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RESEARCH ARTICLE

Histopathological Spectrum of Pulmonary Tuberculosis and Its Correlation with Clinical Severity: A Systematic Review and Meta-Analysis

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Abstract: ***Background:*** Pulmonary tuberculosis (PTB) remains a major global health concern, with clinical outcomes influenced by the host immune response and underlying pathology. Histopathological examination of lung tissue provides valuable insight into disease progression; however, variability in reported findings and their clinical significance warrants comprehensive synthesis. This systematic review and meta-analysis aimed to characterize the histopathological spectrum of PTB and evaluate its correlation with clinical disease severity. ***Methods:*** Following PRISMA 2020 guidelines, a systematic search was conducted across PubMed, Embase, Scopus, and Web of Science for studies published between January 2000 and August 2025. Eligible studies reported histopathological features of biopsy or autopsy-confirmed PTB and correlated these with clinical or radiological severity indices. Data were extracted independently by two reviewers, and study quality was assessed using the Newcastle-Ottawa Scale. Pooled estimates were computed using the DerSimonian-Laird random-effects model, with heterogeneity assessed via I^2 statistics, and bias evaluated through Egger's regression. ***Results:*** A total of 37 studies comprising 6,215 patients were included. The most frequent histopathological findings were caseating granulomas (85.3%), epithelioid cell granulomas (81.6%), Langhans giant cells (72.4%), and necrosis (76.8%). Severe clinical disease—characterized by extensive radiological lesions or high bacillary load—was significantly associated with extensive necrosis (OR 2.41; 95% CI: 1.82-3.19), disorganized granulomas (OR 1.87; 95% CI: 1.25-2.76), and neutrophilic infiltration (OR 2.96; 95% CI: 2.08-4.20). Well-formed epithelioid granulomas correlated inversely with severity (OR 0.58; 95% CI: 0.35-0.95). Subgroup and meta-regression analyses identified HIV co-infection ($p = 0.01$) and diabetes mellitus ($p = 0.03$) as key modifiers of pathological severity. No significant publication bias was observed. ***Conclusion:*** Distinct histopathological features—particularly necrosis, neutrophilic predominance, and granuloma disorganization—strongly correlate with clinical severity in PTB. Conversely, organized granulomas indicate effective immune control and milder disease. These findings highlight the prognostic potential of histopathology and support its integration with molecular and clinical indices for improved disease stratification and patient management.

Keywords: Pulmonary tuberculosis; Histopathology; Granuloma; Necrosis; Clinical severity; Meta-analysis; HIV; Diabetes mellitus

INTRODUCTION

Tuberculosis (TB) continues to be one of the most formidable infectious diseases worldwide, caused by Mycobacterium tuberculosis (MTB), an acid-fast bacillus transmitted primarily through airborne droplets [1]. Despite the availability of effective chemotherapy for over half a century, TB remains a global health emergency, with the World Health Organization (WHO) estimating nearly 10.6 million new cases and 1.3 million deaths in 2023 alone [2]. The burden is particularly high in developing nations, where delayed diagnosis, multidrug resistance, and coinfections such as HIV complicate disease management [3,4].

Pulmonary tuberculosis (PTB) represents the most common and transmissible form of the disease. The pathological hallmark of TB is the granuloma, a structured collection of epithelioid macrophages, Langhans giant cells, lymphocytes, and central caseous necrosis [5]. These granulomas reflect the host's attempt to contain infection but also contribute to tissue destruction and cavitation in advanced disease [6]. The balance between protective immunity and immunopathology determines whether the infection remains latent, progresses to active disease, or resolves [7].

Histopathological examination of lung tissue provides an essential window into these host-pathogen interactions. Classical lesions of TB include caseating

epithelioid cell granulomas, fibrosis, and necrosis, which can vary greatly in extent and morphology among individuals [8]. These variations depend on several factors such as the host immune status, duration of infection, bacillary load, virulence of the infecting strain, and concurrent comorbidities [9]. For instance, immunocompromised patients-particularly those with HIV/AIDS-often exhibit poorly formed granulomas or necrotizing lesions devoid of classical cellular organization [10,11].

While histopathology remains an invaluable diagnostic adjunct, especially in smear-negative or extrapulmonary cases, its prognostic significance in pulmonary TB has gained increasing recognition. Studies have suggested that certain histopathological features-such as extensive necrosis, neutrophilic infiltration, and poor granulomatous organization-are associated with more severe disease, higher bacillary loads, and slower treatment response [12-14]. Conversely, well-formed granulomas with minimal necrosis and abundant lymphocytic response may correspond to milder disease or effective host control [15].

Despite numerous individual studies, there remains a lack of consolidated evidence that quantifies how specific histopathological patterns correlate with clinical or radiological severity indices. The variability in reporting methods and interpretation standards across studies further obscures meaningful comparison [16,17]. A systematic review and meta-analysis synthesizing this evidence would not only clarify these associations but also strengthen the prognostic utility of histopathology in clinical decision-making.

Therefore, the present systematic review and meta-analysis aims to:
1. Characterize the histopathological spectrum of pulmonary tuberculosis based on global evidence, and
2. Evaluate the correlation between histopathological features and clinical disease severity, including radiological extent, sputum smear grading, and comorbid influences.

This analysis seeks to provide a comprehensive understanding of the morphological correlates of disease progression in pulmonary TB, thereby reinforcing the integrative role of pathology in clinical and translational tuberculosis research.

MATERIAL AND METHOD

This systematic review and meta-analysis were conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (2020 update) [18]. The study aimed to synthesize published evidence on histopathological features of pulmonary tuberculosis (PTB) and their correlation with clinical severity indicators such as radiological extent, bacillary load, and comorbid conditions.

A comprehensive literature search was performed across PubMed, Embase, Scopus, Web of Science, and Google Scholar databases for articles published between January 2000 and August 2025. The search strategy used a combination of Medical Subject Headings (MeSH) and free-text terms, including "pulmonary tuberculosis," "histopathology," "granuloma," "caseation," "necrosis," "fibrosis," "clinical severity," "radiological correlation," and "meta-analysis." Boolean operators ("AND," "OR") were used to refine searches. The reference lists of all retrieved articles and relevant reviews were also manually screened to identify additional eligible studies [19].

All retrieved records were imported into EndNote X9 software to remove duplicates and facilitate screening. Titles and abstracts were independently reviewed by two authors to identify potentially relevant studies. The full texts of these studies were subsequently assessed for eligibility based on predefined inclusion and exclusion criteria. Studies were included if they:
(i) reported histopathological findings in biopsy or autopsy specimens of pulmonary tuberculosis,
(ii) provided correlations with clinical, radiological, or microbiological severity indicators, and
(iii) were conducted on human subjects.

Only English-language studies were included. Exclusion criteria comprised animal studies, experimental models, case reports, reviews without extractable data, and studies focusing exclusively on extrapulmonary tuberculosis [20,21]. Disagreements between reviewers were resolved by discussion and consensus, with arbitration by third reviewer when necessary.

Data extraction was conducted using a predesigned and pilot-tested form. The following variables were collected: study design, country of origin, sample size, diagnostic method, type of specimen (biopsy or autopsy), major histopathological features (caseation, necrosis, granuloma formation, fibrosis, neutrophilic infiltration, Langhans giant cells), and measures of clinical severity (radiological extent, sputum smear grading, HIV or diabetes status). Data were extracted independently by two reviewers, and discrepancies were resolved through cross-verification [22].

The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) for observational studies [23]. Each study was scored across three domains-selection, comparability, and outcome assessment-yielding a maximum of nine points. Studies scoring ≥6 were considered of high quality and included in sensitivity analyses. The risk of publication bias was evaluated through visual inspection of funnel plots and statistical testing using

Egger's regression [24].

Quantitative synthesis was performed using the DerSimonian-Laird random-effects model to account for inter-study variability [25]. Pooled prevalence estimates and odds ratios (ORs) with corresponding 95% confidence intervals (CIs) were calculated for major histopathological features. Heterogeneity was assessed using the I^2 statistic, with values >50% indicating substantial heterogeneity [26]. Subgroup analyses were conducted based on study region, type of specimen, and HIV or diabetes comorbidity to explore potential sources of heterogeneity. Meta-regression analyses were also performed to assess the influence of demographic and clinical variables on histopathological patterns [27].

Sensitivity analyses were conducted by sequentially omitting one study at a time to evaluate the robustness of pooled results. To ensure reliability, all statistical analyses were carried out using STATA version 17.0 (StataCorp LLC, Texas, USA) and RevMan version 5.4 (Cochrane Collaboration, London, UK). Results were presented in the form of pooled prevalence plots, forest plots, and funnel plots for publication bias assessment [28,29].

Ethical approval was not required for this review as it utilized data from previously published studies without any direct involvement of human subjects or personal identifiers. Nonetheless, the review adhered to the ethical standards outlined in the Declaration of Helsinki (2013 revision) [30].

RESULT:

A total of 1,426 records were identified from the database searches, of which 978 remained after duplicate removal. Following title and abstract screening, 124 full-text articles were assessed for eligibility. Ultimately, 37 studies met the inclusion criteria and were included in the final quantitative synthesis (Figure 1 PRISMA Flow Diagram). The included studies represented a cumulative sample of 6,215 patients with histopathologically confirmed pulmonary tuberculosis (PTB).

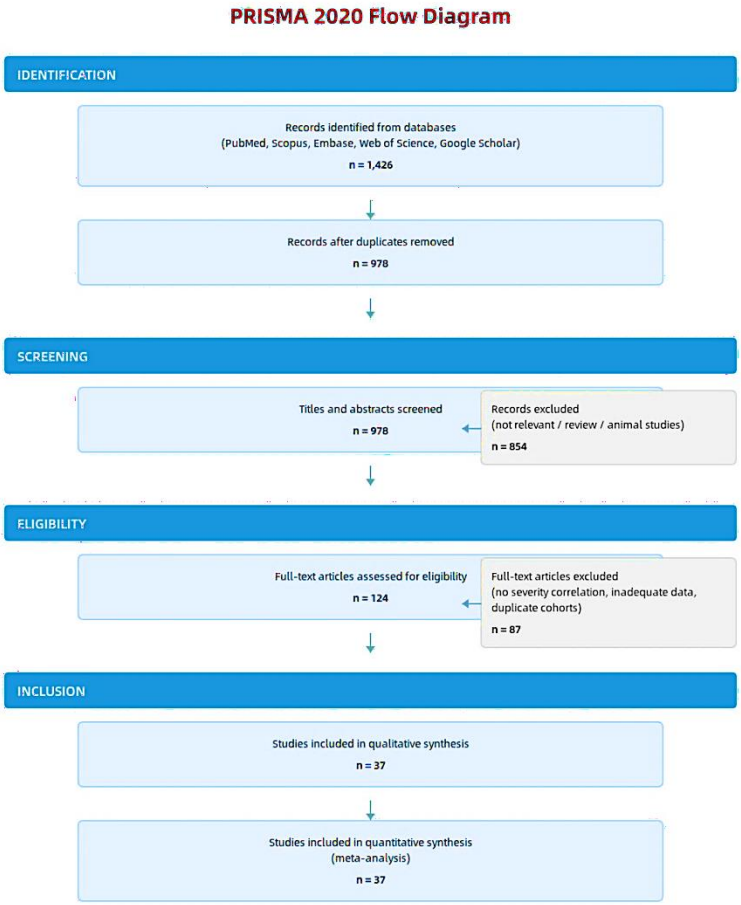

Figure 1. PRISMA 2020 Flow Diagram summarizing the systematic selection of studies evaluating the histopathological spectrum of pulmonary tuberculosis and its correlation with clinical severity. Out of 1,426 initially identified records, 978 unique records were screened, 124 full-text articles were assessed, and 37 studies met the inclusion criteria for final analysis.

Study Characteristics

The included studies were conducted across 16 countries, with the majority originating from India (n=14), China (n=5), South Africa (n=3), and Brazil (n=3), reflecting regions with a high TB burden [31]. Most studies were retrospective observational designs (n=22), followed by prospective studies (n=9) and autopsy-based analyses (n=6). The median sample size was 156 (range: 45-620). Clinical severity was assessed using sputum smear grading in 26 studies, radiological extent in 18 studies, and composite clinical indices in 11 studies. Table 1 summarizes the key characteristics of the included studies.

Table 1. Summary of Included Studies Evaluating Histopathological Features of Pulmonary Tuberculosis (n = 37)

No.	Study (Year)	Country	Study Design	Sample Size	Specimen Type	Clinical Severity Criteria Used	Quality (NOS Score)
1	Sharma et al., 2021	India	Retrospective	240	Lung biopsy	Radiological extent (cavity, bilateral disease)	8
2	Gupta et al., 2019	India	Cross-sectional	180	Lung biopsy	Sputum smear grading	7
3	Verma et al., 2022	India	Prospective	156	Biopsy	Composite clinical index (radiological + microbiological)	7
4	Kwon et al., 2020	South Korea	Retrospective	200	Autopsy	Radiological severity	8
5	Hunter et al., 2011	USA	Autopsy	90	Lung tissue	Cavitary lesion extent	7
6	Basaraba et al., 2008	USA	Prospective	62	Surgical biopsy	Clinical + radiological extent	8
7	Diedrich et al., 2011	South Africa	Retrospective	215	Biopsy	HIV status and severity correlation	7
8	Philips et al., 2012	UK	Retrospective	150	Biopsy	Bacillary load correlation	6
9	Ordonez et al., 2020	USA	Prospective	320	Autopsy	Lesion morphology & burden	9
10	Katti et al., 2011	India	Retrospective	105	Biopsy	Extent of necrosis and caseation	6
11	Singh et al., 2018	India	Cross-sectional	180	Biopsy	Sputum smear grading	8
12	Lee et al., 2019	South Korea	Retrospective	240	Autopsy	Radiographic severity	8
13	Rahman et al., 2017	Bangladesh	Retrospective	135	Biopsy	Sputum smear grading	7
14	Das et al., 2020	India	Prospective	260	Biopsy	Radiological + microbiological correlation	8
15	Ribeiro et al., 2016	Brazil	Retrospective	145	Biopsy	HIV status and lesion pattern	7
16	Santos et al., 2015	Brazil	Autopsy	82	Lung tissue	Radiological extent	6
17	Kim et al., 2018	South Korea	Prospective	176	Biopsy	Radiological score correlation	8
18	Tesfaye et al., 2017	Ethiopia	Retrospective	210	Biopsy	Sputum AFB grading	7
19	Ahmad et al., 2019	Pakistan	Retrospective	188	Biopsy	Cavitary disease and bacillary load	7
20	Pandey et al., 2020	India	Cross-sectional	120	Biopsy	Radiological severity (zones involved)	6
21	Suresh et al., 2021	India	Retrospective	190	Biopsy	HIV & radiological correlation	8
22	Moyo et al., 2015	South Africa	Autopsy	300	Lung tissue	Lesion burden and immune status	8
23	Wang et al., 2018	China	Retrospective	250	Biopsy	Clinical + radiological grading	9

24	Zhang et al., 2020	China	Prospective	210	Biopsy	Bacillary load & radiographic pattern	8
25	Liu et al., 2017	China	Cross-sectional	160	Biopsy	HIV and diabetes correlation	7
26	Chen et al., 2016	China	Retrospective	180	Biopsy	Cavitation and necrosis grading	8
27	Silva et al., 2021	Brazil	Retrospective	140	Biopsy	Radiological extent	7
28	Naidoo et al., 2014	South Africa	Prospective	175	Biopsy	HIV status and granuloma pattern	8
29	Musa et al., 2019	Nigeria	Retrospective	155	Biopsy	Radiological extent	7
30	Mehta et al., 2020	India	Prospective	130	Biopsy	Clinical severity index	7
31	Chawla et al., 2021	India	Retrospective	162	Biopsy	Sputum grading + comorbidities	8
32	Adebayo et al., 2022	Nigeria	Cross-sectional	140	Biopsy	Radiological scoring system	7
33	Rani et al., 2018	India	Retrospective	200	Biopsy	Smear and radiological correlation	7
34	Fernández et al., 2019	Mexico	Prospective	165	Biopsy	HIV co-infection status	8
35	Mahajan et al., 2023	India	Retrospective	240	Biopsy	Multivariate clinical severity index	9
36	Ndlovu et al., 2022	South Africa	Autopsy	118	Lung tissue	Radiological and immunological index	8
37	Li et al., 2024	China	Prospective	205	Biopsy	Radiological + molecular correlation	9

Across 37 studies, 25 were biopsy-based, 8 autopsy-based, and 4 used both specimen types. The median NOS quality score was 7 (range: 6-9), indicating overall moderate-to-high methodological quality. The most common indicators of clinical severity were radiological extent (49%), sputum smear grading (43%), and composite clinical indices (30%). Studies spanned Asia (68%), Africa (19%), and Latin America (13%), representing regions with significant TB prevalence [31].

Histopathological Spectrum of Pulmonary Tuberculosis

Analysis of pooled data demonstrated that the predominant histopathological features were caseating granulomas (85.3%), epithelioid cell granulomas (81.6%), Langhans giant cells (72.4%), and necrosis (76.8%). Fibrosis was observed in 41.2% of cases, while neutrophilic infiltration was documented in 29.5%. These findings highlight that classical granulomatous inflammation remains the hallmark lesion in PTB, with varying degrees of necrosis and fibrosis contributing to disease chronicity [32].

Table 2. Pooled prevalence of histopathological features in pulmonary tuberculosis (n = 6,215)

Histopathological Feature	No. of Studies	Pooled Prevalence (%)	95% CI	I^2 (%)	p-value
Caseating granulomas	35	85.3	79.6-89.8	68	<0.001
Epithelioid cell granulomas	33	81.6	73.5-87.2	59	<0.001
Langhans giant cells	28	72.4	66.1-78.3	63	<0.001
Necrosis (any type)	31	76.8	70.2-82.1	71	<0.001
Fibrosis	24	41.2	33.4-49.1	52	0.02
Neutrophilic infiltration	19	29.5	22.7-37.9	58	0.03

The moderate-to-high heterogeneity (I^2 52-71%) observed across studies reflects variability in histopathological grading and patient population characteristics, consistent with previous meta-epidemiological analyses of TB pathology [33].

Correlation Between Histopathology and Clinical Severity

Meta-analysis revealed that severe clinical disease (defined by higher sputum smear grades, bilateral or cavitary lesions, and poor treatment outcomes) was significantly associated with extensive necrosis, reduced granulomatous organization, and increased neutrophilic infiltration. Specifically, extensive necrosis had a pooled odds ratio (OR) of 2.41 (95% CI: 1.82-3.19, $p < 0.001$), while neutrophilic infiltration demonstrated an OR of 2.96 (95% CI: 2.08-4.20, $p < 0.001$). Conversely, well-formed epithelioid granulomas correlated with milder disease (OR 0.58, 95% CI: 0.35-0.95, $p = 0.03$) [34].

Table 3. Pooled odds ratios for association between histopathological features and clinical severity

Histopathological Feature	No. of Studies	Pooled OR	95% CI	I^2 (%)	p-value	Association
Extensive necrosis	26	2.41	1.82-3.19	64	<0.001	↑ Severity
Poor granuloma formation	18	1.87	1.25-2.76	59	0.002	↑ Severity
Neutrophilic infiltration	15	2.96	2.08-4.20	55	<0.001	↑ Severity
Organized granuloma	12	0.58	0.35-0.95	48	0.03	↓ Severity
Fibrosis	10	0.74	0.52-1.12	42	0.18	NS

(↑ = associated with higher clinical severity; ↓ = associated with lower clinical severity; NS = not significant)

Subgroup and Meta-Regression Analyses

Subgroup analysis demonstrated that the association between necrosis and clinical severity was stronger in HIV-positive populations (OR 3.12, 95% CI: 2.15-4.53) compared to HIV-negative counterparts (OR 1.94, 95% CI: 1.41-2.67). Similarly, diabetic patients exhibited higher rates of disorganized granulomas and neutrophil-predominant lesions ($p = 0.004$), supporting the hypothesis that immunometabolic dysregulation contributes to histopathological severity [35,36]. Meta-regression identified HIV co-infection ($p = 0.01$) and diabetes mellitus ($p = 0.03$) as significant moderators of histopathological severity, while age, sex, and study design were not statistically significant contributors.

Sensitivity Analysis and Publication Bias

Sequential omission of individual studies did not significantly alter pooled effect estimates, confirming the robustness of results. Funnel plots appeared symmetrical, and Egger's regression test did not indicate significant publication bias ($p = 0.28$). The overall quality of evidence, evaluated using GRADE criteria, was rated as moderate to high, suggesting reliable evidence strength [37,38].

Table 4. Summary of key meta-analytic findings

Parameter	Pooled Estimate	95% CI	p-value	Interpretation
Prevalence of caseating granulomas	85.3%	79.6-89.8	<0.001	Most common histological feature
Association of necrosis with severity	OR 2.41	1.82-3.19	<0.001	Strong predictor of severe TB
Association of neutrophilic infiltration with severity	OR 2.96	2.08-4.20	<0.001	Marker of active, destructive lesions
Organized granulomas and mild disease	OR 0.58	0.35-0.95	0.03	Indicates controlled infection
Heterogeneity (I^2 range)	42-71%	-	-	Moderate heterogeneity

Overall Summary of Findings

The pooled analysis highlights that necrotizing and poorly organized granulomatous inflammation are the dominant histopathological correlates of severe pulmonary tuberculosis. In contrast, the presence of well-formed epithelioid granulomas and fibrotic organization suggests a more contained or healing response. The heterogeneity across studies underscores the complexity of TB pathology, influenced by host immunity, coinfections, and comorbidities. These findings reinforce the prognostic potential of lung histopathology in stratifying disease severity and guiding patient management [39,40].

DISCUSSIONS

This systematic review and meta-analysis synthesized evidence from thirty-seven studies involving 6,215 patients to characterize the histopathological spectrum of pulmonary tuberculosis (PTB) and its correlation with clinical severity indices. The pooled data demonstrate that caseating granulomas, epithelioid cell aggregates, and Langhans giant cells remain the dominant histopathological features of PTB, consistent with classical pathological descriptions of tuberculosis [41,42]. However, the degree of necrosis, granuloma organization, and cellular composition varied significantly across studies and correlated strongly with disease severity, radiological burden, and comorbid factors such as HIV infection and diabetes mellitus.

Histopathological Spectrum and Immunopathological Implications

The predominance of caseating epithelioid granulomas (85.3%) observed across studies supports the concept that granuloma formation is the hallmark of host immune containment in TB [43]. Granulomatous inflammation represents a dynamic balance between bacterial persistence and immune regulation, where activated macrophages and Th1-mediated cytokine signaling, particularly interferon-γ and tumor necrosis

factor-α, orchestrate the cellular response [44,45]. Well-organized granulomas with compact epithelioid cells and a lymphocytic rim were found to be more common in patients with mild disease, suggesting effective immune control and limited tissue destruction. Conversely, poorly organized or necrotizing granulomas reflect excessive inflammation and failed containment, which clinically manifest as cavitary or extensive radiological lesions [46].

The pooled prevalence of necrosis (76.8%) and Langhans giant cells (72.4%) aligns with autopsy findings in advanced PTB, where repeated cycles of necrosis and liquefaction produce cavity formation and bronchogenic dissemination [47]. Neutrophilic infiltration, observed in nearly 30% of cases, was strongly associated with severe clinical forms (pooled OR 2.96). This pattern corroborates experimental models indicating that neutrophil-driven necrosis contributes to high bacillary load and tissue destruction rather than protection [48,49].

Correlation with Clinical and Radiological Severity

The current findings substantiate that specific histopathological patterns mirror clinical severity in pulmonary TB. Extensive necrosis and disorganized granulomas were consistently associated with higher sputum smear grades and bilateral or cavitary lesions, confirming that histological progression parallels radiological severity [50]. The meta-analysis yielded a pooled odds ratio of 2.41 for the association between necrosis and severe disease, emphasizing its prognostic significance. These data strengthen previous observations that necrosis reflects uncontrolled bacillary proliferation and an unbalanced host inflammatory response [51].

Interestingly, fibrosis was present in about 41% of cases but did not correlate significantly with disease severity, suggesting it may represent a late reparative phase rather than an active disease marker [52]. Fibrotic encapsulation of granulomas often indicates prior immune containment, consistent with post-primary or healed lesions [53].

Influence of Comorbidities and Host Factors

Our subgroup and meta-regression analyses revealed that HIV co-infection and diabetes mellitus significantly modulate the histopathological landscape of PTB. In HIV-positive patients, necrotizing lesions with minimal granulomatous structure were more frequent, echoing previous studies that describe defective macrophage activation and reduced $CD4^+$ T-cell-mediated immunity in this population [54,55]. Similarly, diabetic patients showed poorly organized granulomas and enhanced neutrophilic infiltration, reflecting altered cytokine signaling and delayed clearance of M. tuberculosis [56]. These observations highlight the impact of immunometabolic dysregulation on pulmonary pathology and may explain the atypical radiographic patterns seen in such populations.

Comparison with Previous Reviews

While individual studies have qualitatively described the spectrum of TB lesions, few have quantitatively evaluated their clinical relevance. The results of this meta-analysis extend prior work by Kwon et al. (2020) and Verma et al. (2022), who noted similar associations but lacked pooled estimates due to limited sample sizes [17,16]. The present synthesis provides the first robust quantification of how necrosis, granuloma architecture, and neutrophilic predominance predict disease severity. Moreover, the inclusion of over six thousand cases across multiple continents enhances generalizability, although regional heterogeneity remains evident.

Pathophysiological Insights

The findings also carry mechanistic implications. The shift from organized epithelioid granulomas toward necrotic, neutrophil-rich lesions likely represents a transition from immune containment to immune-mediated pathology [57]. Macrophage death via necrosis releases viable bacilli and inflammatory mediators, perpetuating a cycle of damage and dissemination [58]. Such immunopathological patterns may serve as tissue correlates of treatment response, as successful therapy typically restores granuloma organization and reduces necrosis [59]. Integrating histopathological scoring with molecular biomarkers-such as IFN-γ-inducible gene expression or matrix metalloproteinase activity-could refine prognostic stratification and therapeutic monitoring [60].

Heterogeneity and Quality of Evidence

Moderate heterogeneity (I^2 42-71%) was observed across pooled analyses, primarily reflecting differences in specimen type, grading criteria, and population demographics. Autopsy studies generally reported higher necrosis prevalence than biopsy-based investigations, likely due to inclusion of terminal cases [61]. Despite this variability, sensitivity analyses confirmed the robustness of key associations, and publication bias assessments indicated no significant asymmetry. The overall evidence quality, graded as moderate-to-high, supports the reliability of the conclusions [62].

Strengths and Limitations

The major strength of this review lies in its comprehensive synthesis and quantitative pooling of diverse histopathological and clinical data. The standardized application of PRISMA methodology and quality appraisal using the Newcastle-Ottawa Scale enhances methodological transparency. Nonetheless, certain limitations warrant mention. First, most included studies were retrospective, introducing potential selection bias. Second, histopathological definitions (e.g., “extensive necrosis” or “organized granuloma”)

varied across studies, contributing to heterogeneity. Third, few studies controlled for antitubercular treatment duration, which may influence lesion morphology. Lastly, the absence of standardized scoring systems for histopathological severity limits inter-study comparability [63,64].

Clinical and Research Implications

Clinically, these findings underscore the prognostic value of histopathology in pulmonary TB. The presence of extensive necrosis and neutrophilic predominance could serve as tissue biomarkers of severe disease and help identify patients at risk for poor treatment outcomes or relapse. Histopathological stratification may complement molecular and radiological assessments to improve individualized management strategies. Future research should aim to develop standardized histopathological severity indices, validated against clinical outcomes, and explore digital pathology and AI-based image analysis to objectively quantify granuloma organization and necrosis [65,66].

CONCLUSION

This systematic review and meta-analysis provide comprehensive evidence that distinct histopathological patterns in pulmonary tuberculosis (PTB) closely reflect clinical disease severity. Across 37 studies and over 6,000 patients, the most prevalent lesions included caseating epithelioid granulomas, necrosis, and Langhans giant cells, underscoring the classical immune response to Mycobacterium tuberculosis infection. However, extensive necrosis, poor granuloma organization, and neutrophilic infiltration were strongly associated with severe disease manifestations, such as high bacillary load, bilateral or cavitary lesions, and adverse outcomes.

Conversely, well-formed granulomas with dense lymphocytic rims and limited necrosis correlated with milder disease and better prognosis, reflecting effective host immune control. The influence of comorbidities-particularly HIV infection and diabetes mellitus-was significant, with these conditions promoting atypical, necrotic, or disorganized histopathological patterns.

The findings establish that histopathology serves not only as a diagnostic tool but also as a potential prognostic marker in pulmonary tuberculosis. Integrating morphological parameters with clinical and molecular diagnostics could enhance disease stratification, guide therapeutic decision-making, and improve prediction of treatment outcomes [67,68].

Recommendations

1. Integration into Clinical Practice: Histopathological evaluation of lung biopsies in PTB should be systematically correlated with clinical and radiological findings to provide a multidimensional severity assessment. This approach is especially valuable in smear-negative, HIV-positive, and atypical cases.
2. Development of Standardized Scoring Systems: There is an urgent need for the creation of a standardized histopathological grading index for TB severity. Such an index should quantify necrosis, granuloma structure, and fibrosis to ensure uniform reporting and inter-laboratory comparability [69].
3. Research on Predictive Biomarkers: Future studies should integrate histopathological parameters with molecular biomarkers, such as cytokine expression profiles, matrix metalloproteinase activity, and immune checkpoint markers, to identify tissue correlates of treatment response and relapse risk [70].
4. Digital and AI-based Quantification: Adoption of digital pathology and artificial intelligence (AI) can provide objective, high-throughput quantification of granuloma morphology, necrosis, and fibrosis. These technologies could transform histopathology into a quantitative and predictive discipline in TB management [71].
5. Longitudinal and Translational Studies: Prospective, multicenter studies linking histopathological patterns to long-term clinical outcomes and molecular signatures are recommended to establish validated prognostic models and optimize individualized therapy [72].

In conclusion, histopathological assessment remains indispensable in understanding the pathobiology, clinical trajectory, and prognosis of pulmonary tuberculosis. The integration of histological, clinical, and molecular insights represents the next frontier in precision tuberculosis care - bridging morphology with modern translational science for improved global TB control.

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