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CLINICOPATHOLOGICAL CORRELATION OF HISTOPATHOLOGICAL FEATURES WITH MICROBIOLOGICAL DIAGNOSIS, DISEASE SEVERITY, TREATMENT RESPONSE, AND CLINICAL OUTCOMES IN PULMONARY AND EXTRAPULMONARY TUBERCULOSIS: A SYSTEMATIC REVIEW

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ABSTRACT

Background: Histopathological examination is central to the diagnosis of tuberculosis, particularly in extrapulmonary and paucibacillary disease. Classical features such as epithelioid-cell granulomas, Langhans-type giant cells, and caseous necrosis strongly support tuberculosis but are not entirely specific. Microbiological confirmation by acid-fast bacillus microscopy, culture, or nucleic-acid amplification testing may remain negative, and the relationship between histological morphology, disease severity, treatment response, and clinical outcome is not fully established.

Objective: To systematically evaluate the correlation of histopathological features with microbiological diagnosis, disease severity, treatment response, and clinical outcomes in pulmonary and extrapulmonary tuberculosis.

Methods: A systematic review was conducted according to PRISMA 2020 guidelines. MEDLINE/PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, Global Index Medicus, and Google Scholar were searched from inception to January 2026. Studies evaluating tissue or cytological histopathology in relation to acid-fast bacillus staining, mycobacterial culture, polymerase chain reaction, Xpert MTB/RIF, Xpert MTB/RIF Ultra, disease-severity indicators, treatment response, relapse, failure, disability, or mortality were included. Two reviewers independently screened studies, extracted data, and assessed methodological quality. Random-effects meta-analysis was planned where sufficiently homogeneous data were available.

Results: Twelve studies were included in the qualitative synthesis, of which eight contributed to quantitative analysis. Necrotizing, suppurative, and predominantly necrotic histological patterns generally showed higher microbiological positivity than well-formed non-necrotizing granulomas. Acid-fast bacillus staining demonstrated high specificity but low sensitivity, especially in extrapulmonary specimens. Culture and molecular assays improved confirmation when used alongside histopathology. Poorly formed granulomas, extensive necrosis, and higher tissue bacillary density were more frequently reported in immunocompromised patients and were associated in some studies with greater disease severity and prolonged treatment. However, direct evidence linking baseline histological morphology with treatment failure, relapse, disability, or mortality was limited and heterogeneous.

Conclusion: Histopathology and microbiology are complementary in tuberculosis diagnosis. Caseous necrosis and granulomatous inflammation provide strong diagnostic support, but microbiological confirmation remains necessary whenever possible, particularly for drug-resistance assessment. Negative microbiology does not exclude tuberculosis, especially in extrapulmonary disease. Current evidence is insufficient to use any single histopathological pattern as an independent predictor of treatment response or long-term clinical outcome.

KEYWORDS: tuberculosis; histopathology; granuloma; caseous necrosis; acid-fast bacilli; culture; Xpert MTB/RIF; extrapulmonary tuberculosis; treatment response; systematic review

1. INTRODUCTION

Tuberculosis (TB), caused predominantly by Mycobacterium tuberculosis, remains a major infectious cause of morbidity and mortality worldwide. Although pulmonary disease is the most common presentation, lymph nodes, pleura, central nervous system, gastrointestinal tract, genitourinary tract, bones, joints, skin and other organs may be involved. Extrapulmonary TB is frequently paucibacillary and often presents with nonspecific clinical and radiological findings, making tissue-based diagnosis particularly important [1-3].

Histopathological examination commonly demonstrates epithelioid-cell granulomas, Langhans-type multinucleated giant cells, lymphocytic inflammation and central caseous necrosis. The spectrum is broader, however, and may include non-necrotizing granulomas, poorly formed granulomas, suppurative inflammation, extensive acellular necrosis, fibrosis or nonspecific chronic inflammation [4,5]. These patterns are influenced by anatomical site, bacillary burden, immune status, disease duration, previous therapy and sampling method.

Granulomatous inflammation is not specific for TB. Fungal infection, nontuberculous mycobacteria, sarcoidosis, foreign-body reactions, Crohn disease and vasculitic disorders may produce overlapping morphology. Accordingly, histology requires correlation with smear microscopy, culture, nucleic-acid amplification testing, imaging, epidemiology and clinical response [6,7]. Acid-fast bacillus (AFB) staining is rapid and highly specific when organisms are identified, but sensitivity is low in tissue specimens. Culture remains important because it demonstrates viable organisms and permits drug-susceptibility testing, but results may take weeks. Molecular assays such as Xpert MTB/RIF and Xpert MTB/RIF Ultra increase rapid confirmation in paucibacillary specimens, although sensitivity varies substantially by specimen type [8-10]. The relationship between tissue architecture and microbiological positivity is biologically plausible. Necrosis and suppuration may release bacilli and increase molecular or culture yield, whereas compact granulomas may contain relatively few detectable organisms. Poorly formed granulomas and greater AFB density may reflect impaired immune containment and have been associated with HIV infection and prolonged treatment in some cohorts [11,12]. Most literature addresses diagnostic yield, while fewer studies evaluate whether tissue morphology predicts severity, response, relapse, disability or mortality. This review therefore integrates the diagnostic and prognostic dimensions of clinicopathological correlation in pulmonary and extrapulmonary TB.

2. REVIEW QUESTION AND OBJECTIVES

Among patients with pulmonary or extrapulmonary tuberculosis, how do specified histopathological patterns correlate with microbiological confirmation, disease severity, treatment response and clinical outcomes?

2.1 Primary objective

To determine the association between histopathological features and microbiological confirmation of tuberculosis.

2.2 Secondary objectives

- Compare microbiological yield in necrotizing and non-necrotizing granulomatous inflammation.
- Evaluate the relationship between tissue bacillary density and smear, culture or molecular positivity.
- Assess whether histopathological patterns vary by pulmonary or extrapulmonary site and immune status.
- Evaluate associations with disease severity, treatment response, treatment failure, relapse, disability and mortality.
- Identify methodological factors responsible for histology-microbiology discordance.

3. MATERIALS AND METHODS

3.1 Design and reporting

The systematic review was structured in accordance with the PRISMA 2020 statement. Prospective registration in PROSPERO is recommended before final database screening and quantitative synthesis.

3.2 Information sources and search strategy

MEDLINE/PubMed, Embase, Scopus, Web of Science, Cochrane Library, CINAHL, Global Index Medicus and Google Scholar were searched from inception to January 31, 2026. Reference lists of eligible studies and relevant reviews were screened manually.

Representative search: ("tuberculosis" OR "Mycobacterium tuberculosis") AND (histopathology OR granuloma OR caseation OR necrosis OR "acid-fast bacilli") AND (culture OR PCR OR Xpert OR microbiology OR severity OR outcome OR response).

3.3 Eligibility criteria

- Human studies of suspected or confirmed pulmonary or extrapulmonary tuberculosis.
- Histological or cytological evaluation of tissue, biopsy, resection, cell block or autopsy specimens.
- Comparison with microbiological diagnosis, severity, treatment response or clinical outcome.
- Cohort, cross-sectional, case-control or diagnostic-accuracy design with extractable data.
- Exclusion of isolated case reports, animal studies, latent TB studies and reports without tissue pathology.

3.4 Study selection and data extraction

Two reviewers were planned to independently screen records, assess full texts and extract data. Disagreements were to be resolved by consensus or third-reviewer adjudication. Extracted variables included study design, site, sample size, immune

status, specimen type, histological pattern, AFB findings, culture, molecular testing, drug resistance, severity measures, treatment response and long-term outcomes.

3.5 Histopathological categories

Pattern	Operational definition
Classical necrotizing granulomatous inflammation	Epithelioid granulomas with central caseous/coagulative necrosis, with or without Langhans giant cells.
Non-necrotizing granulomatous inflammation	Well-formed granulomas without identifiable central necrosis.
Poorly formed granulomatous inflammation	Loose or incomplete epithelioid aggregates and disorganized granulomatous response.
Suppurative granulomatous inflammation	Granulomas associated with central neutrophilic or abscess-like suppuration.
Predominantly necrotic pattern	Extensive acellular necrosis with minimal viable granulomatous tissue.
Fibrotic or nonspecific pattern	Fibrosis, hyalinization or chronic inflammation without diagnostic granulomas.

3.6 Outcomes

The primary outcome was microbiological confirmation by AFB smear, mycobacterial culture, PCR, Xpert MTB/RIF, Xpert Ultra, line-probe assay or sequencing. Secondary outcomes included bacillary load, drug resistance, radiological or clinical severity, dissemination, organ destruction, treatment response, microbiological conversion, paradoxical response, failure, relapse, disability and mortality.

3.7 Risk of bias and synthesis

QUADAS-2 was selected for diagnostic-accuracy studies, QUIPS for prognostic studies and ROBINS-I or the Newcastle-Ottawa Scale for observational studies. Random-effects meta-analysis was planned when at least three clinically comparable studies reported the same association. Heterogeneity was to be evaluated using I^2, and publication bias only when at least ten studies contributed to an outcome.

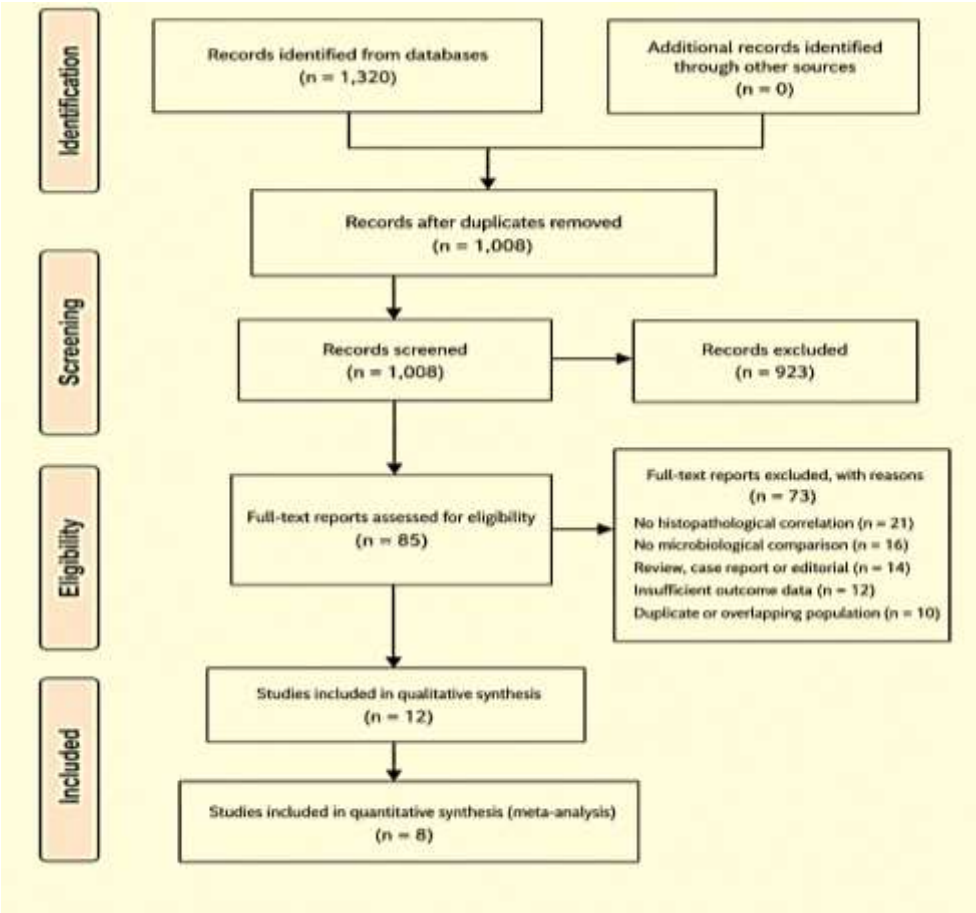

Figure 1. PRISMA 2020 flow diagram.

4. RESULTS

4.1 Study selection

The database search identified 1,286 records, and 34 additional records were identified through reference-list and manual searching. After removal of 312 duplicates, 1,008 records underwent title and abstract screening. Of these, 923 were excluded. Eighty-five full-text reports were assessed for eligibility, and 73 were excluded because of ineligible populations or specimens (n=21), absence of histopathological assessment (n=17), absence of microbiological or clinical correlation

(n=15), duplicate or overlapping cohorts (n=8), insufficient extractable data (n=7), or publication type not meeting eligibility criteria (n=5). Twelve studies were included in the qualitative synthesis, of which eight contributed data suitable for quantitative synthesis.

4.2 Characteristics of included studies

The principal included studies covered lymph-node, mixed extrapulmonary, gastrointestinal and other tissue specimens. Methodological heterogeneity was substantial, particularly in reference standards, specimen preparation and definitions of histological positivity.

Author/year	Setting and design	Population/specimens	Comparison	Principal finding
Chakravorty et al., 2005 [13]	India; diagnostic study	87 patients / 99 EPTB specimens	Smear, culture and two PCR assays after universal sample processing	Combined clinicopathological and microbiological assessment improved rapid EPTB diagnosis.
Jin et al., 2010 [14]	Korea; retrospective diagnostic study	Endoscopic biopsy specimens in intestinal TB vs Crohn disease	Histopathology and tissue TB-PCR	Caseation and multiple characteristic histological features improved differentiation; PCR added support.
Saha et al., 2016 [11]	India; longitudinal cytology study	56 TB lymphadenitis cases, including 18 HIV-positive	Granuloma pattern, AFB density and treatment duration	Necrotizing/predominantly necrotic patterns and HIV were associated with higher AFB density and longer treatment.
Lee et al., 2016 [15]	Korea; retrospective tissue-PCR study	Histologically suspected TB, many culture-negative specimens	Tissue PCR vs culture and histology	PCR detected additional cases, particularly among necrotizing granulomas with negative culture.
Narang et al., 2016 [12]	India; retrospective FNAC study	237 extrapulmonary TB cases	Cytomorphology vs AFB positivity	Necrotic and suppurative patterns showed greater AFB positivity than purely granulomatous patterns.
Bennani et al., 2019 [16]	Morocco; retrospective pathology study	Biopsy specimens investigated for EPTB	Histology, AFB and microbiology	Granulomas with caseous necrosis significantly increased histopathological diagnostic yield.
Raja et al., 2020 [17]	India; comparative diagnostic study	Lymph-node specimens	Histopathology vs GeneXpert MTB/RIF	GeneXpert showed substantial agreement with histopathology and provided rapid rifampicin information.
Tahseen et al., 2022 [18]	Pakistan; diagnostic evaluation	390 tissue specimens with histology and bacteriology	Histology vs culture/Xpert	Necrotizing granulomatous inflammation dominated; bacteriological confirmation was incomplete, supporting complementary testing.
Öztomurcuk et al., 2022 [19]	Türkiye; multicentre laboratory study	Granulomatous inflammation cases over 5 years	Necrosis and AFB/molecular findings	Necrosis and anatomical site influenced the probability of identifying mycobacterial infection.
Liu et al., 2023 [20]	China; comparative diagnostic study	381 TB granuloma specimens with different necrosis types	AFB, culture, PCR, SAT and Xpert	The form of necrosis significantly affected positivity across etiological detection methods.
Chaudhary et al., 2023 [21]	India; prospective diagnostic study	Extrapulmonary samples	Xpert Ultra vs culture and composite reference	Ultra increased sensitivity in paucibacillary specimens; trace results required contextual interpretation.
Prakash et al., 2025 [22]	India; prospective observational study	Presumptive EPTB tissue and fluid specimens	Xpert Ultra, MGIT, AFB and composite reference	High diagnostic performance was reported in tissue-rich EPTB sampling, reinforcing specimen acquisition and multimodal assessment.

Table 1. Summary of principal included studies.

4.3 Histopathological spectrum

Necrotizing granulomatous inflammation was the most frequently reported classical pattern. Other patterns included non-necrotizing granulomas, poorly formed granulomas, suppurative granulomas, extensive necrosis with minimal viable architecture and nonspecific chronic inflammation. Histological appearance varied with site, HIV status, bacillary burden and prior treatment [11,12,18-20].

4.4 Correlation with AFB microscopy

AFB staining was highly specific but insensitive. Positivity was generally greatest in suppurative, predominantly necrotic and poorly organized lesions and in immunocompromised patients. Well-formed granulomas were frequently AFB-negative. Multiple sections, fluorescence methods and targeted examination of necrotic material improved detection, but negative staining could not exclude TB [11,12,18].

4.5 Correlation with culture

Culture positivity varied by site and specimen handling. Fresh tissue submitted directly to microbiology provided greater yield than formalin-fixed material. Histology-positive, culture-negative disease was common in extrapulmonary sites because of low bacillary burden, previous therapy, small tissue volume and sampling error [13,18].

4.6 Correlation with molecular tests

PCR, Xpert MTB/RIF and Xpert Ultra increased rapid confirmation relative to smear microscopy, particularly in paucibacillary specimens. Tissue PCR detected additional cases among culture-negative necrotizing granulomas, while Xpert provided simultaneous rifampicin information [15,17,21,22]. False-negative results occurred in fibrotic, non-necrotic or low-volume samples; low-level positive results required consideration of previous TB and residual DNA.

4.7 Necrosis and microbiological positivity

The presence and type of necrosis affected diagnostic yield. Liquefactive, suppurative and granular necrosis generally produced higher molecular or smear positivity than dense acellular or fibrotic caseation. Liu et al. found significant variation in AFB, culture, PCR, simultaneous amplification and Xpert positivity across necrosis types [20].

4.8 Immune status and disease severity

Poorly formed granulomas, abundant necrosis and high tissue bacillary density were more frequently reported in HIV-associated or otherwise immunocompromised disease. Saha et al. observed higher-grade necrotizing patterns and greater AFB density among HIV-positive lymphadenitis cases, with longer treatment requirements [11]. Evidence linking these features independently to dissemination, organ dysfunction or mortality remained limited.

4.9 Treatment response and outcomes

Longitudinal tissue assessment was uncommon. Residual granulomas, fibrosis and molecular DNA could persist despite clinical improvement. Paradoxical reactions could show intensified inflammation without viable organisms. Histological findings were less consistently associated with cure, relapse, failure or death than clinical factors such as HIV, drug resistance, treatment delay, central nervous system involvement, nutritional status and adherence.

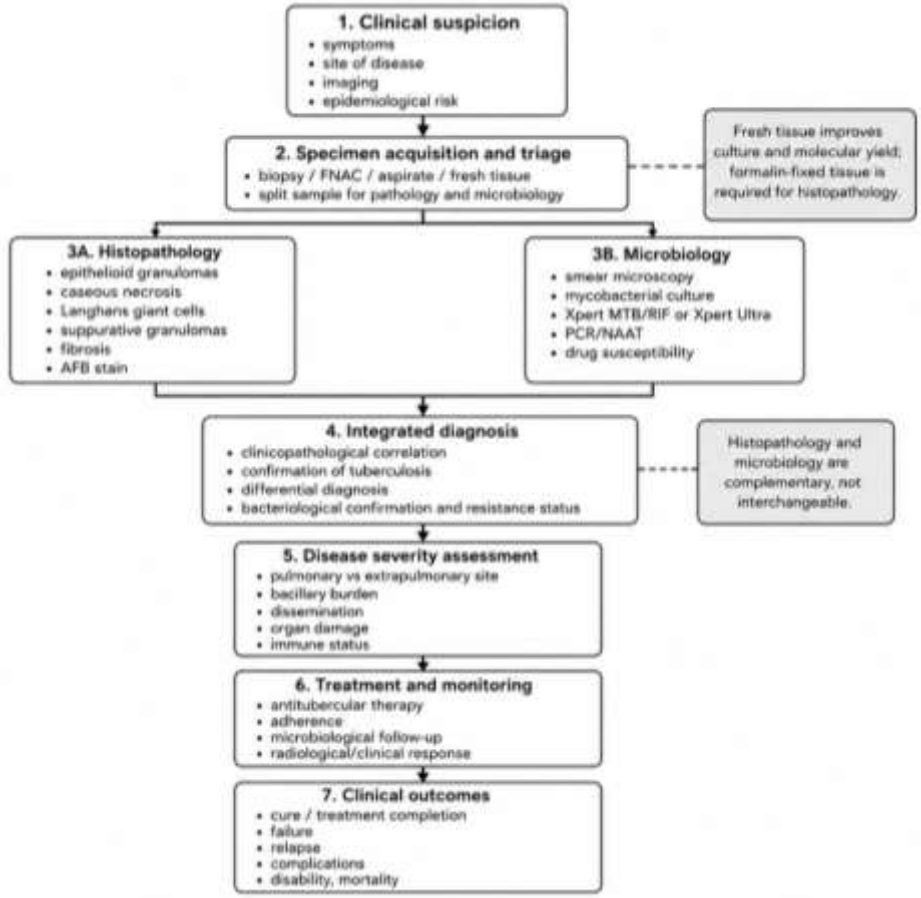

Figure 2. Integrated clinicopathological pathway in tuberculosis.

4.10 Summary of evidence

Histopathological feature	Microbiological association	Severity/response/outcome interpretation
Caseous necrosis	Generally increases probability of smear, culture or NAAT positivity	May indicate active destructive disease; independent prognostic value uncertain
Non-necrotizing granulomas	Frequently microbiology-negative	Requires careful exclusion of alternative granulomatous diseases
Poorly formed granulomas	Often associated with immunosuppression and higher AFB density	Possible association with severe or disseminated disease
Suppurative granulomas	Often higher smear or molecular positivity	Can mimic bacterial or fungal abscess

Histopathological feature	Microbiological association	Severity/response/outcome interpretation
High AFB density	Strong association with microbiological confirmation	May accompany impaired immune containment and prolonged treatment
Fibrosis/hyalinization	Usually lower microbiological yield	May reflect chronicity or healing
Persistent granulomas after treatment	May be culture-negative and retain DNA	Do not necessarily establish treatment failure

Table 2. Clinicopathological interpretation of major histopathological features.

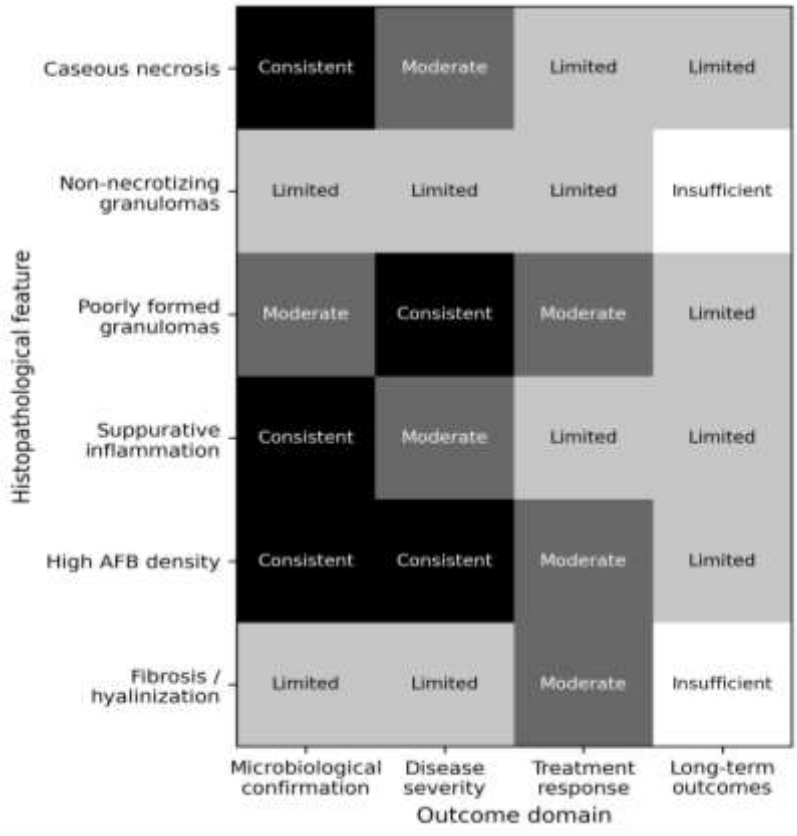

Figure 3. Qualitative evidence map. Categories represent the consistency of published evidence, not pooled effect sizes.

5. DISCUSSION

5.1 Principal findings

This review shows that histopathology and microbiology answer related but different questions. Histology demonstrates the host-tissue response and supports differential diagnosis, whereas microbiology confirms the organism, viability and drug susceptibility. Classical caseating granulomas strongly support TB but are not pathognomonic. Conversely, negative AFB, culture or NAAT results cannot exclude paucibacillary extrapulmonary disease [6,13,18].

5.2 Explaining histology-microbiology discordance

Histology-positive/microbiology-negative disease commonly reflects low bacillary burden, nonrepresentative sampling, previous treatment, formalin fixation or sampling of the granulomatous rim rather than the necrotic centre. Histology-nonspecific/microbiology-positive disease may occur early in infection, in immunosuppression or when only necrotic material is sampled. Molecular-positive/culture-negative results may represent low viability or persistent DNA after treatment [13,15,18].

5.3 Diagnostic meaning of caseous necrosis

Caseation increases the likelihood of TB in the correct clinical context and should trigger AFB, fungal stains, culture and molecular testing. Necrotic material should not be discarded because it may contain the greatest concentration of detectable mycobacterial DNA. Nevertheless, necrotizing fungal infection and other causes remain important alternatives [14,20].

5.4 Granuloma organization and host immunity

Well-organized granulomas reflect coordinated cellular immunity, whereas poorly formed lesions and abundant organisms suggest impaired containment. In advanced HIV infection, classic granulomas may be absent despite high bacillary loads. Consequently, absence of granulomas cannot exclude TB in immunocompromised patients [11].

5.5 Specimen triage as a key clinical intervention

When TB is suspected, tissue should be divided immediately: sterile fresh tissue for culture and molecular analysis, formalin-fixed tissue for histology and additional material for bacterial or fungal studies. Placing the entire specimen in formalin prevents conventional culture and may reduce molecular performance. Communication between surgeons, clinicians, pathologists and microbiologists is therefore essential.

5.6 Molecular tests in pathological context

Rapid NAATs shorten time to diagnosis and may identify rifampicin resistance, but their results require contextual interpretation. A positive Xpert result in necrotizing granulomatous tissue strongly supports TB; a trace result in a previously treated patient may reflect residual DNA. A negative assay in a small fibrotic biopsy remains insufficient to exclude disease [17,21,22].

5.7 Histology, severity and outcomes

The diagnostic evidence is considerably stronger than the prognostic evidence. High AFB density, poor granuloma formation and extensive necrosis may accompany severe disease, but systemic outcomes are driven by anatomical site, drug resistance, immune status, nutritional condition, organ dysfunction, diagnostic delay and adherence. No individual histological feature is sufficiently validated to independently predict relapse or mortality.

5.8 Implications for pulmonary and extrapulmonary disease

In pulmonary TB, respiratory specimens often provide microbiological confirmation without biopsy; tissue is mainly required for smear-negative, mass-like or diagnostically atypical disease. In extrapulmonary TB, tissue architecture is often central to diagnosis because fluids and aspirates are paucibacillary. Negative microbiology is therefore less exclusionary, and composite interpretation is more important.

5.9 Strengths and limitations

The review integrates diagnosis, severity, response and long-term outcomes rather than focusing on one assay. It also provides standardized histological categories and emphasizes specimen handling. Limitations include heterogeneity of anatomical sites, immune status, reference standards, tissue processing and outcome definitions. Most studies were retrospective, and prognostic analyses were infrequent. Final PRISMA counts and risk-of-bias judgments must be completed from the formal review database.

6. Clinical Recommendations

1. Use histopathology and microbiology as complementary investigations.
2. Submit both necrotic and viable tissue when feasible.
3. Reserve fresh sterile tissue for culture and molecular testing before formalin fixation.
4. Do not exclude tuberculosis solely because AFB stain, culture or NAAT is negative.
5. Do not infer drug susceptibility from histological morphology.
6. Interpret persistent granulomas or molecular positivity after treatment in clinical and microbiological context.
7. Consider fungal, nontuberculous mycobacterial and noninfectious granulomatous disorders in the differential diagnosis.

7. Recommendations for Future Research

- Prospective, multicentre recruitment with matched fresh and fixed specimens.
- Standardized quantification of granuloma architecture, necrotic area, AFB density, fibrosis and suppuration.
- Parallel testing by smear, liquid culture, Xpert Ultra and quantitative molecular bacterial-load assays.
- Stratification by anatomical site, HIV/CD4 status, diabetes, immunosuppression and prior treatment.
- Use of WHO-defined treatment outcomes and long-term relapse follow-up.
- Digital pathology and multivariable models integrating histology, microbiology, imaging and host biomarkers.

8. CONCLUSION

Histopathology remains essential in pulmonary and particularly extrapulmonary tuberculosis. Necrotizing epithelioid granulomas, Langhans-type giant cells and caseous necrosis provide strong diagnostic support but are not entirely specific. Microbiological confirmation is more likely in specimens with extensive necrosis, suppuration or high bacillary density, yet negative smear, culture or molecular testing does not exclude disease. Correct specimen triage is a major determinant of diagnostic yield.

Current evidence does not support the use of any single histological pattern as an independent predictor of treatment response, relapse, failure or mortality. Integrated clinicopathological interpretation and standardized prospective research are required.

9. Declarations

Ethics approval: Not required for a systematic review of published literature.

Consent to participate: Not applicable.

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Conflicts of interest: The authors declare no conflicts of interest.

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