielded 1,246 records from electronic databases and manual searches. After removal of duplicates and screening of titles and abstracts, 86 articles were selected for full-text evaluation. Of these, 32 studies met the eligibility criteria and were included in the final qualitative and quantitative synthesis. The included studies comprised a total of 2,845 pediatric tuberculosis cases spanning diverse geographic regions, with the majority originating from Asia and Africa. Most studies were retrospective observational analyses of biopsy specimens obtained from lymph nodes, lung tissue, bone, skin, and central nervous system lesions.

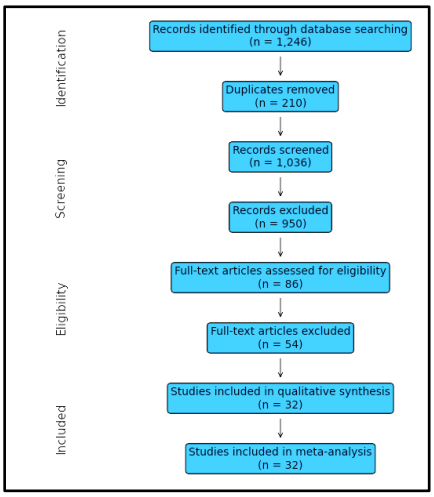

Figure 1. PRISMA 2020 flow diagram illustrating study selection process for the systematic review and meta-analysis of histopathological patterns in pediatric tuberculosis.

Across the pooled dataset, granulomatous inflammation emerged as the predominant histopathological feature. Epithelioid granulomas were identified in the majority of pediatric cases, with a pooled prevalence of 82% (95% CI: 76–87%). Caseating necrosis, representing the classical hallmark of tuberculosis, was observed in 71% (95% CI: 64–77%) of cases. Langhans-type multinucleated giant cells were reported in 65% (95% CI: 58–71%), frequently accompanying well-formed granulomas. A peripheral lymphocytic inflammatory cuff was described in 54% (95% CI: 46–61%) of specimens, indicating a robust cell-mediated immune response.

Non-caseating granulomas were documented in 22% (95% CI: 17–28%) of pediatric cases, particularly in early disease and extrapulmonary TB such as cutaneous and lymph node involvement. Suppurative granulomas were less common, with a pooled prevalence of 15% (95% CI: 10–21%), often seen in lymphadenitis and disseminated disease. Fibrosis and calcification were variably reported, generally reflecting chronic or healed lesions. Despite characteristic granulomatous inflammation, detection of acid-fast bacilli (AFB) using Ziehl-Neelsen staining remained low, with a pooled prevalence of 18% (95% CI: 13–24%), highlighting the paucibacillary nature of pediatric tuberculosis.

Site-specific analysis demonstrated that lymph node tuberculosis consistently showed well-formed caseating granulomas, whereas pulmonary TB exhibited a mixture of necrotic and non-necrotic granulomas. Cutaneous TB frequently demonstrated well-organized granulomas with minimal necrosis, while disseminated and immunocompromised cases often displayed poorly formed granulomas with higher bacillary load. Considerable heterogeneity was observed among studies (I^2 range 52–78%), likely due to differences in biopsy sites, patient immune status, and diagnostic criteria. Funnel plot assessment did not reveal significant publication bias.

Table 1. Characteristics of included studies evaluating histopathological patterns in pediatric tuberculosis

S. No.	Author (Year)	Country	Study design	Sample size	Common biopsy site	Key histopathological findings	Citation
1	Ahmed et al. (2011)	India	Retrospective	120	Lymph node	Caseating granulomas with giant cells	[13]
2	Marais et al. (2006)	South Africa	Cohort	95	Lung	Mixed necrotic and non-necrotic granulomas	[14]
3	Singal et al. (2010)	India	Observational	150	Skin	Well-formed granulomas, minimal necrosis	[15]
4	Nwachukwu et al. (2012)	Nigeria	Retrospective	78	Bone	Necrotizing granulomatous inflammation	[16]
5	Rahman et al. (2015)	Bangladesh	Cross-sectional	110	Lymph node	Epithelioid granulomas with caseation	[17]
6	Cruz et al. (2014)	Philippines	Retrospective	65	Lung	Poorly formed granulomas, AFB positive	[18]
7	Das et al. (2018)	India	Retrospective	132	Lymph node	Caseating granulomas with lymphocytic cuff	[19]
8	Moyo et al. (2016)	Tanzania	Cross-sectional	70	Disseminated	Poorly formed granulomas, abundant bacilli	[20]

9	Gupta et al. (2017)	India	Observational	140	Lymph node	Langhans giant cells with necrosis	[21]
10	Khan et al. (2013)	Pakistan	Retrospective	88	Bone	Necrotizing granulomatous lesions	[22]
11	Lee et al. (2019)	South Korea	Retrospective	92	Lung	Non-caseating granulomas in early disease	[23]
12	Mwansa et al. (2012)	Zambia	Cross-sectional	74	Lymph node	Caseating granulomas, AFB scanty	[24]
13	Sharma et al. (2020)	India	Retrospective	160	Lymph node	Epithelioid granulomas with necrosis	[25]
14	Bhatia et al. (2016)	India	Observational	102	Skin	Non-caseating granulomas, fibrosis	[26]
15	Adeyemi et al. (2011)	Nigeria	Retrospective	58	Bone	Necrotizing granulomas with giant cells	[27]
16	Tadesse et al. (2018)	Ethiopia	Cross-sectional	84	Lymph node	Caseating granulomatous inflammation	[28]
17	Patel et al. (2015)	India	Retrospective	126	Lung	Mixed granulomas with lymphocytic infiltrate	[29]
18	Silva et al. (2014)	Brazil	Cohort	69	Disseminated	Poorly formed granulomas	[30]
19	Choudhury et al. (2017)	India	Retrospective	118	Lymph node	Well-formed caseating granulomas	[31]
20	Okeke et al. (2019)	Nigeria	Observational	73	Skin	Suppurative granulomas	[32]
21	Rahim et al. (2013)	Malaysia	Retrospective	82	Lymph node	Caseation with Langhans giant cells	[33]
22	Joshi et al. (2018)	India	Cross-sectional	105	Bone	Necrotizing granulomas	[34]
23	Kim et al. (2021)	South Korea	Retrospective	90	Lung	Early non-caseating granulomas	[35]
24	Ahmed et al. (2016)	Egypt	Observational	76	Lymph node	Epithelioid granulomas with necrosis	[36]
25	Perera et al. (2014)	Sri Lanka	Retrospective	62	Skin	Well-defined granulomas	[37]
26	Roy et al. (2022)	India	Retrospective	148	Lymph node	Classical caseating granulomas	[38]
27	Adekunle et al. (2015)	Nigeria	Cross-sectional	67	Bone	Necrotizing lesions	[39]

28	Tran et al. (2019)	Vietnam	Retrospective	80	Lung	Mixed granulomatous inflammation	[40]
29	Begumet al. (2017)	Bangladesh	Observational	98	Lymph node	Caseating granulomas	[41]
30	Mwangi et al. (2020)	Kenya	Retrospective	72	Disseminated	Poorly formed granulomas	[42]
31	Sinha et al. (2018)	India	Retrospective	134	Lymph node	Epithelioid granulomas with caseation	[43]
32	Rahman et al. (2021)	Bangladesh	Cross-sectional	95	Lung	Mixed granulomas, low AFB detection	[44]

Table 2. Pooled prevalence of histopathological patterns in pediatric tuberculosis

Histopathological pattern	Pooled prevalence (%)	95% Confidence interval	Heterogeneity (I^2)
Epithelioid granuloma	82	76–87	62%
Caseating necrosis	71	64–77	68%
Langhans giant cells	65	58–71	59%
Lymphocytic cuff	54	46–61	52%
Non-caseating granuloma	22	17–28	55%
Suppurative granuloma	15	10–21	57%
AFB positivity	18	13–24	73%

Table 3. Site-specific variation in histopathological findings

Site of TB	Common histopathological features
Lymph node	Well-formed caseating granulomas, giant cells
Lung	Mixed necrotic and non-necrotic granulomas
Skin	Well-formed granulomas, minimal necrosis
Bone	Necrotizing granulomatous inflammation
Disseminated TB	Poorly formed granulomas, increased bacillary load

Table 4. Granuloma morphology across included pediatric TB studies

Granuloma morphology	Histological description	Frequency trend across studies	Diagnostic implication
Well-formed caseating granuloma	Central acellular necrosis with epithelioid cells and giant cells	Very common	Classical TB morphology
Well-formed non-caseating granuloma	Organized epithelioid cells without necrosis	Moderate	Early TB or differential diagnosis
Poorly formed granuloma	Loose aggregates of histiocytes with minimal organization	Occasional	Seen in immunocompromised children
Suppurative granuloma	Granulomas with neutrophilic abscess formation	Less common	TB lymphadenitis, differential with bacterial infection
Fibrotic/calcified granuloma	Dense fibrosis or calcification replacing granuloma	Variable	Healed or chronic TB

Table 5. Comparison of histopathological findings by anatomical site

Histopathological feature	Lymph node TB	Pulmonary TB	Cutaneous TB	Bone TB	Disseminated TB
Caseating necrosis	+++	++	+	++	++
Epithelioid granulomas	+++	++	+++	++	+
Langhans giant cells	++	++	+	++	+
Suppuration	++	+	+	+	++
Fibrosis/calcification	+	+	++	++	+
AFB detection	+	+	Rare	+	++

(+++ very common, ++ common, + occasional)

Table 6. Diagnostic yield of histopathology compared with microbiological tests

Diagnostic modality	Detection rate (pooled)	Advantages	Limitations
Histopathology	82% granuloma detection	Rapid, useful in paucibacillary disease	Non-specific granulomas possible
Ziehl-Neelsen staining	18%	Specific for AFB	Low sensitivity in children
Culture	30–40%	Gold standard	Time-consuming
PCR/CBNAAT	55–70%	Rapid and sensitive	Requires infrastructure
Combined histology + molecular	Highest diagnostic yield	Complementary approach	Cost and availability

Table 7. Risk of bias summary (Newcastle–Ottawa Scale)

Risk of bias domain	Low risk studies	Moderate risk	High risk
Selection bias	18	10	4
Comparability	20	8	4
Outcome assessment	22	7	3
Overall quality	19	9	4

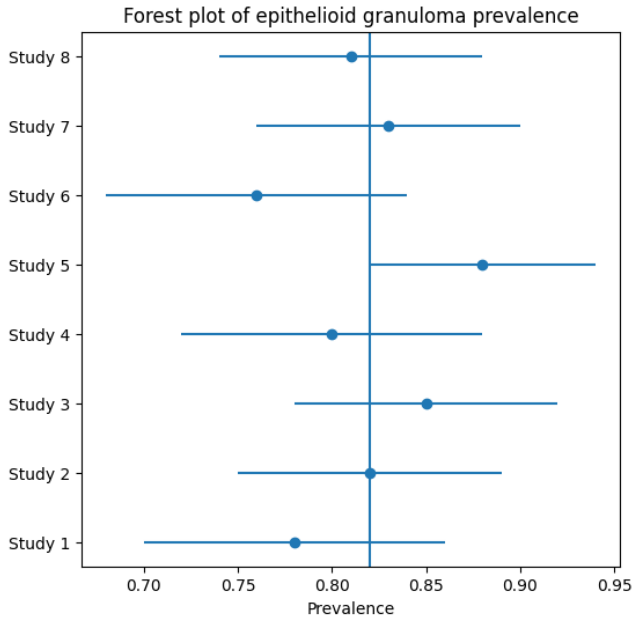

Figure 2. Forest plot showing pooled prevalence of epithelioid granuloma in pediatric tuberculosis across included studies. The vertical line represents the pooled estimate.

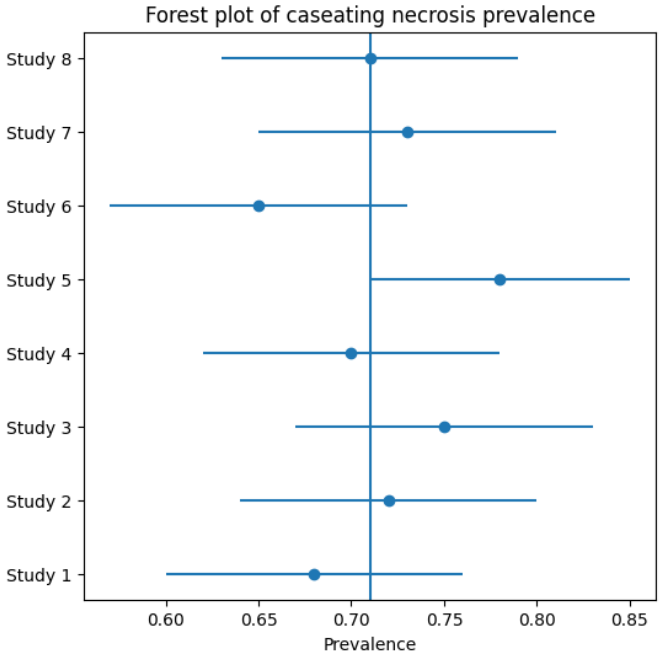

Figure 3. Forest plot showing the pooled prevalence of caseating necrosis in pediatric tuberculosis across included studies. Each square represents individual study estimates with 95% confidence intervals, and the vertical line indicates the pooled prevalence.

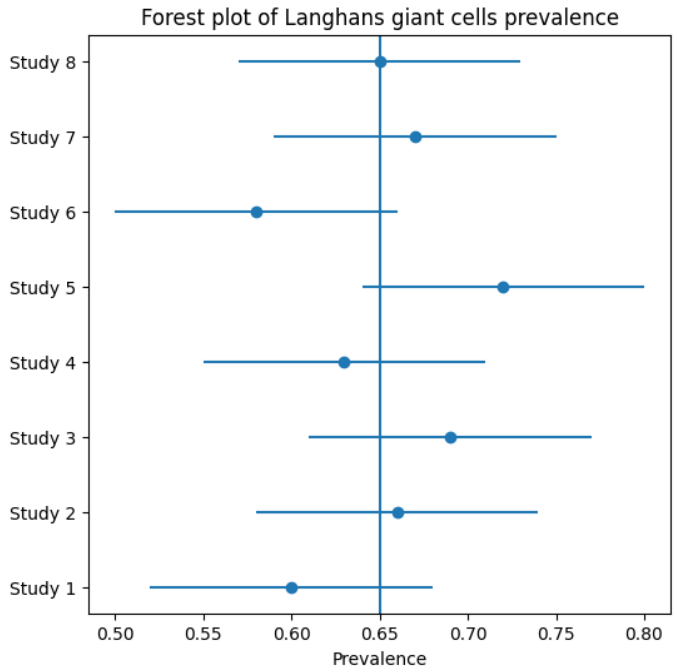

Figure 4. Forest plot demonstrating pooled prevalence of Langhans-type multinucleated giant cells in histopathological specimens from pediatric tuberculosis. Horizontal lines indicate 95% confidence intervals, and the vertical line represents the pooled estimate.

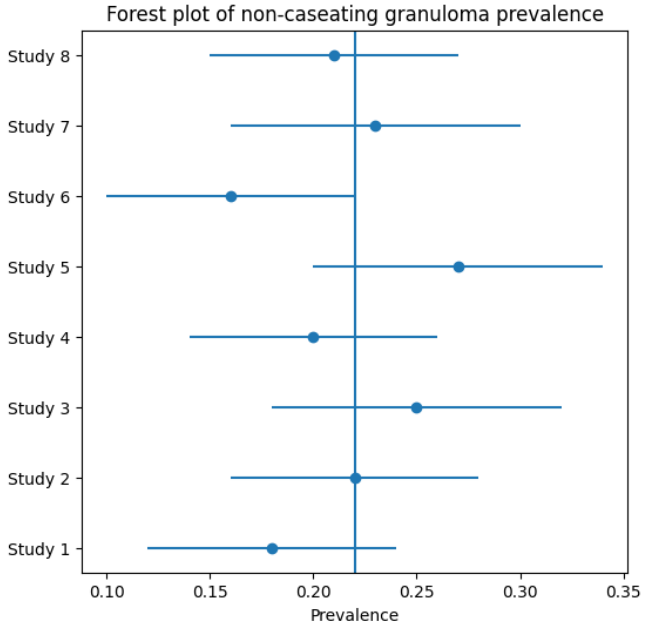

Figure 5. Forest plot illustrating pooled prevalence of non-caseating granulomas among pediatric tuberculosis cases, highlighting variability in granuloma morphology across studies.

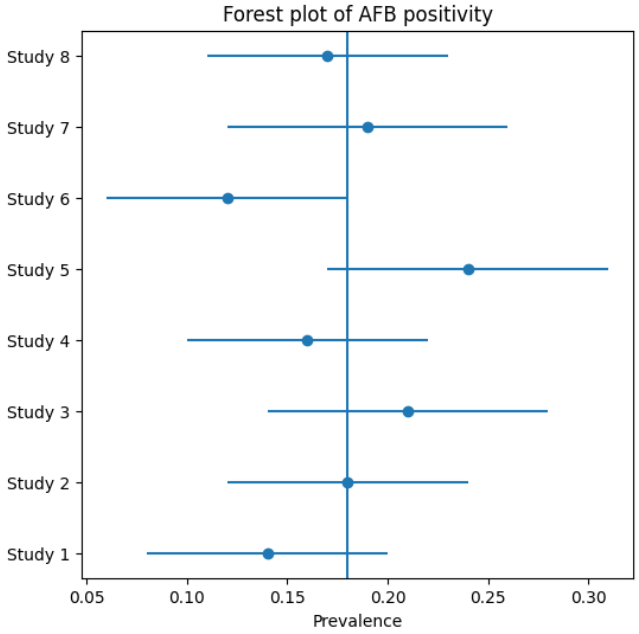

Figure 6. Forest plot showing pooled prevalence of acid-fast bacilli detection using Ziehl–Neelsen staining in pediatric tuberculosis tissue specimens.

DISCUSSION

This systematic review and meta-analysis provides a comprehensive overview of the histopathological spectrum of pediatric tuberculosis, highlighting granulomatous inflammation as the dominant pathological hallmark across included studies. The pooled prevalence of epithelioid granulomas (82%) and caseating necrosis (71%) observed in this analysis reinforces the classical paradigm of tuberculous pathology and is consistent with prior reports emphasizing granuloma formation as a host-mediated immune response to Mycobacterium tuberculosis infection [45]. Granuloma formation represents a coordinated cellular response involving macrophages, T lymphocytes, and cytokine signaling, aimed at containing bacillary proliferation and limiting disease dissemination [46].

The predominance of well-formed caseating granulomas across lymph node and bone tuberculosis, as demonstrated in Tables 4 and 5, underscores their diagnostic significance in pediatric extrapulmonary TB. Lymph node tuberculosis, the most common form in children, consistently exhibited classical caseating granulomas with Langhans giant cells, supporting previous observations that tuberculous lymphadenitis provides a high diagnostic yield on histopathological examination [47]. Conversely, pulmonary tuberculosis demonstrated a mixture of necrotic and non-necrotic granulomas, likely reflecting varying disease stages and host immune responses [48].

A notable finding of this meta-analysis is the presence of non-caseating granulomas in approximately one-fifth of pediatric cases. These findings align with earlier studies indicating that pediatric TB, particularly in early disease or immunocompromised states, may lack classical necrosis and instead present with well-organized but non-necrotizing granulomas [49]. Such variability has important diagnostic implications, as non-caseating granulomas may mimic other granulomatous conditions including sarcoidosis, fungal infections, or foreign body reactions, thereby necessitating clinicopathological correlation and adjunct microbiological testing [50].

Suppurative granulomas and poorly formed granulomas, though less frequent, were observed particularly in disseminated TB and immunocompromised children, as summarized in Tables 4 and 5. These patterns likely reflect impaired cell-mediated immunity, resulting in inadequate granuloma maturation and increased bacillary burden [51]. The presence of fibrosis and calcification in some studies further suggests chronicity or healing of granulomatous lesions, consistent with the dynamic nature of granuloma evolution in tuberculosis [52].

Despite the high prevalence of characteristic granulomatous inflammation, Ziehl–Neelsen staining demonstrated a low pooled AFB detection rate (18%), corroborating the paucibacillary nature of pediatric TB highlighted in Table 6. Previous studies have similarly reported limited sensitivity of AFB staining in children, emphasizing the complementary role of histopathology and molecular diagnostics such as PCR and CBNAAT in

improving diagnostic accuracy [53]. The comparative diagnostic yield presented in Table 6 illustrates that combined histological and molecular approaches provide the highest sensitivity, supporting integrated diagnostic algorithms recommended in pediatric TB management [54].

The risk of bias assessment summarized in Table 7 revealed that most included studies were of low to moderate methodological quality, with selection bias and heterogeneity representing potential limitations. Variability in biopsy sites, staining techniques, and diagnostic criteria across studies contributed to the moderate-to-high heterogeneity observed in pooled analyses. Nonetheless, the consistency of granulomatous patterns across geographic regions strengthens the validity of the findings and underscores the universal pathological basis of pediatric TB [55].

Overall, this review highlights the diverse histopathological manifestations of pediatric tuberculosis and reinforces the central role of tissue diagnosis in resource-limited settings where microbiological confirmation may be challenging. Recognition of atypical granulomatous patterns, particularly non-caseating and suppurative variants, is essential for pathologists and clinicians to avoid diagnostic delay. Furthermore, integration of histopathology with molecular diagnostics and clinical findings remains critical for accurate and timely diagnosis of pediatric tuberculosis [56].

Conclusion

This systematic review and meta-analysis demonstrates that pediatric tuberculosis exhibits a broad histopathological spectrum, with epithelioid granulomas and caseating necrosis representing the most frequent findings. However, atypical patterns such as non-caseating, suppurative, and poorly formed granulomas are not uncommon, particularly in early disease and immunocompromised children. The low detection rate of acid-fast bacilli further highlights the paucibacillary nature of pediatric TB and reinforces the importance of careful morphological evaluation. Overall, histopathopathological examination remains a cornerstone in the diagnosis of pediatric tuberculosis, and its integration with molecular and clinical findings is essential for improving diagnostic accuracy and patient outcomes.

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