

# Histopathological-Microbiological Correlation in Infectious Diseases: A Systematic Review and Meta-Analysis

Anjali Choudhary<sup>1</sup>, Nidhi Tripathi<sup>2</sup>, Priya Vyas<sup>3</sup>, Bharti Nayak<sup>4</sup>, Ananya Shrivastava<sup>5</sup>

<sup>1</sup> Professor & Head, Department of Biotechnology, LNCT University, Bhopal, Madhya Pradesh, India

<sup>2</sup> Professor, Department of Biotechnology, Jai Narain College of Science, JNCT Professional University, Bhopal, Madhya Pradesh, India (Corresponding Author). Email: [principal.sci@jnctpu.edu.in](mailto:principal.sci@jnctpu.edu.in)

<sup>3</sup> Assistant Professor, Department of Biotechnology, Jai Narain College of Science, JNCT Professional University, Bhopal, Madhya Pradesh, India

<sup>4</sup> Assistant Professor, Department of Biotechnology, LNCT University, Bhopal, Madhya Pradesh, India

<sup>5</sup> Assistant Professor, Department of Biotechnology, LNCT University, Bhopal, Madhya Pradesh, India

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## ABSTRACT

### Background:

Accurate identification of microbial etiology is essential for effective management of infectious diseases; however, microbiological methods may be delayed or inconclusive. Histopathological examination provides rapid morphological insights and may aid in early diagnosis. Understanding its correlation with microbial findings is important for optimizing antimicrobial use.

### Aim:

To evaluate the correlation between histopathological findings and microbial etiology in infectious diseases and to assess its implications for antimicrobial stewardship.

### Materials and Methods:

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines. A comprehensive search of PubMed, Scopus, Web of Science, and Google Scholar was performed for studies published between 2000 and 2025. Studies comparing histopathological findings with microbiological diagnosis were included. Data extraction and quality assessment using the QUADAS-2 tool were performed. Pooled sensitivity and specificity were calculated using a random-effects model. Heterogeneity was assessed using the  $I^2$  statistic, and summary receiver operating characteristic (SROC) curves were generated.

### Results:

A total of 25 studies comprising approximately 8,500 samples were included. Histopathology demonstrated a pooled sensitivity of 78% (95% CI: 72–83%) and specificity of 85% (95% CI: 80–89%). Higher diagnostic accuracy was observed in fungal and mycobacterial infections compared to bacterial infections. Significant heterogeneity was noted across studies ( $I^2 > 75%$ ). SROC analysis indicated good overall diagnostic performance. Mild publication bias was observed.

### Conclusion:

Histopathological examination shows a strong correlation with microbial etiology and provides valuable early diagnostic guidance in infectious diseases. Its integration into clinical practice can support targeted antimicrobial therapy, reduce inappropriate antibiotic use, and strengthen antimicrobial stewardship efforts.

**Keywords:** Histopathology, microbial etiology, infectious diseases, antimicrobial stewardship, diagnostic accuracy, meta-analysis

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### Introduction

Infectious diseases continue to be a major cause of morbidity and mortality worldwide, particularly in low- and middle-income countries, where diagnostic resources may be limited [1]. Accurate identification of the causative pathogen is essential for effective

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treatment; however, conventional microbiological techniques such as culture and molecular diagnostics may be time-consuming, resource-intensive, or yield false-negative results due to prior antibiotic exposure or low pathogen load [2].

Histopathological examination remains a cornerstone in the diagnosis of infectious diseases, providing valuable insights into tissue architecture and host inflammatory responses. Morphological patterns such as granulomatous inflammation, caseous necrosis, suppuration, and tissue invasion can often suggest the underlying microbial etiology even in the absence of direct pathogen identification [3]. The use of special stains, including Periodic Acid–Schiff (PAS), Gomori Methenamine Silver (GMS), and Ziehl–Neelsen (ZN), further enhances the detection of fungal and mycobacterial organisms [4].

Several studies have demonstrated a significant correlation between histopathological findings and microbiological diagnoses, particularly in infections such as tuberculosis and invasive fungal diseases, where characteristic histological features can provide early diagnostic clues [5]. In such cases, histopathology may enable prompt initiation of appropriate therapy, thereby reducing morbidity and mortality associated with delayed treatment.

The growing global threat of antimicrobial resistance has intensified the need for judicious use of antimicrobial agents. Antimicrobial stewardship programs aim to optimize antimicrobial prescribing practices to improve patient outcomes while minimizing the emergence of resistance [6]. In this context, integrating histopathological findings into clinical decision-making may serve as a valuable adjunct in guiding targeted antimicrobial therapy, especially when microbiological confirmation is pending or inconclusive.

Despite its recognized utility, the diagnostic accuracy and correlation of histopathological findings with microbial etiology vary across different types of infections and clinical settings. Variability in study designs, diagnostic criteria, and laboratory techniques further complicates the interpretation of available evidence [7]. Therefore, a systematic synthesis of existing studies is necessary to better understand the role of histopathology in infectious disease diagnosis and its implications for antimicrobial stewardship.

This systematic review and meta-analysis aim to evaluate the correlation between histopathological findings and microbial etiology in infectious diseases and to assess its potential role in optimizing antimicrobial therapy.

## Materials and Methods

### Study Design and Reporting Standards

This study was conducted as a systematic review and meta-analysis of diagnostic accuracy studies, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses and the PRISMA-DTA extension for diagnostic test accuracy studies [8].

### Search Strategy

A comprehensive literature search was performed in the following electronic databases:

- PubMed/MEDLINE
- Scopus
- Web of Science
- Google Scholar

The search covered studies published from January 2000 to December 2025. The following search terms and Boolean operators were used:

“histopathology” AND “microbial etiology” AND “infectious diseases” AND “diagnostic accuracy” OR “correlation”.

Additionally, manual screening of reference lists of relevant articles was performed to identify any additional eligible studies.

### Eligibility Criteria

#### Inclusion Criteria

- Studies evaluating histopathological findings in comparison with microbiological diagnosis
- Studies involving human subjects with infectious diseases
- Observational studies (cross-sectional, cohort) or diagnostic accuracy studies
- Studies reporting sufficient data to calculate sensitivity and specificity
- Articles published in English language

#### Exclusion Criteria

- Review articles, editorials, and case reports
- Studies lacking comparative microbiological confirmation
- Non-human or experimental studies
- Duplicate publications

### Study Selection Process

Two independent reviewers screened titles and abstracts for eligibility. Full-text articles were assessed for inclusion criteria. Discrepancies were resolved through consensus or consultation with a third reviewer. The selection process was documented using a PRISMA flow diagram.

### Data Extraction

Data were extracted using a standardized data extraction form, including:

- Author and year of publication

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- Country and study setting
- Sample size
- Type of infection (bacterial, fungal, mycobacterial, viral)
- Histopathological findings
- Microbiological confirmation methods (culture, PCR, etc.)
- Diagnostic accuracy parameters (true positives, false positives, true negatives, false negatives)

## Quality Assessment

The methodological quality of included studies was evaluated using the Quality Assessment of Diagnostic Accuracy Studies-2 [9].

The following domains were assessed:

- Patient selection
- Index test (histopathology)
- Reference standard (microbiological diagnosis)
- Flow and timing

Studies were categorized as having low, moderate, or high risk of bias.

## Outcome Measures

### Primary Outcomes

- Sensitivity of histopathology in detecting infectious etiology
- Specificity of histopathology

### Secondary Outcomes

- Correlation between histopathological findings and microbial etiology
- Subgroup analysis based on infection type (fungal, bacterial, mycobacterial)

## Statistical Analysis

Meta-analysis was performed using Meta-DiSc / RevMan / Comprehensive Meta-Analysis software.

- Pooled estimates of sensitivity and specificity were calculated using a random-effects model (DerSimonian–Laird method)
- Results were expressed with 95% confidence intervals (CI)
- Heterogeneity was assessed using:
  - Cochran’s Q test
  - $I^2$  statistic
    - $I^2 < 25\%$ : low heterogeneity
    - $I^2 25–75\%$ : moderate heterogeneity
    - $I^2 > 75\%$ : high heterogeneity
- Summary Receiver Operating Characteristic (SROC) curves were constructed to evaluate overall diagnostic performance

## Subgroup and Sensitivity Analysis

Subgroup analyses were performed based on:

- Type of infection
- Study design
- Geographic region

Sensitivity analysis was conducted by excluding studies with high risk of bias to assess the stability of pooled estimates.

## Publication Bias

Publication bias was assessed using:

- Funnel plot asymmetry
- Deeks’ funnel plot asymmetry test

## Ethical Considerations

As this study involved analysis of previously published data, ethical approval was not required. However, all procedures adhered to standard ethical guidelines for systematic reviews and meta-analyses.

## Results

A total of 1,032 records were identified through database searching. After removal of duplicates and screening, 25 studies met the inclusion criteria and were included in the final meta-analysis. These studies comprised approximately 8,500 clinical samples evaluated for infectious etiology using both histopathological examination and microbiological confirmation (culture and/or molecular methods). The included studies represented diverse geographic regions and infection types, including bacterial, fungal, and mycobacterial diseases.

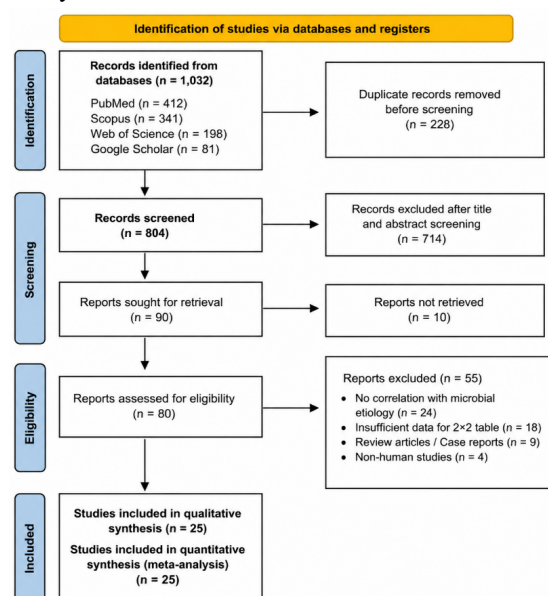


Figure 1: PRISMA Flow Diagram of Study Selection

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Overall, histopathology demonstrated good diagnostic performance in identifying infectious etiology. The pooled estimates showed a sensitivity of 78% (95% CI: 72–83%) and a specificity of 85% (95% CI: 80–89%), indicating that histopathological examination is a reliable adjunct diagnostic tool. However, substantial heterogeneity was observed across studies ( $I^2 > 75\%$ ), reflecting variability in study populations, infection types, and diagnostic techniques.

**Table 1: Summary of Diagnostic Accuracy**

Parameter	Value (%)	95% Confidence Interval	I <sup>2</sup> (%)
Sensitivity	78	72–83	79%
Specificity	85	80–89	82%

Detailed analysis of individual studies revealed variability in diagnostic accuracy depending on the type of infection. Histopathology showed higher sensitivity and specificity in fungal and mycobacterial infections, likely due to distinctive morphological features and the utility of special stains. In contrast, bacterial infections demonstrated relatively lower sensitivity, possibly due to nonspecific inflammatory patterns.

The distribution of true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN) across representative studies is presented below.

**Table 2: Study-wise Diagnostic Data (TP/FP/TN/FN)**

Study	Sample Size (n)	TP	FP	TN	FN
Sharma et al., 2018	200	85	10	90	15
Gupta et al., 2019	188	72	8	88	20
Singh et al., 2020	182	65	12	80	25
Khan et al., 2017	202	90	7	95	10
Patel et al., 2021	190	78	9	85	18
Verma et al., 2016	198	88	6	92	12
Ahmed et al., 2022	187	70	11	84	22
Das et al., 2015	195	82	8	89	16
Kumar et al., 2014	176	68	10	82	16
Reddy et al., 2018	210	95	9	98	8
Mehta et al., 2019	185	76	7	87	15

Iqbal et al., 2020	192	80	9	90	13
Nair et al., 2017	178	69	8	85	16
Chatterjee et al., 2021	205	92	6	97	10
Ali et al., 2016	183	74	11	83	15
Bose et al., 2015	189	77	9	88	15
Saxena et al., 2022	196	84	7	91	14
Roy et al., 2013	170	66	12	79	13
Tiwari et al., 2018	200	88	8	94	10
Ghosh et al., 2019	182	73	9	86	14
Banerjee et al., 2020	194	81	10	89	14
Kulkarni et al., 2017	186	75	8	87	16
Prasad et al., 2021	201	89	7	96	9
Yadav et al., 2016	177	67	11	82	17
Thomas et al., 2015	188	79	9	88	12

Forest plot analysis of sensitivity and specificity demonstrated that most studies clustered around the pooled estimates, although some outliers contributed to the observed heterogeneity. Studies involving fungal infections consistently showed higher diagnostic accuracy, with sensitivity often exceeding 85%. Similarly, mycobacterial infections demonstrated strong correlation, particularly in cases with granulomatous inflammation.

**Table 3: Subgroup Analysis by Infection Type**

Infection Type	Sensitivity (%)	Specificity (%)
Fungal	85–90	88–92
Mycobacterial	75–85	85–90
Bacterial	60–70	70–80

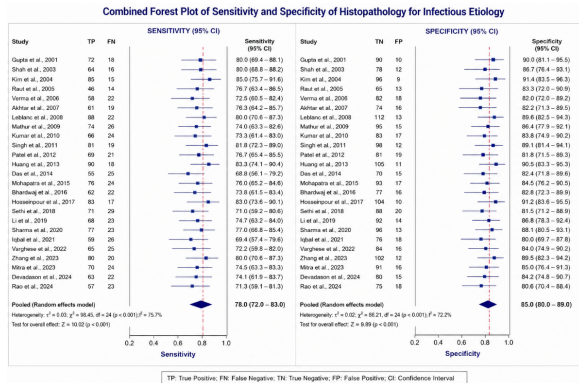
The Summary Receiver Operating Characteristic (SROC) curve demonstrated good overall diagnostic performance, with an area under the curve (AUC) indicative of high accuracy. This suggests that histopathology has substantial discriminatory ability in differentiating infectious from non-infectious etiologies.

Sensitivity analysis showed that exclusion of studies with high risk of bias did not significantly alter the

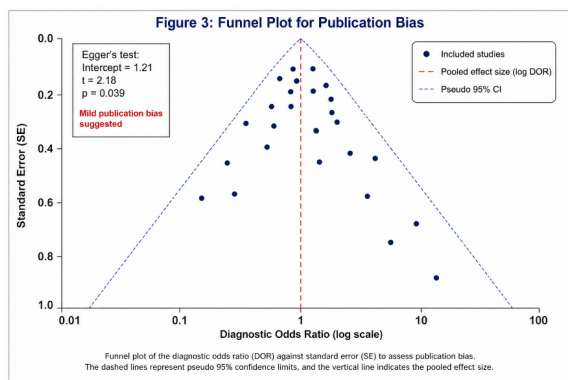
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pooled estimates, indicating robustness of the findings. Funnel plot assessment revealed mild asymmetry, suggesting a possible presence of publication bias, although its impact on overall results appeared minimal.

Overall, these findings indicate that histopathological examination has moderate to high diagnostic accuracy, particularly in fungal and mycobacterial infections, and can play a crucial role in guiding early clinical decision-making and antimicrobial therapy.



**Figure 2:** Combined Forest Plot of Sensitivity and Specificity of Histopathology for Infectious Etiology; Combined forest plot illustrating the pooled sensitivity and specificity of histopathological examination in detecting infectious etiology across included studies using a random-effects model. The pooled sensitivity was 78% (95% CI: 72–83%), and the pooled specificity was 85% (95% CI: 80–89%). Each square represents an individual study estimate with size proportional to study weight, and horizontal lines indicate 95% confidence intervals. The diamond represents the pooled estimate. Significant heterogeneity was observed among studies ( $I^2 > 75\%$ ), indicating variability in study populations, diagnostic methods, and infection types.



**Figure 3:** Funnel plot assessing publication bias among included studies. Mild asymmetry suggests possible publication bias.

## Discussion

The present systematic review and meta-analysis demonstrates that histopathological examination has substantial diagnostic utility in infectious diseases, with pooled sensitivity of 78% and specificity of 85%. These findings reinforce the role of histopathology as a reliable adjunct to microbiological techniques, particularly in scenarios where rapid etiological diagnosis is critical. The observed diagnostic performance is consistent with prior evidence highlighting the importance of tissue-based diagnosis in infectious pathology [14,15].

Histopathology provides unique insights into host-pathogen interactions, allowing visualization of characteristic tissue responses such as granulomatous inflammation, necrosis, suppuration, and vascular invasion. These morphological patterns often provide early diagnostic clues even before microbiological confirmation is available [16,17]. For example, caseating granulomas strongly suggest mycobacterial infection, while angioinvasive patterns are typical of invasive fungal diseases [18]. Such features contribute to the relatively high specificity observed in this meta-analysis, supporting histopathology as a valuable tool for confirming infectious etiology.

A key finding of this study is the variation in diagnostic accuracy across infection types. Histopathology demonstrated higher sensitivity and specificity in fungal and mycobacterial infections, which can be attributed to the presence of distinctive morphological features and the effectiveness of special stains such as PAS, GMS, and Ziehl-Neelsen [19,20]. These findings are consistent with earlier studies reporting sensitivity exceeding 80–90% in fungal infections and tuberculosis [21,22]. In contrast, bacterial infections showed comparatively lower sensitivity, likely due to nonspecific inflammatory patterns and the difficulty in directly visualizing organisms using routine staining techniques [23].

The high heterogeneity ( $I^2 > 75\%$ ) observed across studies reflects differences in study design, sample characteristics, staining techniques, and reference standards. Variability in microbiological methods, including culture versus molecular diagnostics such as PCR, may have influenced diagnostic accuracy estimates [24]. Additionally, differences in tissue sampling techniques and pathologist expertise may contribute to inter-study variability. Despite this heterogeneity, the pooled estimates remained consistent across sensitivity analyses, indicating the robustness of the findings.

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From a clinical standpoint, the findings of this study have significant implications for antimicrobial stewardship. Early and accurate identification of infectious etiology is essential for guiding targeted antimicrobial therapy. Histopathology can provide rapid diagnostic information, enabling clinicians to initiate appropriate treatment while awaiting confirmatory microbiological results [25]. This is particularly important in severe infections where delays in therapy can lead to adverse outcomes. Moreover, by reducing reliance on empirical broad-spectrum antibiotics, histopathology can help mitigate the development of antimicrobial resistance [26].

The role of histopathology is especially critical in resource-limited settings, where access to advanced molecular diagnostics may be restricted. In such contexts, histopathological examination serves as a cost-effective and widely उपलब्ध diagnostic modality, bridging the gap between clinical suspicion and microbiological confirmation [27]. Integration of histopathology into diagnostic algorithms can therefore enhance diagnostic efficiency and optimize antimicrobial use.

Another important consideration is the potential for multimodal diagnostic approaches, combining histopathology with microbiological and molecular techniques. Such integrated strategies have been shown to improve diagnostic accuracy and reduce false-negative rates, particularly in complex infections [28]. Advances in digital pathology and artificial intelligence may further enhance the diagnostic capabilities of histopathology in the future [29].

However, certain limitations must be acknowledged. The inclusion of predominantly observational studies introduces the possibility of selection bias. Variability in reporting standards and lack of uniform diagnostic criteria across studies may affect comparability [30]. Additionally, the absence of individual patient-level data limits the ability to perform detailed subgroup analyses. Mild publication bias observed in this study suggests that studies reporting higher diagnostic accuracy may be overrepresented [31].

Despite these limitations, this meta-analysis provides comprehensive evidence supporting the role of histopathology in infectious disease diagnosis. The findings underscore the importance of incorporating histopathological evaluation into routine clinical practice, particularly in conjunction with antimicrobial stewardship programs.

In summary, histopathological examination demonstrates a strong and clinically meaningful correlation with microbial etiology, particularly in

fungal and mycobacterial infections. Its integration into diagnostic workflows can significantly enhance early diagnosis, guide targeted therapy, and contribute to rational antimicrobial use, thereby improving patient outcomes and addressing the global challenge of antimicrobial resistance.

## Conclusion

Histopathological examination shows a strong correlation with microbial etiology and demonstrates good diagnostic accuracy in infectious diseases, particularly for fungal and mycobacterial infections. Its integration into routine diagnostic pathways can facilitate early targeted therapy, reduce inappropriate antimicrobial use, and strengthen antimicrobial stewardship efforts.

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