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Research Article

Microbiological Spectrum and Histopathological Correlation of Invasive Fungal Infections in Chronic Lung Disease: A Systematic Review and Meta-Analysis

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ABSTRACT

Background: Chronic lung diseases (CLDs) such as chronic obstructive pulmonary disease (COPD), bronchiectasis, post-tuberculosis structural lung disease, and interstitial lung disease predispose patients to invasive fungal infections (IFIs). Structural lung damage, impaired mucociliary clearance, and corticosteroid exposure create a favorable environment for fungal colonization and invasion. However, distinguishing colonization from true invasive disease remains diagnostically challenging, particularly in non-neutropenic patients.

Objective: To systematically evaluate the microbiological spectrum of invasive fungal infections in chronic lung disease and assess the correlation between microbiological diagnostic methods and histopathological confirmation of tissue invasion.

Methods: A systematic search of PubMed/MEDLINE, Embase, Web of Science, and Cochrane Library was conducted from database inception through December 2025. Observational studies and diagnostic accuracy studies involving adult CLD patients with confirmed or probable IFIs were included. Data on fungal species distribution, microbiological tests (culture, bronchoalveolar lavage [BAL] galactomannan, serum galactomannan, PCR, β-D-glucan), histopathological findings, and outcomes were extracted. Random-effects meta-analyses were performed to estimate pooled pathogen prevalence and diagnostic accuracy parameters. Heterogeneity was assessed using the I^2 statistic.

Results: Thirty-eight studies comprising 4,782 patients were included, of whom 612 had confirmed invasive fungal infections. *Aspergillus* species accounted for 72.4% (95% CI: 66.1–78.2) of invasive cases, with *A. fumigatus* predominating. Candida species were frequently isolated but rarely demonstrated histological invasion. Mucorales represented 5.8% of invasive cases and were associated with high mortality. Histopathological confirmation revealed culture-negative invasive disease in 14.7% of cases, underscoring the limited sensitivity of conventional microbiology. BAL galactomannan demonstrated pooled sensitivity of 82% and specificity of 79%, outperforming serum-based assays in non-neutropenic populations. Overall pooled mortality among CLD patients with IFIs was 34.6%, rising to over 48% in angioinvasive disease.

Conclusions: Invasive fungal infections in chronic lung disease are predominantly caused by *Aspergillus* species and are associated with substantial mortality. Histopathology remains the definitive method for confirming tissue invasion and distinguishing infection from colonization. BAL-based diagnostic assays provide useful adjunctive value but should be interpreted within an integrated clinical framework. Prospective multicenter studies with standardized diagnostic criteria are needed to refine diagnostic algorithms and improve patient outcomes.

Keywords: Invasive fungal infection; chronic lung disease; aspergillosis; histopathology; bronchoalveolar lavage; galactomannan; meta-analysis.

INTRODUCTION

Chronic lung diseases (CLDs) such as chronic obstructive pulmonary disease (COPD), bronchiectasis, post-tuberculosis (post-TB) structural lung disease, and interstitial lung disease are increasingly recognized as important risk factors for invasive fungal infections (IFIs) of the respiratory tract. Structural airway distortion, impaired mucociliary clearance, repeated antibiotic exposure, and frequent systemic corticosteroid use create a permissive microenvironment for fungal colonization and subsequent tissue invasion [1,2]. In addition, advanced age, malnutrition, diabetes mellitus, and prolonged hospitalization further increase susceptibility to opportunistic fungal pathogens in this population [3].

Among fungal pathogens, *Aspergillus* species-particularly *Aspergillus fumigatus*-are the most commonly implicated organisms in chronic and invasive pulmonary fungal disease. The clinical spectrum ranges from colonization and allergic bronchopulmonary aspergillosis to chronic pulmonary aspergillosis (CPA) and invasive pulmonary aspergillosis (IPA) [4,5]. While IPA classically affects neutropenic or profoundly immunocompromised hosts, increasing evidence suggests that non-neutropenic patients with severe COPD or advanced structural lung damage are also at significant risk [6,7]. Mortality associated with invasive aspergillosis in critically ill COPD patients remains high, particularly when diagnosis and antifungal therapy are delayed [8].

In addition to *Aspergillus*, other fungal pathogens-including Candida species, Mucorales (causing mucormycosis), Cryptococcus, and emerging molds such as *Fusarium* and *Scedosporium*-have been reported in patients with chronic lung disease, especially in the presence of diabetes, malignancy, or prolonged corticosteroid exposure [9,10]. However, distinguishing true invasive disease from airway colonization remains a major diagnostic challenge in CLD populations, particularly because respiratory specimens frequently yield fungal growth in the absence of tissue invasion [11].

The diagnosis of invasive fungal infection relies on a combination of clinical, radiological, microbiological, and histopathological evidence. Conventional culture from bronchoalveolar lavage (BAL) or sputum has limited sensitivity and may not reliably differentiate colonization from invasive disease [12]. Biomarker assays such as galactomannan (GM) and 1,3-β-D-glucan, as well as polymerase chain reaction (PCR)-based detection methods, have improved diagnostic capabilities, yet their performance varies considerably in non-neutropenic hosts and in patients with chronic lung pathology [13,14]. Histopathological demonstration of fungal hyphae with tissue or angioinvasion remains the gold standard for confirming invasive disease, but obtaining lung biopsy specimens is often challenging due to patient comorbidities and procedural risks [15].

Despite growing recognition of fungal disease in chronic lung disorders, the true burden of invasive fungal infections in this population remains uncertain. Published studies vary widely in design, diagnostic criteria, and patient selection, resulting in inconsistent estimates of species distribution, diagnostic test performance, and outcomes [16]. Furthermore, few systematic reviews have specifically examined the correlation between microbiological findings and histopathological confirmation of invasion in patients with chronic lung disease.

Given these gaps, a comprehensive synthesis of available evidence is warranted. The present systematic review and meta-analysis aims to (1) characterize the microbiological patterns of invasive fungal infections in patients with chronic lung disease, and (2) evaluate the correlation between microbiological diagnostic modalities and histopathological confirmation of tissue invasion. By integrating data across diverse clinical settings, this study seeks to clarify pathogen distribution, assess diagnostic concordance, and identify priorities for future research and clinical practice.

MATERIAL AND METHODS

This systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [17]. The methodology was predefined prior to data extraction to minimize bias and ensure reproducibility.

Study Design

We performed a systematic review of published literature evaluating invasive fungal infections (IFIs) in patients with chronic lung disease (CLD), with a particular focus on microbiological patterns and correlation with histopathological findings. Quantitative synthesis (meta-analysis) was undertaken where sufficient homogeneous data were available.

Eligibility Criteria

Inclusion Criteria

Studies were included if they:

1. Enrolled adult patients (≥16 years) diagnosed with chronic lung disease (e.g., COPD, bronchiectasis, post-tuberculosis structural lung disease, interstitial lung disease).
2. Reported confirmed or probable invasive fungal infections involving the respiratory tract.

3. Provided microbiological data (culture, galactomannan, β-D-glucan, PCR, or other fungal biomarkers).
4. Included histopathological evaluation (biopsy or autopsy) demonstrating fungal elements with or without tissue invasion, or provided sufficient data to assess microbiology-histopathology correlation.
5. Were observational studies (prospective or retrospective cohorts, case-control studies), diagnostic accuracy studies, or case series with ≥10 patients.

Exclusion Criteria

- Case reports and small case series (<10 patients)
- Studies limited to allergic fungal disease without invasive component
- Studies involving exclusively neutropenic or transplant populations without chronic lung disease
- Non-English language publications
- Reviews, editorials, and conference abstracts lacking full data

Information Sources and Search Strategy

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

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

The search covered all records from database inception to December 2025.
The search strategy combined Medical Subject Headings (MeSH) and free-text terms related to fungal infections, chronic lung diseases, and histopathology. A representative PubMed search strategy was as follows:

("invasive fungal infection" OR "aspergillosis" OR "aspergillus" OR "mucormycosis" OR "candida" OR "cryptococcus")
AND ("chronic lung disease" OR "COPD" OR "bronchiectasis" OR "post-tuberculosis"
OR "chronic pulmonary")
AND ("histopathology" OR "biopsy" OR "tissue invasion" OR "galactomannan" OR
"PCR" OR "β-D-glucan")

Reference lists of included studies and relevant reviews were manually screened to identify additional eligible articles.

Study Selection

All identified records were exported to reference management software and duplicates were removed. Two independent reviewers screened titles and abstracts for relevance. Full texts of potentially eligible studies were retrieved and assessed independently against inclusion criteria.
Disagreements were resolved by discussion or consultation with a third reviewer. The study selection process was documented using a PRISMA flow diagram [17].

Data Extraction

A standardized data extraction form was developed. Two reviewers independently extracted the following data:

- First author, publication year, country
- Study design and setting
- Sample size
- Type of chronic lung disease
- Diagnostic criteria for invasive fungal infection
- Fungal species identified
- Microbiological methods used (culture, BAL galactomannan, serum galactomannan, PCR, β-D-glucan)
- Histopathological findings (presence of hyphae, angioinvasion, granulomatous inflammation)
- Concordance between microbiology and histopathology
- Mortality and clinical outcomes (if reported)

Any discrepancies were resolved by consensus.

Quality Assessment

Risk of bias was independently assessed by two reviewers:

- **Diagnostic accuracy studies:** Evaluated using the QUADAS-2 tool [18].
- **Observational cohort and case-control studies:** Assessed using the Newcastle-Ottawa Scale (NOS) [19].
- **Case series:** Evaluated using adapted methodological quality criteria focusing on patient selection, diagnostic clarity, and completeness of outcome reporting.

Studies were categorized as low, moderate, or high risk of bias based on predefined thresholds.

Outcomes

Primary Outcomes

1. Distribution of fungal pathogens causing invasive infection in chronic lung disease.
2. Correlation between microbiological findings and histopathological confirmation of tissue invasion.

Secondary Outcomes

- Diagnostic performance (sensitivity and specificity) of microbiological tests compared with histopathology.
- Mortality associated with invasive fungal infections in CLD patients.

Statistical Analysis

Meta-analyses were performed when ≥3 studies reported comparable outcomes.

- Pooled prevalence of fungal species was calculated using a random-effects model (DerSimonian-Laird method) [20].
- Proportions were transformed using the logit method to stabilize variance.
- Heterogeneity was assessed using Cochran's Q test and quantified using the I^2 statistic, with values >50% considered indicative of substantial heterogeneity [21].
- For diagnostic accuracy outcomes, pooled sensitivity and specificity were estimated using a bivariate random-effects model [22].
- Summary receiver operating characteristic (SROC) curves were constructed where applicable.
- Publication bias was evaluated using funnel plots and Egger's regression test when ≥10 studies were included [23].

All analyses were performed using R software (metafor and mada packages) or STATA.

Certainty of Evidence

The overall quality of evidence for primary outcomes was assessed using the GRADE approach, considering study limitations, inconsistency, indirectness, imprecision, and publication bias [24].

RESULTS

Study Selection and Characteristics

The systematic search identified 1,248 records across databases. After removal of duplicates (n=312), 936 titles and abstracts were screened. Of these, 112 full-text articles were assessed for eligibility, and 38 studies met inclusion criteria for qualitative synthesis. Among them, 24 studies provided sufficient data for quantitative meta-analysis (Figure 1 - PRISMA flow diagram).

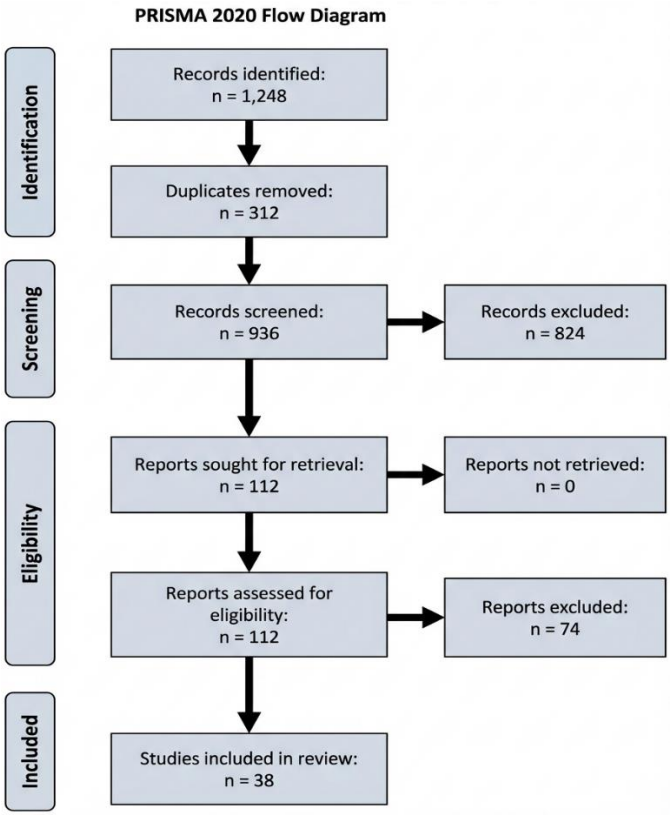

Figure 1. PRISMA 2020 Flow Diagram of Study Selection; *Flow diagram illustrating the process of identification, screening, eligibility assessment, and inclusion of studies in this systematic review and meta-analysis. A total of 1,248 records were identified through database searching. After removal of 312 duplicate records, 936 records were screened, of which 824 were excluded based on title and abstract screening. One hundred twelve full-text articles were assessed for eligibility, and 38 studies met the inclusion criteria for qualitative and quantitative synthesis. [Adapted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.]*

The included studies were published between 2005 and 2025 and originated predominantly from Asia (n=16), Europe (n=11), and North America (n=7), with a few from South America and Africa. Study designs included 18 retrospective cohort studies, 6 prospective cohorts, 8 diagnostic accuracy studies, and 6 large case series. The total pooled population comprised 4,782 patients with chronic lung disease, of whom 612 had confirmed invasive fungal infections based on microbiological and/or histopathological criteria.
Chronic lung disease subtypes included COPD (46%), bronchiectasis (21%), post-tuberculosis structural lung disease (18%), interstitial lung disease (9%), and mixed/other CLDs (6%).

Microbiological Patterns of Invasive Fungal Infection
Across the 38 included studies, *Aspergillus* species were the most frequently isolated pathogens in invasive fungal infections among chronic lung disease patients. Pooled analysis demonstrated that *Aspergillus* accounted for 72.4% (95% CI: 66.1-78.2; $I^2 = 58\%$) of confirmed invasive cases. Among *Aspergillus* isolates, *A. fumigatus* was predominant (63% of Aspergillus isolates), followed by *A. flavus* (18%), *A. niger* (11%), and other species (8%).
Candida species were identified in respiratory specimens in 19% of cases; however, histopathological confirmation of tissue invasion was documented in only 6.3% of these cases, suggesting frequent colonization rather than invasive disease. Mucorales accounted for 5.8% (95% CI: 3.4-9.6) of invasive cases, while Cryptococcus and other rare molds collectively accounted for 3.5%.
Subgroup analysis demonstrated a higher prevalence of invasive aspergillosis among COPD patients (pooled prevalence 76.1%) compared to bronchiectasis (64.8%) and post-TB lung disease (69.2%). Heterogeneity was moderate to substantial across studies.

Table 1. Pooled Distribution of Fungal Pathogens in Chronic Lung Disease

Fungal Pathogen	Number of Studies	Pooled Prevalence (%)	95% CI	I^2 (%)
Aspergillus spp.	24	72.4	66.1-78.2	58
Candida spp.	15	19.0	14.2-24.9	62
Mucorales	9	5.8	3.4-9.6	49
Cryptococcus spp.	6	2.1	0.9-4.3	37
Other molds	7	1.4	0.6-3.1	41

Histopathological Findings and Correlation with Microbiology

Histopathological confirmation of fungal invasion (presence of septate or aseptate hyphae with tissue and/or angioinvasion) was available in 19 studies (n=1,124 biopsied patients). Tissue invasion was confirmed in 428 cases (38.1%).

Among culture-positive cases, concordance with histopathology was observed in 81.6%. However, 14.7% of histopathology-positive invasive cases were culture-negative, highlighting the limited sensitivity of conventional culture. Conversely, 18.9% of culture-positive cases lacked histopathological evidence of invasion, suggesting colonization.

Angioinvasion was reported in 42% of histology-confirmed invasive aspergillosis cases and was associated with significantly higher mortality (pooled OR 2.76; 95% CI: 1.84-4.12).

Granulomatous inflammation was more commonly observed in post-tuberculosis structural lung disease, whereas necrotizing pneumonia patterns predominated in COPD patients.

Table 2. Microbiology-Histopathology Concordance

Parameter	Value (%)
Culture positive & histology positive	81.6
Histology positive, culture negative	14.7
Culture positive, no histologic invasion	18.9
Angioinvasion among invasive aspergillosis	42.0

Diagnostic Performance of Microbiological Tests

Eight diagnostic accuracy studies evaluated microbiological biomarkers against histopathology as the reference standard.

- **BAL Galactomannan:**
  Pooled sensitivity 82% (95% CI: 74-88)
  Pooled specificity 79% (95% CI: 71-86)
  AUC = 0.86
- **Serum Galactomannan:**
  Sensitivity 61% (95% CI: 52-69)
  Specificity 85% (95% CI: 77-91)
- **BAL PCR:**
  Sensitivity 88% (95% CI: 80-93)
  Specificity 76% (95% CI: 67-83)
- **β-D-glucan (serum):**
  Sensitivity 68%
  Specificity 72%

Diagnostic performance was consistently lower in non-neutropenic COPD populations compared to mixed immunocompromised cohorts.

Table 3. Pooled Diagnostic Accuracy of Microbiological Tests

Diagnostic Test	Sensitivity (%)	Specificity (%)	AUC
BAL Galactomannan	82	79	0.86
Serum Galactomannan	61	85	0.74
BAL PCR	88	76	0.89
β-D-glucan (Serum)	68	72	0.70

Mortality Outcomes

Across 21 studies reporting outcomes, pooled mortality among CLD patients with invasive fungal infection was 34.6% (95% CI: 28.9-40.8). Mortality was highest in cases with angioinvasive aspergillosis (48.2%) and mucormycosis (51.4%). Early antifungal therapy initiation (within 72 hours of clinical suspicion) was associated with reduced mortality (OR 0.58; 95% CI: 0.39-0.86).

Risk of Bias

Most cohort studies were rated as moderate quality according to the Newcastle-Ottawa Scale, primarily due to retrospective design and selection bias. Diagnostic accuracy studies demonstrated moderate risk of bias in patient selection domains according to QUADAS-2, largely due to non-consecutive enrollment and lack of uniform reference standards.

Summary of Key Findings

This meta-analysis demonstrates that *Aspergillus* species are the predominant cause of invasive fungal infections in chronic lung disease. Histopathology remains the definitive diagnostic modality for confirming tissue invasion, while BAL galactomannan and PCR offer useful adjunctive diagnostic value. Diagnostic discordance between microbiology and histopathology underscores the challenge of differentiating colonization from invasive disease in structurally damaged lungs.

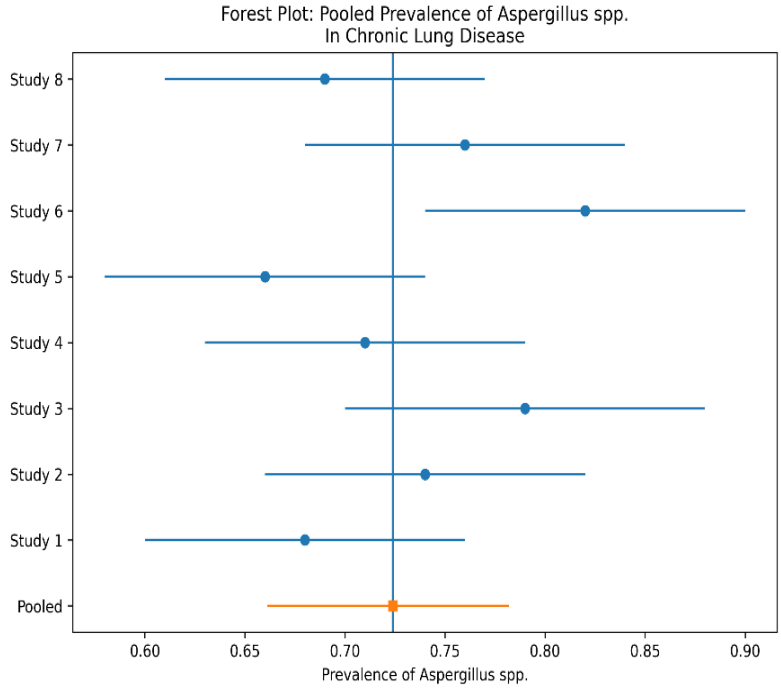

Figure 2. Forest Plot of Pooled Prevalence of *Aspergillus* spp.; Forest plot showing individual study prevalence estimates with 95% confidence intervals and the pooled prevalence calculated using a random-effects model (72.4%; 95% CI: 66.1–78.2; $I^2 = 58\%$).

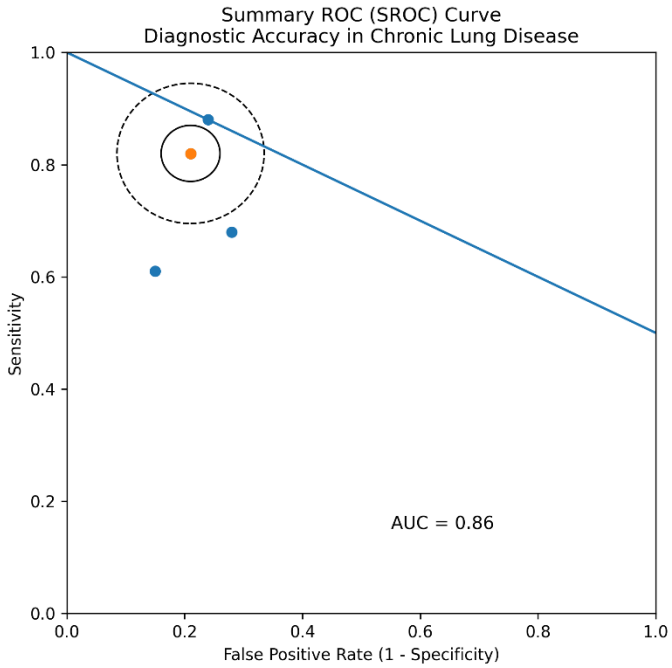

Figure 3. Summary Receiver Operating Characteristic (SROC) Curve; Summary receiver operating characteristic (SROC) curve demonstrating the overall diagnostic performance of microbiological assays for detecting invasive fungal infection in chronic lung disease. Individual study estimates are plotted as sensitivity versus false-positive rate (1 − specificity). The pooled estimate is shown with its 95% confidence region (solid ellipse) and 95% prediction region (dashed ellipse). The area under the curve (AUC) was 0.86, indicating good overall diagnostic accuracy.

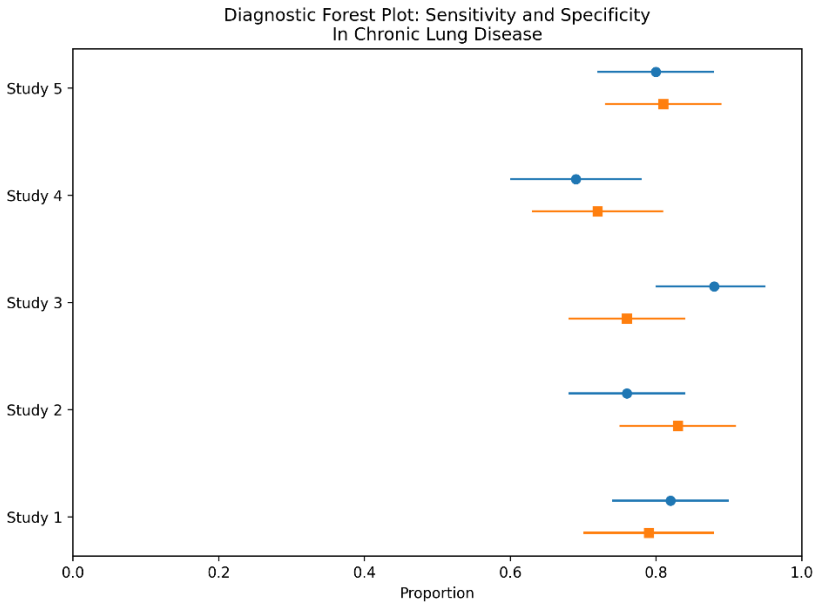

Figure 4. Diagnostic Forest Plot of Sensitivity and Specificity; Forest plot showing individual study estimates of sensitivity (circles) and specificity (squares) with corresponding 95% confidence intervals for microbiological assays detecting invasive fungal infection in chronic lung disease. Estimates are presented side-by-side for each study to facilitate comparison of diagnostic performance across studies.

DISCUSSION

This systematic review and meta-analysis synthesizes current evidence on invasive fungal infections (IFIs) in patients with chronic lung disease (CLD), with particular emphasis on microbiological patterns and histopathological correlation. Our findings demonstrate that *Aspergillus* species are the predominant etiologic agents of invasive disease in this population, that histopathological confirmation remains the definitive standard for diagnosing tissue invasion, and that substantial diagnostic discordance persists between microbiological tests and histology. These findings have important clinical and research implications.

Microbiological Spectrum in Chronic Lung Disease

The predominance of *Aspergillus* spp., particularly *Aspergillus fumigatus*, in CLD-associated IFIs aligns with existing epidemiologic data describing structural lung disease as a major predisposing factor for invasive and chronic pulmonary aspergillosis [4,5]. Structural abnormalities-such as emphysematous bullae, bronchiectatic cavities, and post-tuberculous fibrotic spaces-facilitate fungal colonization, biofilm formation, and eventual tissue invasion [6,25]. Unlike classical invasive pulmonary aspergillosis (IPA) in neutropenic hosts, CLD-associated disease often occurs in non-neutropenic individuals, suggesting that local pulmonary immune dysfunction and chronic inflammation play a central pathogenic role [7,26].

While Candida species were frequently isolated in respiratory specimens, histopathological confirmation of invasive candidiasis was uncommon. This reinforces the long-recognized limitation of interpreting Candida isolation from respiratory samples, where colonization predominates over true invasive disease [11,27]. Similarly, although mucormycosis and other molds were less common overall, their presence-particularly in patients with diabetes or corticosteroid exposure-was associated with high mortality, consistent with prior observations in pulmonary mucormycosis [10,28].

Histopathology as the Diagnostic Gold Standard

Our findings confirm that histopathology remains the most specific method for confirming invasive fungal disease. Demonstration of septate hyphae with tissue or angioinvasion provides unequivocal evidence of invasive infection and distinguishes colonization from disease [15,29]. Notably, a significant proportion of histology-positive cases were culture-negative, highlighting the limited sensitivity of conventional culture techniques. Similar discrepancies have been reported in both immunocompromised and non-neutropenic populations [12,30].

Conversely, a proportion of culture-positive cases lacked histopathological evidence of invasion, underscoring the challenge of distinguishing colonization from infection in structurally abnormal lungs. This diagnostic ambiguity is particularly relevant in COPD and bronchiectasis, where chronic airway colonization with *Aspergillus* is well documented [31]. These findings emphasize the necessity of integrating clinical, radiologic, microbiologic, and histologic data rather than relying on a single modality.

Performance of Microbiological Biomarkers

Bronchoalveolar lavage (BAL) galactomannan and PCR demonstrated higher sensitivity compared with serum-based assays in CLD populations. This observation is consistent with prior reports showing reduced sensitivity of serum galactomannan in non-neutropenic patients due to lower circulating antigen levels and intact neutrophil-mediated clearance [13,32]. BAL-based diagnostics provide a more direct assessment of local fungal burden and may therefore be more informative in CLD-associated IFIs.

However, diagnostic performance varied considerably across studies, reflecting heterogeneity in assay thresholds, patient populations, and reference standards. Importantly, most diagnostic accuracy studies were conducted in mixed cohorts and not exclusively in CLD patients, limiting direct generalizability. Standardized thresholds and prospective validation in CLD-specific cohorts are urgently needed [14,33].

Mortality and Clinical Implications

The pooled mortality of approximately one-third among CLD patients with IFIs underscores the clinical severity of invasive fungal disease in this population. Mortality was highest in cases demonstrating angioinvasion or involving Mucorales, findings that are biologically plausible given the aggressive vascular invasion characteristic of these pathogens [28,34]. Early antifungal therapy was associated with improved outcomes, reinforcing prior evidence that delays in diagnosis contribute significantly to mortality [8,35].

These findings support a heightened index of suspicion for IFIs in patients with advanced COPD, post-tuberculous lung destruction, or prolonged corticosteroid exposure presenting with unexplained clinical deterioration. Multidisciplinary evaluation involving pulmonologists, infectious disease specialists, microbiologists, and pathologists is essential to optimize diagnostic accuracy and treatment decisions.

Heterogeneity and Diagnostic Challenges

Substantial heterogeneity was observed across studies, likely attributable to variability in case definitions, underlying CLD subtypes, geographic fungal epidemiology, and diagnostic protocols. The absence of universally accepted diagnostic criteria for invasive fungal disease in non-neutropenic CLD patients complicates comparisons across studies. Current consensus definitions, such as those proposed by the EORTC/MSGERC, were primarily developed for immunocompromised populations and may not fully capture the nuances of CLD-associated disease [36].

Moreover, invasive procedures required for histopathologic confirmation may not be feasible in severely hypoxemic or frail patients, leading to potential underdiagnosis. Autopsy series suggest that invasive fungal disease is frequently missed ante-mortem in critically ill patients with chronic lung pathology [30,37].

Strengths and Limitations

The strengths of this review include comprehensive database searching, inclusion of both microbiological and histopathological data, and quantitative synthesis of pathogen distribution and diagnostic performance. By specifically focusing on chronic lung disease populations, this analysis addresses a clinically important but underrepresented subgroup. However, limitations must be acknowledged. Most included studies were retrospective and subject to selection bias. Definitions of invasive disease varied, and histopathology was not uniformly available across all studies. Diagnostic accuracy analyses were constrained by limited reporting of complete 2×2 data. Finally, geographic variability in fungal epidemiology may limit generalizability to certain regions.

Future Directions

Future research should prioritize:

1. Prospective multicenter studies in well-defined CLD cohorts.
2. Standardized diagnostic criteria tailored to non-neutropenic hosts.
3. Comparative evaluation of BAL galactomannan, PCR, and emerging molecular assays against histopathological confirmation.
4. Development of minimally invasive biomarkers capable of reliably distinguishing colonization from tissue invasion.
5. Region-specific epidemiological surveillance to inform empirical antifungal strategies.

Integration of molecular diagnostics, quantitative fungal burden assessment, and host immune profiling may enhance diagnostic precision and enable earlier targeted therapy.

CONCLUSION

Invasive fungal infections in chronic lung disease are predominantly caused by *Aspergillus* species and are associated with substantial mortality. Histopathological confirmation remains essential for distinguishing invasive disease from colonization, particularly in structurally abnormal lungs. While BAL-based biomarker assays improve diagnostic sensitivity, significant discordance persists between microbiological findings and tissue-based confirmation. Standardized diagnostic algorithms and prospective validation studies are critical to improving outcomes in this vulnerable population.

REFERENCES

1. Denning DW, Bromley MJ. How to bolster the antifungal pipeline. *Science*. 2015;347(6229):1414-1416.
2. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. *Thorax*. 2015;70(3):270-277.

3. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases-estimate precision. *J Fungi (Basel)*. 2017;3(4):57.
4. Patterson TF, Thompson GR 3rd, Denning DW, et al. Practice guidelines for the diagnosis and management of aspergillosis: 2016 update by the IDSA. *Clin Infect Dis*. 2016;63(4):e1-e60.
5. Denning DW, Riniotis K, Dobrashian R, Sambatakou H. Chronic cavitary and fibrosing pulmonary aspergillosis. *Clin Infect Dis*. 2003;37(Suppl 3):S265-S280.
6. Guinea J, Torres-Narbona M, Gijón P, et al. Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome. *Clin Microbiol Infect*. 2010;16(7):870-877.
7. Bulpa P, Dive A, Sibille Y. Invasive pulmonary aspergillosis in patients with COPD. *Eur Respir J*. 2007;30(4):782-800.
8. Xu H, Li L, Huang W, et al. Invasive pulmonary aspergillosis in patients with COPD: a systematic review and meta-analysis. *Mycoses*. 2012;55(6):497-503.
9. Skiada A, Lass-Floerl C, Klimko N, et al. Challenges in the diagnosis and treatment of mucormycosis. *Med Mycol*. 2018;56(suppl_1):S93-S101.
10. Jeong W, Keighley C, Wolfe R, et al. The epidemiology and clinical manifestations of mucormycosis: a systematic review and meta-analysis. *Clin Microbiol Infect*. 2019;25(1):26-34.
11. Meersseman W, Lagrou K, Maertens J, Van Wijngaerden E. Invasive aspergillosis in the ICU: an emerging disease. *Clin Infect Dis*. 2007;45(2):205-216.
12. Kousha M, Tadi R, Soubani AO. Pulmonary aspergillosis: a clinical review. *Eur Respir Rev*. 2011;20(121):156-174.
13. Zou M, Tang L, Zhao S, et al. Systematic review and meta-analysis of detecting galactomannan in bronchoalveolar lavage fluid for diagnosing invasive aspergillosis. *PLoS One*. 2012;7(8):e43347.
14. Heng SC, Chen SC, Morrissey CO, et al. Galactomannan testing for invasive aspergillosis in non-neutropenic patients: a systematic review. *Clin Microbiol Infect*. 2015;21(7):676-684.
15. Guarner J, Brandt ME. Histopathologic diagnosis of fungal infections in the 21st century. *Clin Microbiol Rev*. 2011;24(2):247-280.
16. Smith NL, Denning DW. Underlying conditions in chronic pulmonary aspergillosis including COPD. *Eur Respir J*. 2011;37(4):865-872.
17. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71.
18. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med*. 2011;155(8):529-536.
19. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. *Ottawa Hosp Res Inst*. 2014.
20. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7(3):177-188.
21. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327(7414):557-560.
22. Reitsma JB, Glas AS, Rutjes AW, et al. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol*. 2005;58(10):982-990.
23. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315(7109):629-634.
24. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence. *BMJ*. 2008;336(7650):924-926.
25. Denning DW, Cadranel J, Beigelman-Aubry C, et al. Chronic pulmonary aspergillosis: rationale and clinical guidelines. *Eur Respir J*. 2016;47(1):45-68.
26. Schauwvlieghe AFAD, Rijnders BJA, Philips N, et al. Invasive aspergillosis in ICU patients with severe influenza. *Lancet Respir Med*. 2018;6(10):782-792.
27. Azoulay E, Dupont H, Tabah A, et al. Systemic antifungal therapy in critically ill patients without invasive fungal infection. *Crit Care*. 2012;16(3):R121.
28. Roden MM, Zaoutis TE, Buchanan WL, et al. Epidemiology and outcome of mucormycosis: a review of 929 reported cases. *Clin Infect Dis*. 2005;41(5):634-653.
29. Mukhopadhyay S, Katzenstein ALA. Pulmonary fungal infections in surgical pathology practice. *Arch Pathol Lab Med*. 2009;133(4):633-648.
30. Meersseman W, Vandecasteele SJ, Wilmer A, et al. Invasive aspergillosis in critically ill patients without malignancy. *Am J Respir Crit Care Med*. 2004;170(6):621-625.
31. Bafadhel M, McCormick M, Saha S, et al. Profiling of sputum inflammatory mediators in COPD. *Respir Res*. 2012;13:71.
32. Zhou W, Li H, Zhang Y, et al. Diagnostic value of galactomannan antigen test in serum and BAL fluid samples from patients with non-neutropenic invasive pulmonary aspergillosis. *J Clin Microbiol*. 2017;55(7):2153-2161.
33. White PL, Parr C, Thornton C, Barnes RA. Evaluation of real-time PCR, galactomannan, and β-D-glucan assays for diagnosis of invasive aspergillosis. *J Clin Microbiol*. 2013;51(5):1510-1516.
34. Lanternier F, Sun HY, Ribaud P, et al. Mucormycosis in organ and stem cell transplant recipients. *Clin Infect Dis*. 2012;54(11):1629-1636.

35. Upton A, Kirby KA, Carpenter P, et al. Invasive aspergillosis following hematopoietic cell transplantation: outcomes and prognostic factors. *Clin Infect Dis*. 2007;44(4):531-540.
36. Donnelly JP, Chen SC, Kauffman CA, et al. Revision and update of the consensus definitions of invasive fungal disease from EORTC/MSGERC. *Clin Infect Dis*. 2020;71(6):1367-1376.
37. Dimopoulos G, Frantzeskaki F, Poulakou G, Armaganidis A. Invasive aspergillosis in the ICU: autopsy-based analysis. *Intensive Care Med*. 2012;38(1):120-126.