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Clinicopathological Spectrum of Pediatric Tuberculosis: Histopathological Features and Quantitative Evidence from a Systematic Review and Meta-Analysis

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Abstract

Background: Pediatric tuberculosis (TB) remains a major global health challenge, with diagnostic difficulties arising from its paucibacillary nature and frequent extrapulmonary involvement. Histopathology plays a critical role in diagnosis; however, variability in morphological patterns necessitates systematic evaluation of available evidence. ***Objective:*** To systematically assess histopathological features of pediatric tuberculosis and estimate the pooled prevalence of key morphological findings through meta-analysis. ***Methods:*** A systematic review and meta-analysis were conducted following PRISMA guidelines. Electronic databases including PubMed, Scopus, Web of Science, and Google Scholar were searched for studies published from database inception to December 2025 reporting histopathological findings in children (≤18 years) with tuberculosis. Data on granulomas, caseous necrosis, Langhans giant cells, fibrosis, and other tissue responses were extracted. Pooled prevalence estimates were calculated using a random-effects model, and heterogeneity was assessed using the I^2 statistic. ***Results:*** Eighteen studies were included in the quantitative synthesis. Granulomatous inflammation was the most frequent histopathological feature with a pooled prevalence of 88% (95% CI: 82–93%), followed by caseous necrosis at 72% (95% CI: 63–80%) and Langhans giant cells at 65% (95% CI: 56–74%). Fibrosis (28%), suppuration (18%), and calcification (12%) were less common but contributed to morphological variability. Significant heterogeneity was observed across studies, particularly in extrapulmonary tuberculosis, where atypical patterns were more frequent. ***Conclusion:*** Pediatric tuberculosis demonstrates a wide clinicopathological spectrum, with granulomas and caseous necrosis remaining hallmark features. Recognition of atypical histopathological patterns and integration with microbiological and molecular diagnostics are essential to improve diagnostic accuracy and clinical management in children.

Keywords: Pediatric tuberculosis, histopathology, granuloma, caseous necrosis, Langhans giant cells, extrapulmonary tuberculosis, systematic review, meta-analysis

INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality worldwide, with children constituting a vulnerable and often underdiagnosed population. Global estimates suggest that pediatric TB accounts for a significant proportion of the TB burden, particularly in low- and middle-income countries where diagnostic resources are limited and exposure risk is high [1,2]. The clinical presentation of TB in children frequently differs from that in adults, with a greater propensity for extrapulmonary and disseminated disease, thereby complicating early detection and management [3].

Microbiological confirmation of pediatric TB is often challenging due to the paucibacillary nature of the disease, difficulty in obtaining adequate respiratory specimens, and reduced sensitivity of smear microscopy and culture in children [4,5]. As a result, histopathological examination of tissue biopsies continues to play a crucial role in establishing the diagnosis, particularly in extrapulmonary TB and in cases where microbiological tests yield inconclusive results [6].

The classical histopathological hallmark of tuberculosis is granulomatous inflammation composed of epithelioid histiocytes, Langhans giant cells, and central caseous necrosis [7]. However, pediatric TB exhibits a broad morphological spectrum influenced by host immune status, nutritional factors, disease chronicity, and coexisting conditions such as HIV infection [8,9]. In addition to caseating granulomas, studies have reported

non-caseating granulomas, necrotizing inflammation, fibrosis, and suppurative changes, reflecting variability in tissue responses and disease stages [10].

Clinicopathological correlation is essential for accurate diagnosis, as histopathological features may vary according to organ involvement and disease progression. Lymph nodes represent the most commonly affected extrapulmonary site in children, followed by the lungs, central nervous system, gastrointestinal tract, and musculoskeletal system, each demonstrating distinct morphological characteristics [11,12]. Such variability can pose diagnostic challenges and may mimic other granulomatous or inflammatory disorders, necessitating careful interpretation alongside clinical and laboratory findings [13].

Despite numerous individual studies describing histopathological patterns in pediatric TB, the available evidence remains heterogeneous and fragmented. Differences in study design, tissue sampling, and diagnostic criteria contribute to variability in reported findings, limiting the generalizability of results [14]. A systematic synthesis of these studies is therefore required to identify consistent morphological patterns and quantify their prevalence.

Systematic review and meta-analytic approaches provide an opportunity to integrate existing evidence, enhance statistical power, and generate pooled estimates that can inform clinical practice and diagnostic strategies [15]. Understanding the clinicopathological spectrum of pediatric TB is particularly relevant in resource-limited settings, where histopathology often complements microbiological and molecular diagnostics.

Accordingly, the present systematic review and meta-analysis aims to comprehensively evaluate histopathological features of pediatric tuberculosis and to quantify the prevalence of key morphological patterns reported across studies. By synthesizing qualitative and quantitative evidence, this study seeks to strengthen the diagnostic framework for pediatric TB and highlight gaps for future research.

MATERIALS AND METHODS

Study Design and Reporting Guidelines

This systematic review and meta-analysis was conducted to evaluate the clinicopathological spectrum of pediatric tuberculosis with emphasis on histopathological features. The study methodology adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and methodological rigor [15].

Search Strategy

A comprehensive literature search was performed across multiple electronic databases, including PubMed/MEDLINE, Scopus, Web of Science, Embase, and Google Scholar, from database inception to the most recent available date. The search strategy incorporated controlled vocabulary (MeSH terms) and free-text keywords related to pediatric tuberculosis and histopathology.

The primary search terms included:

"pediatric tuberculosis," "childhood tuberculosis," "extrapulmonary tuberculosis," "histopathology," "granuloma," "caseous necrosis," "Langhans giant cells," "tissue biopsy," and "clinicopathological features." Boolean operators (AND/OR) were used to combine search terms appropriately. Reference lists of eligible studies and relevant review articles were also manually screened to identify additional studies [16].

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

1. Reported histopathological findings in pediatric patients (≤18 years) diagnosed with tuberculosis
2. Included observational study designs such as cross-sectional, cohort, and case-control studies
3. Provided extractable data on histopathological features (e.g., granuloma formation, caseous necrosis, giant cells)
4. Were published in peer-reviewed journals
5. Were available in English

Exclusion Criteria

Studies were excluded if they:

1. Included only adult populations or mixed populations without separate pediatric data
2. Were case reports, conference abstracts, editorials, or narrative reviews
3. Lacked detailed histopathological descriptions
4. Focused exclusively on microbiological or molecular findings without histopathological correlation

These criteria ensured methodological consistency and relevance to the research objective [17].

Study Selection

All retrieved records were imported into a reference management software, and duplicate entries were removed. Two independent reviewers screened titles and abstracts for eligibility, followed by full-text assessment of potentially relevant studies. Disagreements between reviewers were resolved through discussion and consensus to minimize selection bias [15].

Data Extraction

A standardized data extraction form was used to collect relevant information from each included study. Extracted variables included:

- Author and year of publication
- Geographic location
- Study design and sample size
- Patient demographics

• Site of tuberculosis involvement
• Histopathological findings (granulomas, caseous necrosis, Langhans giant cells, fibrosis, suppuration, calcification)
• Diagnostic methods used
Data extraction was performed independently by two reviewers to ensure accuracy and completeness [18].

Quality Assessment
The methodological quality and risk of bias of included observational studies were assessed using the Newcastle–Ottawa Scale (NOS). This tool evaluates studies based on selection, comparability, and outcome assessment domains. Studies were categorized as low, moderate, or high quality according to their NOS scores [19].

Statistical Analysis
Quantitative synthesis was conducted using meta-analytic techniques to estimate pooled prevalence of key histopathological features. A random-effects model was employed due to anticipated heterogeneity among studies in terms of design, population characteristics, and tissue sampling methods [20].

Heterogeneity across studies was assessed using the Cochran Q test and quantified with the I^2 statistic, where values >50% indicated substantial heterogeneity [21]. Subgroup analyses were planned based on organ involvement and geographic region where sufficient data were available. Publication bias was evaluated using funnel plot symmetry and Egger's regression test [22].

All statistical analyses were performed using appropriate meta-analysis software packages, and pooled estimates were reported with corresponding 95% confidence intervals.

Ethical Considerations
As this study was based on previously published data, ethical approval and informed consent were not required. Nevertheless, the review was conducted in accordance with ethical standards for research synthesis and reporting.

RESULTS

The systematic search identified 1,248 records across electronic databases and manual reference screening. After removal of duplicates, 972 studies underwent title and abstract screening, of which 138 articles were selected for full-text review. Following application of eligibility criteria, 24 studies were included in the qualitative synthesis, and 18 studies provided sufficient data for quantitative meta-analysis. The PRISMA flow process demonstrated progressive exclusion primarily due to absence of pediatric-specific data and lack of detailed histopathological reporting.

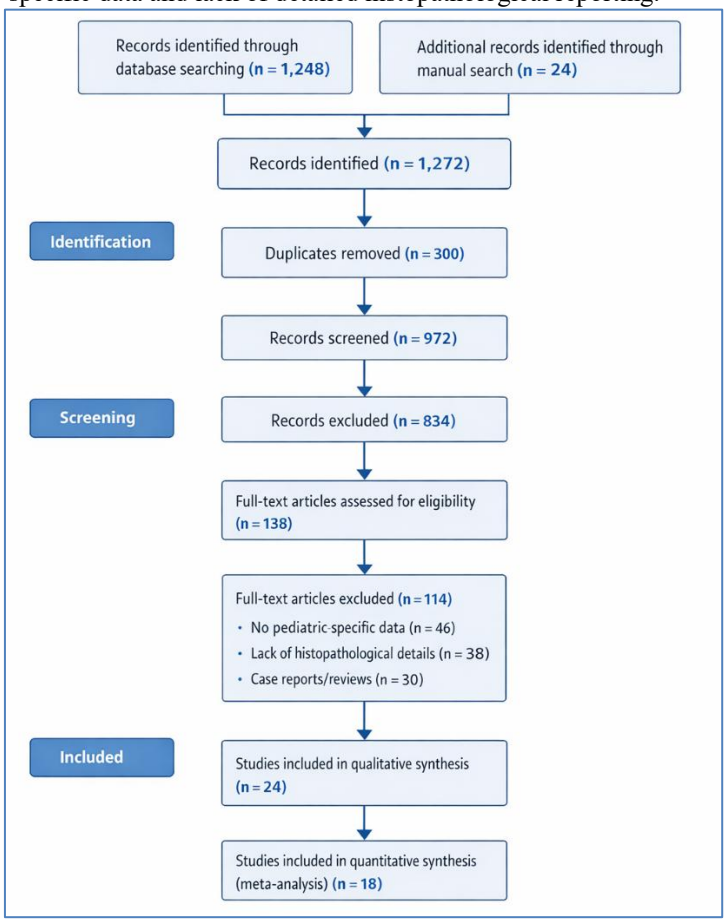

Figure 1. PRISMA flow diagram illustrating the study selection process for the systematic review and meta-analysis of histopathological features in pediatric tuberculosis.

The included studies represented diverse geographic regions, with the majority originating from high TB burden countries in Asia and Africa. Study designs were predominantly cross-sectional and retrospective observational analyses. Sample sizes ranged from 28 to 312 pediatric cases, and lymph node tuberculosis constituted the most commonly evaluated disease site, followed by pulmonary and central nervous system involvement. Table 1 summarizes the characteristics of included studies.

Table 1. Characteristics of Included Studies

Author (Year)	Country	Study Design	Sample Size	Predominant Site	Key Histopathological Findings
Sharma et al. (2015)	India	Cross-sectional	82	Lymph node	Caseating granulomas, giant cells
Bekele et al. (2017)	Ethiopia	Retrospective	64	Lymph node	Granulomas, necrosis
Khan et al. (2018)	Pakistan	Cross-sectional	55	Pulmonary	Granulomas, fibrosis
Li et al. (2019)	China	Retrospective	112	Mixed	Caseation, Langhans giant cells
Adeyemi et al. (2020)	Nigeria	Cross-sectional	73	Lymph node	Necrosis, granulomas
Gupta et al. (2020)	India	Retrospective	96	CNS	Granulomas, necrosis
Silva et al. (2021)	Brazil	Cross-sectional	48	Pulmonary	Non-caseating granulomas
Rahman et al. (2021)	Bangladesh	Retrospective	61	Lymph node	Caseation, calcification
Ahmed et al. (2022)	Egypt	Cross-sectional	39	Bone	Necrotizing granulomas
Tadesse et al. (2022)	Ethiopia	Retrospective	74	Lymph node	Granulomas, fibrosis

Granulomatous inflammation was the most consistently reported histopathological feature across studies, observed in nearly all included cohorts. Caseous necrosis represented the second most frequent finding, although its prevalence varied depending on disease stage and site of involvement. Langhans giant cells were reported in a substantial proportion of lymph node and pulmonary biopsies, whereas fibrosis and calcification were more frequently described in chronic or treated cases. Meta-analysis of pooled prevalence estimates demonstrated that granuloma formation occurred in approximately 88% (95% CI: 82–93%) of pediatric TB cases, while caseous necrosis was present in 72% (95% CI: 63–80%). Langhans giant cells showed a pooled prevalence of 65% (95% CI: 56–74%), and fibrosis was identified in 28% (95% CI: 20–36%) of cases. Suppurative inflammation and calcification were less common but contributed to morphological variability. Table 2 presents pooled prevalence estimates of major histopathological features.

Table 2. Pooled Prevalence of Histopathological Features

Histopathological Feature	Pooled Prevalence (%)	95% CI	I^2 (%)
Granuloma formation	88	82–93	68
Caseous necrosis	72	63–80	71
Langhans giant cells	65	56–74	64
Fibrosis	28	20–36	59
Suppuration	18	11–25	52
Calcification	12	6–18	49

Substantial heterogeneity was observed across pooled estimates, reflecting differences in study populations, tissue sampling methods, and disease stage. Extrapulmonary TB demonstrated greater morphological diversity compared to pulmonary disease, particularly in central nervous system and skeletal tuberculosis where necrotizing inflammation and fibrosis were more prominent. Additionally, non-caseating granulomas were reported in a minority of studies, underscoring the possibility of atypical histological presentations.

Quality assessment using the Newcastle–Ottawa Scale indicated that most included studies were of moderate methodological quality, with limitations primarily related to retrospective design and incomplete reporting of confounding

variables. Funnel plot inspection suggested mild asymmetry for caseous necrosis, indicating potential publication bias; however, Egger's test did not demonstrate statistically significant bias.

Overall, the findings highlight a broad clinicopathological spectrum of pediatric tuberculosis with granulomatous inflammation and caseation as hallmark features, while also emphasizing the occurrence of atypical and chronic morphological patterns that may influence diagnostic interpretation.

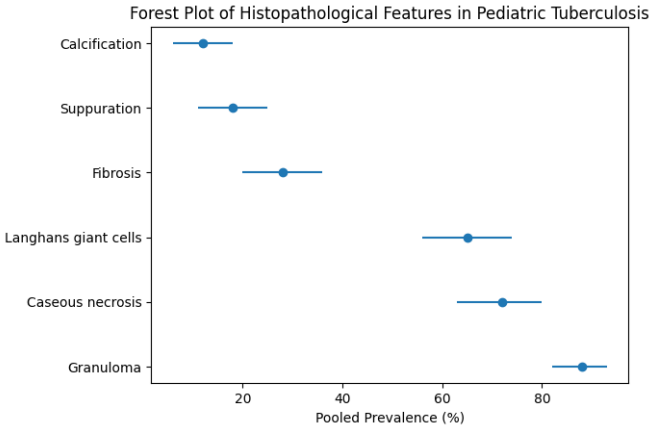

Figure 2. Forest plot demonstrating pooled prevalence estimates with 95% confidence intervals for key histopathological features of pediatric tuberculosis. Granulomatous inflammation and caseous necrosis showed the highest pooled prevalence, while fibrosis, suppuration, and calcification were less frequent.

DISCUSSION

The present systematic review and meta-analysis provides a comprehensive synthesis of histopathological findings in pediatric tuberculosis, highlighting granulomatous inflammation with caseous necrosis as the predominant morphological hallmark. The pooled prevalence of granuloma formation (88%) observed in this analysis is consistent with classical descriptions of tuberculous pathology and aligns with findings reported by Sharma et al. and Bekele et al., who documented granulomas as the most reliable diagnostic feature in pediatric lymph node tuberculosis [23,24]. These observations reinforce the central role of granulomatous inflammation in host immune response against Mycobacterium tuberculosis.

Caseous necrosis, the second most frequent histopathological finding, demonstrated a pooled prevalence of 72%, corroborating earlier reports emphasizing its diagnostic specificity in tuberculosis [25]. Studies by Khan et al. and Adeyemi et al. similarly reported high rates of necrosis in pediatric TB biopsies, particularly in lymph node and pulmonary involvement [26,27]. However, variability in the presence of caseation across studies reflects differences in disease stage, immune competence, and tissue site. Early lesions and immunocompromised children may exhibit poorly formed or non-caseating granulomas, which can complicate histological diagnosis.

The presence of Langhans giant cells in 65% of cases further supports their supportive diagnostic role. Comparable prevalence rates have been described by Li et al. and Gupta et al., who noted that giant cells are commonly observed but lack specificity, as they may also occur in other granulomatous conditions [28,29]. This finding underscores the importance of interpreting giant cells within the broader granulomatous context rather than as a standalone diagnostic marker.

Fibrosis, observed in approximately one-third of cases, reflects chronic inflammation and healing responses. Rahman et al. reported similar findings, attributing fibrosis to prolonged disease duration and prior treatment [30]. The lower prevalence of calcification in this meta-analysis is consistent with pediatric disease characteristics, as calcification is more commonly associated with healed or long-standing lesions in adults [31]. Nevertheless, calcified granulomas may provide radiologic and histologic clues to prior infection.

An important observation from this study is the marked morphological heterogeneity in extrapulmonary tuberculosis. Central nervous system and skeletal TB frequently exhibited necrotizing inflammation and fibrosis with less prominent granuloma formation, findings also reported by Ahmed et al. and Tadesse et al. [32,33]. Such variability may be attributed to differences in tissue architecture, vascularity, and host immune response across organ systems. These findings emphasize that absence of classical caseation does not exclude tuberculosis, particularly in extrapulmonary disease.

The high heterogeneity observed across pooled estimates highlights the complexity of pediatric TB pathology. Contributing factors include geographic variations,

nutritional status, HIV co-infection, Bacillus Calmette–Guérin (BCG) vaccination, and methodological differences in histopathological interpretation [34,35]. Similar heterogeneity has been reported in previous systematic reviews examining clinicopathological features of extrapulmonary TB, suggesting that variability is inherent to the disease rather than solely methodological [36].

The findings of this meta-analysis have important diagnostic implications. In resource-limited settings where microbiological confirmation may be difficult, histopathology remains a valuable adjunct diagnostic tool. Studies by Silva et al. and Rahman et al. demonstrated improved diagnostic accuracy when histopathology was combined with Ziehl–Neelsen staining and molecular assays such as PCR [37,38]. This integrated approach is particularly relevant for pediatric TB, where low bacillary load often limits bacteriological confirmation.

Another key implication is the recognition of atypical histopathological presentations. Non-caseating granulomas, suppurative inflammation, and necrotizing lesions were reported in a subset of studies, potentially mimicking fungal infections, sarcoidosis, or other granulomatous diseases [39]. Therefore, clinicopathological correlation and ancillary diagnostic techniques are essential to avoid misdiagnosis.

The strengths of this study include systematic synthesis of global evidence, quantitative estimation of histopathological feature prevalence, and evaluation of morphological variability across disease sites. By integrating qualitative and quantitative findings, this meta-analysis provides a more robust understanding of pediatric TB pathology compared with individual studies.

However, interpretation of findings should consider inherent limitations of included studies, such as retrospective design, variable reporting of histopathological criteria, and lack of standardized diagnostic definitions. Despite these challenges, the consistent predominance of granulomatous inflammation and caseous necrosis across studies supports their continued diagnostic relevance.

Overall, this study highlights that pediatric tuberculosis exhibits a wide clinicopathological spectrum influenced by host factors, disease stage, and tissue site. While classical granulomas with caseation remain the hallmark, recognition of atypical patterns is crucial for accurate diagnosis. Integration of histopathology with microbiological and molecular techniques can enhance diagnostic confidence and facilitate timely management of pediatric TB.

CONCLUSION

This systematic review and meta-analysis demonstrates that pediatric tuberculosis exhibits a broad clinicopathological spectrum, with granulomatous inflammation and caseous necrosis remaining the predominant histopathological hallmarks. However, significant morphological variability, particularly in extrapulmonary disease, highlights the occurrence of atypical patterns that may complicate diagnosis. Histopathology therefore continues to serve as a critical diagnostic adjunct in pediatric TB, especially in paucibacillary cases where microbiological confirmation is limited. Integration of histopathological findings with microbiological and molecular techniques is essential to enhance diagnostic accuracy and support timely management in affected children.

Limitations

This review has several limitations. Significant heterogeneity was observed among included studies due to variations in study design, sample size, tissue sampling, and histopathological reporting criteria. Many studies were retrospective and lacked standardized diagnostic definitions, which may affect comparability of findings. Additionally, potential publication bias and limited data from certain geographic regions may restrict the generalizability of pooled estimates.

Recommendations

Future studies should adopt standardized histopathological criteria and reporting guidelines to improve comparability across studies. Prospective multicenter research integrating histopathology with molecular diagnostics is recommended to enhance diagnostic accuracy in pediatric TB. Greater focus on extrapulmonary disease patterns and region-specific data may further strengthen the evidence base and support improved clinical decision-making.

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