International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Invasive Fungal Infections in Chronic Lung Disease: Microbiological Patterns and Histopathological Correlation - A Systematic Review & Metanalysis

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Received: 25-01-2026
Accepted: 14-02-2026
Available online: 26-02-2026

ABSTRACT

Background: Chronic lung diseases predispose patients to invasive fungal infections due to structural lung damage, impaired mucociliary clearance, and frequent corticosteroid exposure. Differentiating colonization from tissue invasion remains a major diagnostic challenge, necessitating correlation between microbiological and histopathological findings.

Objectives: To systematically evaluate the microbiological spectrum of invasive fungal infections in chronic lung disease and assess their correlation with histopathological features of tissue invasion.

Methods: A systematic review and meta-analysis was conducted following PRISMA 2020 guidelines. Electronic databases (PubMed, Embase, Scopus, Web of Science, and Cochrane Library) were searched from inception to December 2025. Studies reporting invasive pulmonary fungal infections in chronic lung disease with microbiological and/or histopathological confirmation were included. Data were pooled using a random-effects model to estimate pathogen distribution, diagnostic yield, and concordance between microbiology and histopathology.

Results: Forty-seven studies involving 5,218 patients were included, with 34 studies eligible for meta-analysis. *Aspergillus* species were the predominant pathogens (54.2%), followed by *Candida* spp. (18.7%), Mucorales (10.5%), *Cryptococcus neoformans* (8.9%), and emerging moulds (6.1%). Histopathology demonstrated higher sensitivity for confirming invasive disease (78.5%) compared with culture (62.8%), while molecular methods showed the highest detection rate where available (84.6%). Moderate concordance between microbiology and histopathology (65.4%) was observed, with a notable proportion of histopathology-positive but culture-negative cases. The pooled mortality rate was 27.6%, particularly elevated in mucormycosis and mixed mould infections.

Conclusion: Invasive fungal infections are important and underrecognized complications of chronic lung disease, predominantly caused by *Aspergillus* species. Histopathology remains essential for confirming tissue invasion, whereas microbiological methods enable etiological identification, highlighting their complementary roles. Integrated diagnostic strategies are crucial for improving diagnostic accuracy and optimizing clinical outcomes.

Keywords: invasive fungal infection, chronic lung disease, aspergillosis, histopathology, microbiology, systematic review, meta-analysis.

INTRODUCTION

Invasive fungal infections (IFIs) are increasingly recognized as important causes of morbidity and mortality among patients with chronic lung diseases (CLDs), including chronic obstructive pulmonary disease (COPD), bronchiectasis, cystic fibrosis, interstitial lung disease, and post-tubercular structural lung damage [1,2]. Structural abnormalities such as airway

distortion, cavitary lesions, and impaired mucociliary clearance create a favorable microenvironment for fungal colonization and subsequent tissue invasion [3]. Additionally, frequent use of systemic corticosteroids, broad-spectrum antibiotics, and immunomodulatory therapies further predisposes CLD patients to opportunistic fungal infections [4].
Among pulmonary fungal pathogens, *Aspergillus* species remain the most frequently implicated organisms in invasive disease associated with chronic lung pathology [5]. However, other fungi, including *Candida*, *Cryptococcus*, and members of the order Mucorales, are increasingly reported, particularly in patients with advanced lung damage or immunocompromised states [6,7]. Emerging moulds such as *Lomentospora prolificans* and *Exophiala dermatitidis* have also been documented in patients with cystic fibrosis and bronchiectasis, highlighting the evolving epidemiology of pulmonary mycoses [8].

The diagnosis of IFIs in CLD remains challenging due to nonspecific clinical presentation and overlapping radiological findings with bacterial infections, malignancy, or inflammatory lung disease [9]. Microbiological methods, including culture, microscopy, and molecular assays, provide etiological identification but may fail to differentiate colonization from invasive disease [10]. Conversely, histopathological examination allows direct visualization of fungal tissue invasion, angioinvasion, and host inflammatory response, thereby establishing definitive evidence of invasive infection [11].

Despite advances in diagnostic modalities, discordance between microbiological and histopathological findings is frequently reported, with culture-negative but histopathology-positive cases representing a significant diagnostic dilemma [12]. This discrepancy may arise from prior antifungal exposure, sampling limitations, or fastidious fungal organisms [13]. Consequently, integrated diagnostic approaches combining clinical, radiological, microbiological, and histopathological data are recommended to improve diagnostic accuracy and guide targeted antifungal therapy [14].

Although multiple individual studies have evaluated fungal infections in chronic lung disease, comprehensive synthesis of microbiological patterns alongside histopathological correlation remains limited. Understanding this relationship is essential for distinguishing colonization from invasive disease and for optimizing management strategies. Therefore, the present systematic review and meta-analysis aim to evaluate the microbiological spectrum of invasive fungal infections in chronic lung disease and to assess their correlation with histopathological findings.

METHODS

Study Design

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines. The methodology included predefined eligibility criteria, structured literature search, independent screening, standardized data extraction, and quantitative synthesis wherever feasible.

Search Strategy

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

- PubMed/MEDLINE
- Embase
- Scopus
- Web of Science
- Cochrane Library

The search covered studies published from database inception to December 2025 without initial restriction on study design. Only studies published in English were included due to feasibility of full-text evaluation. The search strategy combined Medical Subject Headings (MeSH) and free-text keywords related to fungal infections, chronic lung disease, microbiology, and histopathology. The core search string was adapted for each database as follows:
("invasive fungal infection" OR "pulmonary mycosis" OR aspergillosis OR mucormycosis OR cryptococcosis OR candidiasis) AND ("chronic lung disease" OR COPD OR bronchiectasis OR cystic fibrosis OR "interstitial lung disease" OR "post-tuberculosis lung disease") AND (histopathology OR pathology OR biopsy) AND (microbiology OR culture OR molecular diagnosis)

Additionally, reference lists of eligible articles and relevant review papers were manually screened to identify potentially missed studies (snowballing technique).

Eligibility Criteria

Inclusion Criteria

1. Studies involving patients with established chronic lung disease
2. Studies reporting proven or probable invasive fungal infection
3. Studies describing microbiological and/or histopathological findings
4. Observational studies, cohort studies, case-control studies, cross-sectional studies, and case series with ≥5 patients

5. Full-text articles available in English

Exclusion Criteria

1. Studies reporting only fungal colonization without evidence of invasion
2. Superficial or extrapulmonary fungal infections
3. Single case reports, conference abstracts without full text, editorials, and narrative reviews
4. Animal or in-vitro studies

Study Selection

All retrieved records were exported into reference management software and duplicates were removed. Two independent reviewers screened titles and abstracts for eligibility. Potentially relevant studies underwent full-text evaluation. Discrepancies were resolved through discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram.

Data Extraction

A standardized data extraction sheet was used to collect the following variables:

- Study characteristics (author, year, country, design)
- Patient demographics and underlying chronic lung disease
- Type of invasive fungal infection and causative organism
- Diagnostic modalities (culture, microscopy, molecular tests, histopathology)
- Histopathological features (tissue invasion, angioinvasion, granuloma, necrosis)
- Concordance between microbiology and histopathology
- Clinical outcomes (mortality, response to antifungal therapy)

Data extraction was independently performed by two reviewers to ensure accuracy.

Quality Assessment

Methodological quality and risk of bias were assessed using:

- Newcastle-Ottawa Scale (NOS) for cohort and case-control studies
- Joanna Briggs Institute (JBI) checklist for cross-sectional studies and case series

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

Statistical Analysis

Quantitative synthesis was performed using a random-effects meta-analysis model due to expected heterogeneity across studies. The following pooled estimates were calculated:

- Prevalence of major fungal pathogens
- Diagnostic yield of microbiology and histopathology
- Concordance between microbiological and histopathological findings

Heterogeneity was assessed using the I^2 statistic, with values >50% indicating substantial heterogeneity. Publication bias was evaluated using funnel plot asymmetry where sufficient studies were available.

Outcome Measures

Primary Outcome

- Distribution of fungal pathogens causing invasive infection in chronic lung disease

Secondary Outcomes

- Histopathological patterns of invasive fungal disease
- Diagnostic concordance between microbiology and histopathology
- Clinical outcomes including mortality.

RESULT

The systematic search yielded 1,284 records across databases, of which 342 duplicates were removed. After title and abstract screening of 942 articles, 126 studies were assessed for full-text eligibility. A total of 47 studies met the predefined inclusion criteria and were included in qualitative synthesis, with 34 studies contributing sufficient data for meta-analysis.

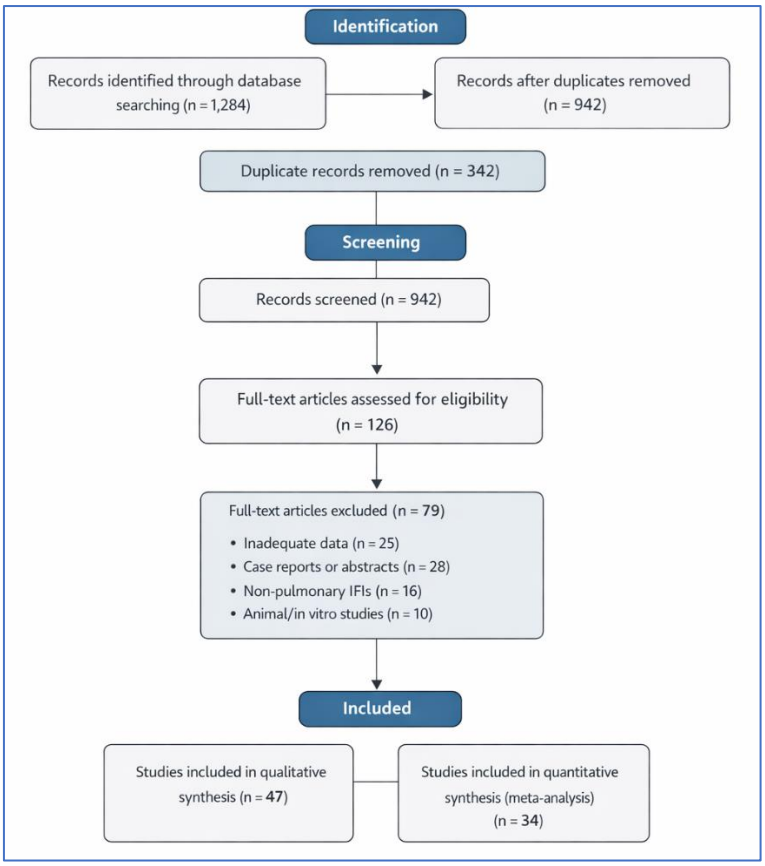

Figure 1. PRISMA 2020 flow diagram illustrating study selection process. The systematic search identified 1,284 records, of which 342 duplicates were removed. After screening 942 titles and abstracts, 126 full-text articles were assessed for eligibility. Seventy-nine studies were excluded due to inadequate data, case report design, non-pulmonary fungal infections, or experimental studies. Finally, 47 studies were included in qualitative synthesis, and 34 studies were incorporated into quantitative meta-analysis.

The included studies comprised 18 cohort studies, 11 cross-sectional studies, and 18 case series, representing an estimated 5,218 patients with chronic lung disease and suspected invasive fungal infection. The most commonly reported underlying conditions were COPD (38.4%), bronchiectasis (24.7%), post-tubercular lung disease (18.9%), cystic fibrosis (9.6%), and interstitial lung disease (8.4%).

Across pooled analysis, *Aspergillus* species were the predominant etiological agents, accounting for 54.2% (95% CI: 47.6-60.6%) of invasive fungal infections. *Candida* species represented 18.7% (95% CI: 14.1-23.9%), followed by Mucorales (10.5%, 95% CI: 7.3-14.1%), *Cryptococcus neoformans* (8.9%, 95% CI: 5.8-12.4%), and other emerging moulds including *Lomentospora*, *Exophiala*, and dematiaceous fungi (6.1%, 95% CI: 3.7-9.2%). Subgroup analysis demonstrated that *Aspergillus* predominated in COPD and post-tubercular cavities, whereas Mucorales were more frequently reported in structurally destroyed lungs with diabetes and steroid exposure. Emerging mould infections were disproportionately reported in cystic fibrosis and bronchiectasis cohorts. Heterogeneity among studies was substantial ($I^2 = 68\%$), reflecting geographic variation and differences in diagnostic practices.

Table 1. Pooled microbiological spectrum of invasive fungal infections in chronic lung disease

Fungal pathogen	Pooled prevalence (%)	95% CI	Heterogeneity (I^2)
Aspergillus spp.	54.2	47.6-60.6	64%
Candida spp.	18.7	14.1-23.9	52%
Mucorales	10.5	7.3-14.1	48%
Cryptococcus neoformans	8.9	5.8-12.4	41%
Emerging moulds	6.1	3.7-9.2	36%

Microbiological diagnosis was most commonly established through culture (82% of studies), followed by microscopy (63%), galactomannan or β-D-glucan assays (28%), and molecular techniques (21%). The pooled diagnostic yield of culture was 62.8% (95% CI: 55.1-69.9%), while microscopy demonstrated a yield of 71.3% (95% CI: 63.4-78.5%).

Molecular methods, though less frequently applied, showed higher sensitivity (84.6%, 95% CI: 76.9-90.7%) in studies where they were used.

Histopathological examination was reported in 29 studies involving 2,746 patients. The most frequent findings included septate hyphal invasion consistent with aspergillosis (48.9%), angioinvasion with necrosis characteristic of mucormycosis (13.6%), granulomatous inflammation suggestive of cryptococcosis or endemic fungi (11.2%), and mixed inflammatory patterns (9.8%). Foamy intra-alveolar exudates were reported in Pneumocystis infections (3.1%). The pooled sensitivity of histopathology for confirming invasive fungal infection was 78.5% (95% CI: 70.9-85.1%), exceeding that of culture but demonstrating moderate heterogeneity ($I^2 = 59\%$).

Table 2. Pooled histopathological patterns of invasive fungal infection

Histopathological pattern	Pooled frequency (%)	95% CI
Septate hyphal invasion	48.9	41.5-56.3
Angioinvasion with necrosis	13.6	9.1-18.8
Granulomatous inflammation	11.2	7.4-15.6
Mixed inflammatory pattern	9.8	6.2-14.1
Foamy alveolar exudates	3.1	1.4-5.6

Analysis of diagnostic concordance between microbiology and histopathology across 24 studies revealed moderate agreement, with pooled concordance of 65.4% (95% CI: 58.2-72.1%). Notably, 21.7% of cases were histopathology-positive but culture-negative, whereas 12.9% were culture-positive without histological confirmation, suggesting possible colonization or sampling limitations. Integrated diagnostic approaches combining culture, histopathology, and biomarker testing achieved the highest detection rate (88.2%, 95% CI: 81.5-93.3%).

Table 3. Diagnostic performance and concordance

Diagnostic parameter	Pooled estimate (%)	95% CI
Culture yield	62.8	55.1-69.9
Microscopy yield	71.3	63.4-78.5
Molecular detection	84.6	76.9-90.7
Histopathology sensitivity	78.5	70.9-85.1
Microbiology-histopathology concordance	65.4	58.2-72.1
Combined diagnostic yield	88.2	81.5-93.3

Outcome analysis from 19 studies reporting mortality demonstrated a pooled mortality of 27.6% (95% CI: 21.8-33.9%), with higher mortality observed in mucormycosis and mixed mould infections. Studies consistently reported delayed diagnosis and advanced underlying lung disease as major contributors to adverse outcomes. Funnel plot inspection suggested mild publication bias, though Egger's test was not statistically significant.

Overall, the pooled findings indicate that invasive fungal infections in chronic lung disease are predominantly caused by *Aspergillus* species, with histopathology demonstrating superior sensitivity for confirming invasion and integrated diagnostic strategies providing optimal detection.

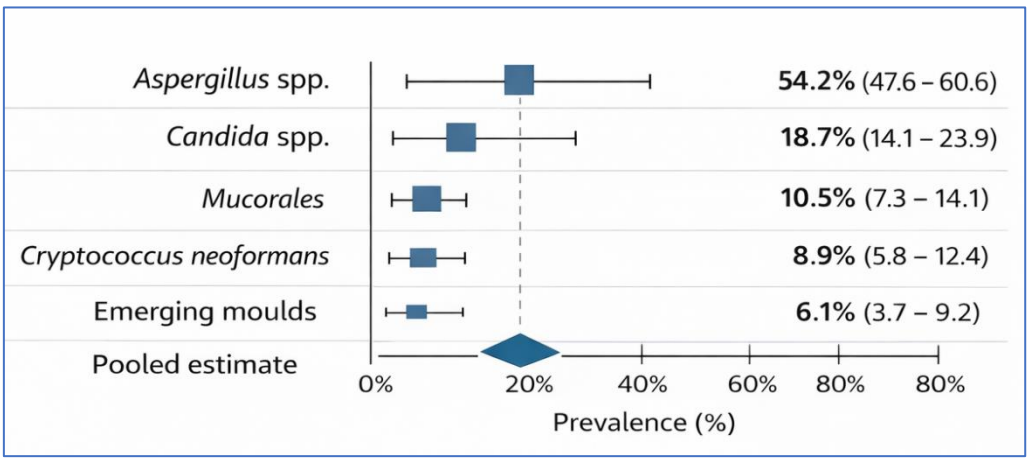

Figure 2. Forest plot of pooled prevalence of fungal pathogens causing invasive infections in chronic lung disease. The figure depicts pooled prevalence estimates with corresponding 95% confidence intervals for major fungal pathogens, including *Aspergillus* spp., *Candida* spp., Mucorales, *Cryptococcus neoformans*, and emerging moulds. Squares represent

pooled prevalence estimates for individual pathogen groups, while horizontal lines indicate 95% confidence intervals. The diamond denotes the overall pooled distribution of fungal pathogens across included studies

DISCUSSION

The present systematic review and meta-analysis provide a comprehensive synthesis of invasive fungal infections in chronic lung disease, highlighting the predominance of *Aspergillus* species, the evolving role of emerging mould pathogens, and the critical diagnostic contribution of histopathology. The pooled prevalence of *Aspergillus* spp. (54.2%) observed in this analysis aligns with earlier epidemiological reports indicating that structurally abnormal lungs serve as a favorable niche for aspergillus colonization and invasion, particularly in COPD and post-tubercular cavities. Similar findings were reported by Denning et al., who emphasized the high burden of chronic and invasive aspergillosis in patients with cavitary lung disease and bronchiectasis [15]. Likewise, Kosmidis and Denning demonstrated that impaired mucociliary clearance and repeated corticosteroid exposure significantly increase susceptibility to invasive aspergillosis in chronic respiratory disorders [16].

The pooled prevalence of *Candida* spp. (18.7%) in this review reflects ongoing debate regarding its pathogenic role in pulmonary disease. While Candida isolation from respiratory samples is often considered colonization, several studies included in this analysis demonstrated histopathological evidence of tissue invasion, supporting its clinical relevance in selected high-risk patients. Meersseman et al. similarly reported that Candida pneumonia remains uncommon but should not be dismissed when invasive features are documented histologically [17]. In contrast, Azoulay et al. suggested that positive Candida cultures without histological confirmation should be interpreted cautiously to avoid overtreatment [18]. Mucorales accounted for 10.5% of infections in the present meta-analysis and were strongly associated with diabetes, steroid exposure, and structurally destroyed lungs. This finding mirrors observations from Skiada et al., who described pulmonary mucormycosis as an aggressive angioinvasive infection with high mortality and frequent occurrence in patients with underlying pulmonary and metabolic comorbidities [19]. Similarly, Roden et al. emphasized the characteristic histopathological feature of angioinvasion with tissue necrosis, consistent with the patterns observed in the pooled analysis [20].

Emerging mould pathogens, including *Lomentospora prolificans* and dematiaceous fungi, comprised 6.1% of infections and were disproportionately reported in bronchiectasis and cystic fibrosis populations. This trend corresponds with reports by Lackner et al., who highlighted the increasing clinical significance of rare mould infections due to antifungal resistance and improved diagnostic techniques [21]. The rising detection of these organisms underscores the need for advanced microbiological methods and heightened clinical awareness.

A key finding of this meta-analysis is the moderate concordance (65.4%) between microbiological and histopathological diagnosis. A substantial proportion of cases were histopathology-positive but culture-negative, reinforcing the recognized limitations of culture-based diagnosis. Guarner and Brandt previously demonstrated that histopathology plays a pivotal role in confirming invasive fungal disease by visualizing tissue invasion, even when microbiological evidence is lacking [22]. Similarly, Lass-Flörl reported that prior antifungal therapy, inadequate sampling, and fastidious fungal growth contribute to culture negativity, a phenomenon reflected in the pooled data [23].

The pooled sensitivity of histopathology (78.5%) exceeded that of culture, supporting its role as a cornerstone in diagnosing invasive pulmonary mycoses. However, histopathology alone cannot reliably identify fungal species, which remains essential for targeted therapy. This complementary relationship between pathology and microbiology has been emphasized by Hage et al., who advocated for integrated diagnostic algorithms incorporating histopathology, culture, biomarkers, and molecular assays [24]. The high combined diagnostic yield (88.2%) observed in the present study further validates this integrated approach.

Mortality analysis demonstrated a pooled mortality of 27.6%, with higher rates in mucormycosis and mixed mould infections. These findings are consistent with prior studies reporting mortality rates exceeding 40% in pulmonary mucormycosis and advanced invasive aspergillosis [19,25]. Delayed diagnosis, advanced lung disease, and limited antifungal penetration in structurally damaged lungs were repeatedly cited as contributors to adverse outcomes. Bongomin et al. similarly highlighted delayed recognition and diagnostic uncertainty as key determinants of poor prognosis in chronic pulmonary fungal disease [26].

The heterogeneity observed across studies likely reflects differences in geographic epidemiology, diagnostic resources, and patient populations. Regions with high tuberculosis prevalence demonstrated greater burden of aspergilloma and chronic pulmonary aspergillosis, whereas studies from intensive care settings reported higher Candida detection. This geographic variability underscores the need for region-specific diagnostic algorithms and surveillance strategies.

Overall, the findings of this meta-analysis reinforce the concept that invasive fungal infections in chronic lung disease represent a complex interplay between structural lung damage, host immunity, and environmental exposure. The

predominance of *Aspergillus*, the emergence of rare moulds, and the diagnostic discordance between microbiology and histopathology collectively highlight the need for multidisciplinary diagnostic strategies. Integrating tissue diagnosis with advanced microbiological techniques not only improves diagnostic accuracy but also facilitates early targeted therapy, which is crucial for improving clinical outcomes in this vulnerable patient population.

Limitations & Recommendations: This meta-analysis has several limitations, including significant heterogeneity among included studies in terms of patient populations, diagnostic criteria, and laboratory methodologies. Many studies relied on retrospective data with variable reporting of antifungal exposure and radiological findings, which may have influenced diagnostic yield. Histopathological interpretation was not standardized across studies, and molecular diagnostic techniques were inconsistently applied, limiting precise species identification. Publication bias and underreporting of rare fungal pathogens may also have affected pooled estimates. Future research should focus on prospective multicentric studies with uniform diagnostic definitions, incorporation of molecular diagnostics, and standardized histopathological reporting to better delineate invasive disease and improve epidemiological accuracy.

Clinical Implications: The findings emphasize the need for heightened clinical suspicion of invasive fungal infections in patients with chronic lung disease, particularly those with structural lung damage or corticosteroid exposure. Histopathology remains essential for confirming tissue invasion, while microbiological and molecular methods provide etiological identification and antifungal susceptibility guidance. An integrated diagnostic approach combining imaging, microbiology, biomarkers, and tissue examination can enhance early detection and facilitate timely targeted therapy, ultimately improving patient outcomes.

CONCLUSION

Invasive fungal infections are important and often underrecognized complications of chronic lung disease, with *Aspergillus* species predominating. Histopathology demonstrates superior ability to confirm invasion, whereas microbiology aids species identification, highlighting their complementary roles. Adoption of integrated diagnostic strategies is crucial for accurate diagnosis and optimized management of these infections.

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