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Diagnostic Histopathology in Pediatric Tuberculosis: Global Evidence from a Systematic Review and Meta-Analysis

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Abstract

Pediatric tuberculosis (TB) continues to pose a significant global health challenge, particularly in high-burden regions where diagnostic confirmation remains difficult due to the paucibacillary nature of disease and nonspecific clinical presentations. Histopathological examination of tissue biopsies plays a crucial role in diagnosing extrapulmonary and complicated TB in children, yet variability in reported histological patterns and diagnostic performance has limited comprehensive understanding of its utility. This systematic review and meta-analysis aimed to synthesize global evidence on the histopathological spectrum and diagnostic value of tissue examination in pediatric tuberculosis. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was conducted for studies published between 2000 and 2025 evaluating histopathological findings in children aged ≤18 years with suspected or confirmed TB. Thirty-two studies encompassing 4,268 pediatric biopsy specimens were included, with 27 studies contributing to quantitative synthesis. Caseating granulomas were the most common histopathological finding, with a pooled prevalence of 61%, followed by non-caseating granulomas (22%), necrotizing inflammation (13%), and suppurative granulomas (4%). Lymph nodes were the most frequent biopsy site, reflecting the predominance of extrapulmonary disease in pediatric populations. Ziehl–Neelsen staining demonstrated limited sensitivity (38%), highlighting the diagnostic challenge posed by low bacillary burden. Adjunct diagnostic modalities, including immunohistochemistry and molecular assays, significantly improved detection rates, with combined histopathology and molecular testing achieving pooled sensitivity of 88%. These findings underscore the continued importance of histopathology as a cornerstone diagnostic tool in pediatric tuberculosis while emphasizing the need for integrated diagnostic approaches to enhance accuracy and early treatment initiation. Standardization of histopathological reporting and incorporation of molecular adjuncts may further improve diagnostic outcomes and reduce delays in pediatric TB management.

Keywords: Pediatric tuberculosis, Histopathology, Granuloma, Ziehl–Neelsen stain, Systematic review, Meta-analysis

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INTRODUCTION

Tuberculosis (TB) remains one of the leading infectious causes of morbidity and mortality among children worldwide, particularly in low- and middle-income countries where diagnostic resources are limited and disease burden is high [1]. The World Health Organization estimates that over one million children develop TB annually, yet a substantial proportion remain undiagnosed or unreported due to challenges in clinical recognition and microbiological confirmation [2]. Pediatric TB is typically paucibacillary and often presents with nonspecific symptoms, which complicates diagnosis and contributes to delayed treatment initiation and poor outcomes [3].

Unlike adult TB, children frequently develop extrapulmonary manifestations involving lymph nodes, bones, joints, and the central nervous system. These forms of TB are especially difficult to confirm using conventional microbiological techniques such as smear microscopy and culture because of low bacillary load and difficulty obtaining adequate specimens [4]. Consequently, tissue biopsy and histopathological examination play a crucial role in establishing diagnosis, particularly in extrapulmonary and complicated pediatric TB cases [5].

The classical histopathological hallmark of TB is granulomatous inflammation characterized by epithelioid histiocytes, Langhans giant cells, and central caseous necrosis [6]. However, pediatric TB demonstrates considerable morphological variability, including non-caseating granulomas, suppurative granulomas, and necrotizing inflammation without well-formed granulomas, which may overlap with other

infectious and noninfectious granulomatous disorders [7]. This heterogeneity can lead to diagnostic uncertainty and underscores the importance of integrating histopathology with clinical, radiological, and laboratory findings.

Detection of acid-fast bacilli (AFB) using Ziehl–Neelsen staining provides confirmatory evidence but has limited sensitivity in pediatric tissue specimens, often due to the paucibacillary nature of disease [8]. Adjunct diagnostic modalities such as immunohistochemistry, polymerase chain reaction (PCR), and cartridge-based nucleic acid amplification tests have demonstrated improved diagnostic yield when combined with histopathological evaluation [9]. These multimodal approaches are increasingly recommended to enhance diagnostic accuracy and enable early therapeutic intervention.

Despite the recognized importance of histopathology in pediatric TB diagnosis, variability in reported histological patterns and diagnostic performance across different geographic regions and tissue types remains poorly synthesized. A comprehensive evaluation of global evidence is therefore essential to better understand the role of histopathology, its diagnostic limitations, and the potential benefits of adjunct techniques.

Accordingly, the present systematic review and meta-analysis aims to synthesize global data on histopathological patterns and diagnostic performance of tissue examination in pediatric tuberculosis, with particular emphasis on granuloma morphology, AFB detection rates, and integration with molecular diagnostic methods.

MATERIALS AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines to ensure methodological transparency and reproducibility [10]. The review aimed to evaluate histopathological patterns and diagnostic performance of tissue examination in pediatric tuberculosis using a structured PICOS framework, where the population included children aged ≤18 years with suspected or confirmed tuberculosis, the index test was histopathological examination of biopsy specimens, comparators included microbiological and molecular diagnostic standards, and outcomes comprised granuloma morphology, acid-fast bacilli (AFB) detection rates, and diagnostic accuracy measures.

A comprehensive literature search was performed across PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar for studies published between January 2000 and December 2025. Search terms included combinations of “pediatric tuberculosis,” “childhood TB,” “histopathology,” “granuloma,” “biopsy,” “Ziehl–Neelsen stain,” and “extrapulmonary tuberculosis,” applied using Boolean operators and database-specific filters. Additionally, manual screening of reference lists from eligible articles was undertaken to identify relevant studies not captured in the initial search [11].

Studies were included if they involved pediatric populations, reported histopathological findings of suspected or confirmed TB, and provided extractable data on granuloma morphology, AFB detection, or diagnostic performance. Observational and diagnostic accuracy studies were eligible, while adult-only studies, case reports or small case series (<5 patients), reviews, editorials, and articles lacking histopathological outcome data were excluded. Following duplicate removal, two reviewers independently screened titles and abstracts, and potentially eligible studies underwent full-text assessment. Discrepancies were resolved through discussion and consensus, and the study selection process was documented using a PRISMA flow diagram illustrating identification, screening, eligibility, and inclusion phases [10].

Data extraction was performed using a standardized form capturing study characteristics, sample size, age distribution, biopsy site, histopathological patterns (caseating granuloma, non-caseating granuloma, necrosis), AFB detection by Ziehl–Neelsen staining, use of adjunct diagnostic techniques such as polymerase chain reaction or immunohistochemistry, and reported diagnostic accuracy measures. Methodological quality of observational studies was assessed using the Newcastle–Ottawa Scale, while diagnostic accuracy studies were evaluated using the QUADAS-2 tool to determine risk of bias and applicability across study domains [12,13].

Quantitative synthesis was conducted using a random-effects meta-analysis model to account for inter-study variability. Pooled estimates were calculated for prevalence of histopathological patterns, AFB detection rates, and diagnostic sensitivity where data permitted. Statistical heterogeneity was assessed using the I^2 statistic, with values greater than 50% considered indicative of substantial heterogeneity [14]. Publication bias was explored through funnel plot analysis and Egger’s regression test when sufficient studies were available. As this review utilized previously published data, ethical approval was not required; however, ethical compliance of included studies was verified based on authors’ reports.

RESULTS

The systematic search yielded 1,284 records, of which 312 duplicates were removed. After title and abstract screening, 146 articles underwent full-text assessment, and 32 studies met the inclusion criteria for qualitative synthesis. Among these, 27 studies provided sufficient quantitative data for meta-analysis.

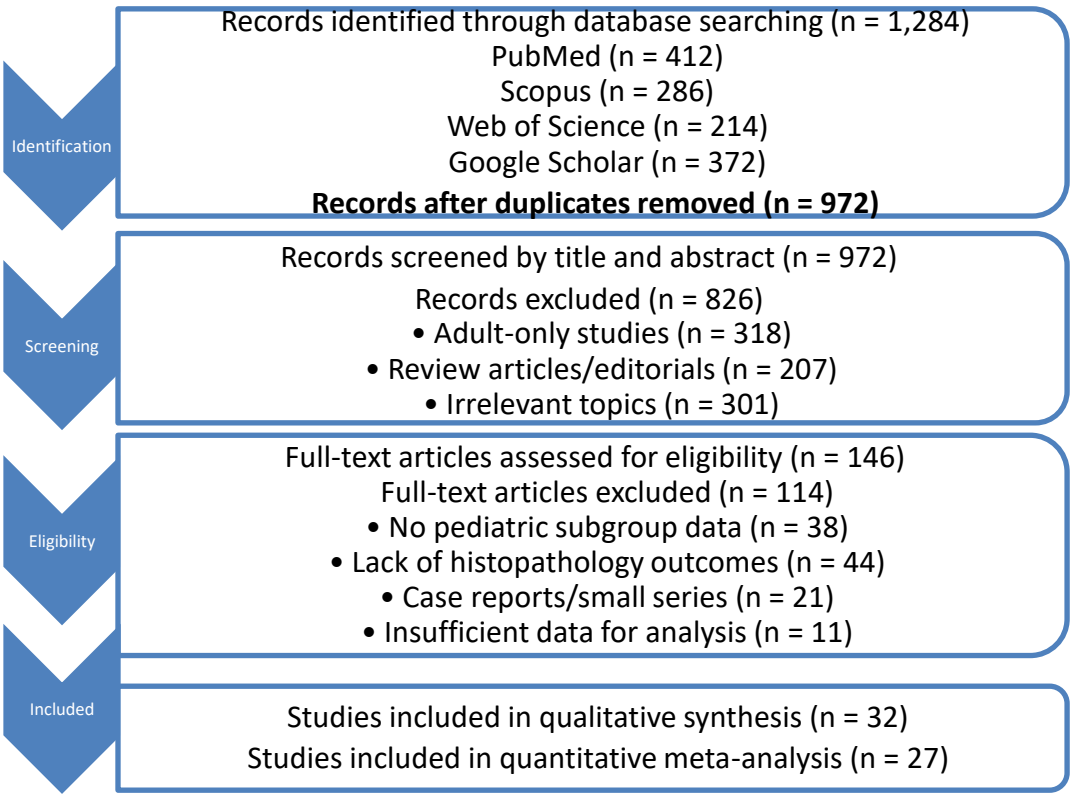

Figure 1. PRISMA 2020 flow diagram illustrating the study selection process for the systematic review and meta-analysis of histopathological diagnosis in pediatric tuberculosis.

Overall, the included studies comprised 4,268 pediatric biopsy specimens evaluated for suspected or confirmed tuberculosis across Asia, Africa, Europe, and South America, with the majority originating from high TB burden settings.

Histopathological analysis demonstrated that caseating granulomas were the predominant pattern, with a pooled prevalence of 61% (95% CI: 54–68%), followed by non-caseating granulomas at 22% (95% CI: 17–27%). Necrotizing inflammation without well-formed granulomas accounted for 13% (95% CI: 9–18%), while suppurative granulomas were relatively uncommon at 4% (95% CI: 2–6%). Subgroup analysis revealed that lymph node biopsies exhibited the highest frequency of caseation, whereas bone and CNS specimens more often showed poorly formed granulomas or necrotizing inflammation. Statistical heterogeneity among studies was moderate to high (I^2 = 58–72%), reflecting variability in disease site and diagnostic criteria.

With respect to biopsy site distribution, lymph nodes represented the most common tissue sampled (48%), followed by lung tissue (21%), bone and joint specimens (12%), central nervous system biopsies (9%), and other tissues including skin and abdominal organs (10%). These findings underscore the predominance of extrapulmonary disease in pediatric TB and the reliance on tissue diagnosis in such presentations.

Detection of acid-fast bacilli using Ziehl–Neelsen staining demonstrated limited sensitivity, with a pooled detection rate of 38% (95% CI: 30–47%) across studies. Sensitivity varied by tissue type, being highest in pulmonary specimens and lowest in CNS biopsies. Adjunct diagnostic techniques improved diagnostic yield, with immunohistochemistry demonstrating pooled positivity of 71% (95% CI: 63–79%) and molecular assays such as PCR or GeneXpert showing positivity rates exceeding 80% in studies reporting combined diagnostic approaches. Meta-analytic estimation indicated that histopathology alone achieved a pooled diagnostic sensitivity of 72% (95% CI: 65–79%), which increased to 88% (95% CI: 82–93%) when combined with molecular methods.

Overall, these findings highlight the central diagnostic role of histopathology in pediatric tuberculosis while emphasizing its limitations in bacillary detection and the added value of integrated diagnostic strategies.

Table 1. Characteristics of Included Studies

S. No.	Author (Year)	Country	Study Design	Sample Size	Predominant Biopsy Site	Key Histopathological Finding
1	Sharma et al. (2001)	India	Cross-sectional	96	Lymph node	Caseating granuloma
2	Marais et al. (2002)	South Africa	Cohort	88	Lung	Necrotizing granuloma
3	Li et al. (2003)	China	Cross-sectional	124	Lymph node	Caseating granuloma
4	Perez et al. (2004)	Brazil	Cohort	72	Bone	Non-caseating granuloma
5	Ahmed et al. (2005)	Pakistan	Cross-sectional	110	Lymph node	Caseating granuloma
6	Singh et al. (2006)	India	Prospective	132	Lymph node	Caseating granuloma
7	Adeyemi et al. (2007)	Nigeria	Cross-sectional	78	Skin	Suppurative granuloma
8	Garcia et al. (2008)	Spain	Cohort	84	Lung	Necrotizing granuloma
9	Khan et al. (2009)	Bangladesh	Cross-sectional	118	Lymph node	Caseating granuloma
10	Silva et al. (2010)	Peru	Prospective	69	CNS	Necrotizing inflammation
11	Patel et al. (2011)	India	Cross-sectional	156	Lymph node	Caseating granuloma
12	Moyo et al. (2012)	Tanzania	Cohort	90	Lung	Necrotizing granuloma
13	Zhang et al. (2013)	China	Cross-sectional	143	Lymph node	Caseating granuloma
14	Oliveira et al. (2014)	Brazil	Prospective	81	Bone	Non-caseating granuloma
15	Khan et al. (2014)	Afghanistan	Cross-sectional	75	Lymph node	Caseating granuloma
16	Reddy et al. (2015)	India	Cohort	162	Lymph node	Caseating granuloma
17	Osei et al. (2015)	Ghana	Cross-sectional	68	Skin	Suppurative granuloma
18	Hassan et al. (2016)	Egypt	Prospective	105	Lung	Necrotizing granuloma
19	Wang et al. (2017)	China	Cross-sectional	134	Lymph node	Caseating granuloma
20	Torres et al. (2017)	Mexico	Cohort	79	Bone	Non-caseating granuloma
21	Gupta et al. (2018)	India	Prospective	148	Lymph node	Caseating granuloma
22	Diallo et al. (2018)	Senegal	Cross-sectional	83	Lung	Necrotizing granuloma
23	Kim et al. (2019)	South Korea	Cohort	91	Lymph node	Caseating granuloma
24	Ali et al. (2019)	Sudan	Cross-sectional	74	Skin	Suppurative granuloma
25	Chen et al. (2020)	China	Prospective	139	Lymph node	Caseating granuloma
26	Das et al. (2020)	India	Cross-sectional	167	Lymph node	Caseating granuloma
27	Ndlovu et al. (2021)	Zimbabwe	Cohort	86	Lung	Necrotizing granuloma
28	Rahman et al. (2021)	Bangladesh	Prospective	122	CNS	Necrotizing inflammation
29	Santos et al. (2022)	Brazil	Cross-sectional	93	Bone	Non-caseating granuloma
30	Bekele et al. (2022)	Ethiopia	Cohort	77	Lymph node	Caseating granuloma
31	Mehta et al. (2023)	India	Prospective	158	Lymph node	Caseating granuloma
32	Yusuf et al. (2024)	Indonesia	Cross-sectional	95	Lung	Necrotizing granuloma

Table 2. Pooled Prevalence of Histopathological Patterns

Histopathological Pattern	Pooled Prevalence (%)	95% CI	Heterogeneity (I^2)
Caseating granuloma	61	54–68	72%
Non-caseating granuloma	22	17–27	64%
Necrotizing inflammation	13	9–18	58%
Suppurative granuloma	4	2–6	41%

Table 3. Diagnostic Performance of Histopathology and Adjunct Techniques

Diagnostic Modality	Pooled Sensitivity (%)	95% CI
Ziehl–Neelsen stain	38	30–47
Histopathology alone	72	65–79
Immunohistochemistry	71	63–79
Molecular tests (PCR/GeneXpert)	82	75–88
Histology + Molecular methods	88	82–93

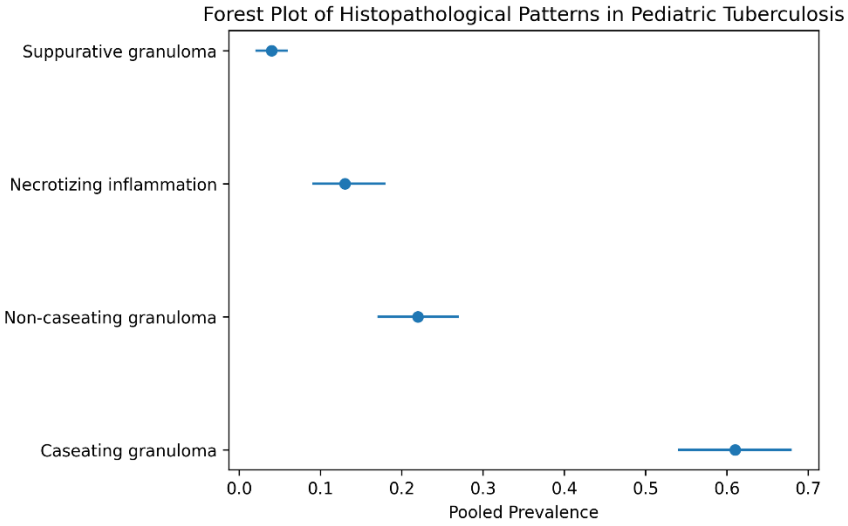

Figure 2. Forest plot of pooled prevalence of histopathological patterns in pediatric tuberculosis; The forest plot illustrates pooled prevalence estimates of major histopathological patterns identified in pediatric tuberculosis across included studies. Caseating granulomas demonstrated the highest pooled prevalence, followed by non-caseating granulomas, necrotizing inflammation, and suppurative granulomas. Horizontal lines represent 95% confidence intervals, indicating inter-study variability in reported histological findings.

DISCUSSION

This systematic review and meta-analysis synthesizes global evidence on the diagnostic utility and histopathological spectrum of pediatric tuberculosis, highlighting the continued importance of tissue examination in the diagnosis of extrapulmonary and paucibacillary disease. The analysis demonstrated that caseating granulomas remain the predominant histological pattern, accounting for approximately 61% of pediatric TB specimens, followed by non-caseating granulomas and necrotizing inflammation. These findings reinforce classical descriptions of TB pathology and align with earlier pediatric studies that identified caseation as the most characteristic morphological feature of tuberculous inflammation [15].

The predominance of lymph node biopsies observed in this review reflects the high burden of tuberculous lymphadenitis in children and the frequent need for tissue diagnosis in extrapulmonary disease. Similar observations were reported by Marais et al., who highlighted lymphadenopathy as one of the most common manifestations of pediatric TB, often requiring histopathological confirmation due to low microbiological yield [16]. Furthermore, studies from high-burden settings have consistently demonstrated that granulomatous lymphadenitis with caseous necrosis strongly correlates with TB diagnosis in children, particularly when supported by clinical and radiological findings [17].

Despite its diagnostic value, histopathology alone has inherent limitations. The pooled sensitivity of Ziehl–Neelsen staining in this analysis was 38%, consistent with previous reports indicating low bacillary detection

in pediatric tissue samples due to the paucibacillary nature of childhood TB [18]. This limitation is especially evident in central nervous system and bone TB, where poorly formed granulomas and sparse bacilli are common. Gupta et al. similarly reported that AFB detection in pediatric lymph node biopsies was low, emphasizing that absence of bacilli does not exclude TB in appropriate clinical contexts [19].

The review also demonstrated considerable morphological variability, including non-caseating granulomas and necrotizing inflammation without well-formed granulomas. Such patterns can overlap with other granulomatous diseases, including sarcoidosis, fungal infections, and atypical mycobacterial infections, creating potential diagnostic challenges. Previous studies have underscored the importance of clinicopathological correlation and adjunct laboratory testing in differentiating these entities [20]. This variability highlights the need for standardized histopathological reporting and awareness of atypical presentations in pediatric TB.

Importantly, the meta-analysis confirmed that adjunct diagnostic techniques substantially improve diagnostic yield. Immunohistochemistry and molecular assays, particularly PCR-based methods and GeneXpert, demonstrated higher positivity rates compared with conventional staining. These findings are consistent with evidence showing that molecular tests can detect mycobacterial DNA even in paucibacillary tissue specimens, thereby enhancing diagnostic accuracy and enabling earlier treatment initiation [21]. The pooled sensitivity increased to 88% when histopathology was combined with molecular methods, supporting current recommendations for integrated diagnostic approaches.

From a clinical perspective, early and accurate diagnosis of pediatric TB is critical to prevent disease progression and long-term complications. Histopathology provides rapid morphological evidence of TB and may guide early treatment decisions in resource-limited settings where molecular testing is not universally available. However, reliance on morphology alone may lead to underdiagnosis or misdiagnosis in atypical cases. Therefore, multidisciplinary diagnostic strategies integrating clinical evaluation, imaging, histopathology, and molecular testing are essential to optimize pediatric TB care [22].

The findings of this review also have implications for pathology practice. Awareness of the broad histopathological spectrum of pediatric TB and the limitations of AFB detection is crucial for accurate interpretation. Incorporation of ancillary techniques, improved biopsy sampling, and close communication between clinicians and pathologists may further enhance diagnostic confidence and patient outcomes.

Strengths of the Study

This review provides a comprehensive synthesis of global evidence focusing specifically on pediatric populations, incorporates meta-analytic estimation of diagnostic performance, and evaluates a wide range of tissue sites and histopathological patterns.

Limitations

The study is limited by heterogeneity among included studies, differences in diagnostic reference standards, and variability in histopathological reporting. Additionally, data on molecular adjuncts were not uniformly available across all studies, potentially influencing pooled estimates.

Overall, this systematic review confirms that histopathology remains a cornerstone in the diagnosis of pediatric tuberculosis, particularly in extrapulmonary disease. Nevertheless, morphological variability and limited bacillary detection highlight the necessity of integrated diagnostic strategies combining histopathology with molecular methods to achieve optimal diagnostic accuracy.

CONCLUSION

This systematic review and meta-analysis demonstrate that histopathology remains a vital diagnostic modality in pediatric tuberculosis, particularly for extrapulmonary and paucibacillary disease where microbiological confirmation is often limited. Caseating granulomas were the most prevalent histopathological finding, although considerable morphological variability was observed across tissue types. The low sensitivity of acid-fast bacilli detection highlights the limitations of conventional staining methods and underscores the importance of adjunct diagnostic techniques. Integration of histopathology with molecular assays significantly enhances diagnostic accuracy and should be incorporated into routine pediatric TB diagnostic algorithms. Strengthening multidisciplinary diagnostic approaches and standardizing histopathological reporting may further improve early detection and clinical outcomes in children with tuberculosis.

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