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Fungal Profile in Patients with Lung Cancer Receiving First-Line Chemotherapy

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ABSTRACT

Introduction: Patients with lung cancer are vulnerable to opportunistic infections, particularly fungal pulmonary infections such as those caused by *Aspergillus* spp., due to immunosuppression from both the disease and chemotherapy. Despite the clinical significance of these infections, data on their prevalence and associated factors in patients with lung cancer remain limited. This study aimed to determine the prevalence of *Aspergillus* spp. and identify associated factors in patients with lung cancer who underwent first-line chemotherapy at a national respiratory referral hospital in Indonesia.

Methods: A cross-sectional study was conducted among 50 patients with lung cancer who had completed at least three cycles of chemotherapy. Sputum cultures were performed using Sabouraud dextrose agar (SDA), and serum immunoglobulin G (IgG) antibodies were tested using immunochromatographic assays. Demographic, clinical, and radiological data were collected. Bivariate and multivariate logistic regression analyses were used to identify factors associated with *Aspergillus* spp. infection.

Results: *Aspergillus* spp. was detected in 92.0% of patients via sputum culture, with *A. niger* and *A. fumigatus* as the most common isolates. Over 30% showed co-colonization with other fungal species, such as *Candida*. Multivariate analysis revealed that a high Brinkman Index was independently associated with *Aspergillus* spp. colonization ($p < 0.05$). Serum IgG antibody positivity was low (4%).

Conclusion: There was a high prevalence of *Aspergillus* spp. colonization among patients with lung cancer undergoing chemotherapy, with smoking history emerging as a key risk factor. Targeted fungal screening is recommended, especially in heavy smokers, to facilitate early detection and improve outcomes.

INTRODUCTION

Lung cancer is a malignant tumor arising from the bronchial epithelium and remains one of the leading causes of cancer-related deaths worldwide. Based on data from the Global Cancer Observatory (GLOBOCAN), it ranks second in incidence after breast cancer but contributes to the highest cancer mortality, responsible for 13.2% of 30,843 cases.¹ Despite the development of targeted therapies such as tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs), the overall five-year survival rate for

patients with lung cancer and distant metastases is still only 7%.²

Patients with lung cancer are particularly vulnerable to complications arising from opportunistic infections due to both disease-related and treatment-related immunosuppression. One of the most serious complications in this population is fungal pulmonary infection, especially those caused by *Aspergillus* spp. Fungal infections have emerged as a significant global health burden, leading to more than 1.5 million deaths annually, particularly affecting immunocompromised individuals such as cancer patients, transplant recipients,

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and those on long-term corticosteroid therapy.^{3,4} Among the various fungi, *Aspergillus fumigatus* is the most common cause of pulmonary fungal disease, presenting in different clinical forms, including invasive and chronic pulmonary aspergillosis.

Invasive pulmonary aspergillosis (IPA) is often found in patients with lung cancer due to factors such as tumor-induced lung damage, formation of cavitory lesions, and the immunosuppressive effects of chemotherapy. Despite the known risks, IPA is frequently underdiagnosed in cancer patients, especially during or after chemotherapy, which may result in worsened outcomes. Existing data on the prevalence of *Aspergillus* spp. and its relationship with chemotherapy in patients with lung cancer remains limited. Previous studies have reported relatively low but clinically significant rates of aspergillosis among cancer patients, and some have noted its association with poorer survival.^{2,5,6} However, the timing of onset and the contributing factors remain unclear in real-world clinical settings. A case report also described rapid clinical deterioration due to chronic pulmonary aspergillosis following cancer treatment.⁷

Recognizing this gap in evidence, this study investigated the prevalence of *Aspergillus* spp. and the associated factors among patients with lung cancer who underwent first-line chemotherapy at Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia. By identifying the extent of fungal colonization or infection in this vulnerable population and examining its clinical associations, this study aimed to contribute to early detection strategies and improve the management of fungal complications in lung cancer care.

METHODS

Study Design and Data Collection

This cross-sectional study was conducted at Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia, between July 2024 and July 2025. This study aimed to assess the prevalence of *Aspergillus* spp. and its associated factors in patients with lung cancer who had completed first-line chemotherapy. Eligible participants were adults (≥ 18 years old) with histologically confirmed lung cancer (stage IIIA or higher), epidermal growth factor receptor (EGFR) wild type, anaplastic lymphoma kinase (ALK) negative, and who had completed at least three cycles of chemotherapy. Additional criteria included a recent thoracic computed tomography (CT) scan (within the past month) and the ability to produce sputum. Patients

were excluded if they had chest wall tumors, mesothelioma, lung metastases, incomplete clinical data, or had used antifungal medications within the past month.

Blood samples were collected from a peripheral vein using a 5cc syringe and stored in sterile, labeled tubes. Samples were kept in a 2-8°C cooler and transported to the laboratory within four hours. *Aspergillus* spp. and serum immunoglobulin G (IgG) antibodies were analyzed using an immunochromatographic test (ICT). The sputum sample was induced by inhalation of 3% sodium chloride (NaCl) and collected in sterile, labeled containers. Like the blood samples, sputum specimens were transported in a 2-8°C cooler within four hours and cultured using Sabouraud dextrose agar (SDA) to detect *Aspergillus* spp. Clinical data collected included age, sex, body mass index (BMI), smoking index, comorbidities, previous cancer history, chemotherapy regimen, cancer staging, chest CT findings, and histopathology. Chemotherapy response was assessed using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria.

Statistical Analysis

Data were analyzed using the International Business Machines Corporation (IBM) Statistical Package for the Social Sciences (SPSS) version 25. The diversity of fungal colonization was presented as descriptive statistics. The association between the presence of *Aspergillus* spp. and independent variables was first analyzed using bivariate tests (Chi-square test). Variables with $p < 0.25$ were further analyzed using multivariate logistic regression to identify significant predictors. A p -value < 0.05 was considered statistically significant.

Ethical Consideration

This study had received ethical approval from the Ethics Committee of National Respiratory Referral Hospital, Jakarta, Indonesia (No. 074/KEPK-RSUPP/04/2025).

RESULTS

A total of 50 patients who met the inclusion criteria were included in this study. Based on sputum culture using SDA, *Aspergillus* spp. was detected in 46 out of 50 patients (92.0%). In contrast, only two patients (4.0%) had positive serum IgG antibodies against *Aspergillus* spp. as determined by the ICT, while 48 patients (96.0%) had negative serological results.

Table 1. Demographic and clinical characteristics of patients (n=50)

Variable	Category	Frequency (n)	Percentage (%)
Age	18-64 years old	34	68
	≥65 years old	16	32
Sex	Male	39	78
	Female	11	22
Body mass index	Underweight (<18.5)	18	36
	Normal (18.5-24.9)	20	40
	Overweight (25-29.9)	12	24
Smoking status (Brinkman Index)	Passive smoker	3	6
	Non-smoker	11	22
	Light smoker	1	2
	Moderate smoker	9	18
	Heavy smoker	26	52
Environmental exposure	No	45	90
	Yes	5	10
Comorbidities	No	28	56
	Yes	22	44
History of cancer (other than lung)	No	48	96
	Yes	2	4
Family history of cancer	No	44	88
	Yes	6	12
Histological subtype	Non-squamous non-small cell lung cancer	49	98
	Squamous non-small cell lung cancer	1	2
Chemotherapy regimen	Carboplatin+paclitaxel	45	90
	Cisplatin+pemetrexed	4	8
	Carboplatin+etoposide	1	2
Clinical symptoms reported by patients	Cough	29	58
	Hemoptysis	3	6
	Shortness of breath	4	8
	Chest pain	9	18
	Weight loss	5	10
Tumor response to chemotherapy based on Response Evaluation Criteria in Solid Tumors criteria	Complete response	1	2
	Partial response	15	30
	Progressive disease	4	8
	Stable disease	30	60

Among 47 sputum specimens collected from patients with lung cancer receiving first-line chemotherapy, *Aspergillus* spp. was identified in 22 samples (46.8%), either as single isolates or in combination with other fungi. The most commonly

identified species were *Aspergillus niger* (n=18), followed by *Aspergillus fumigatus* (n=16) and *Aspergillus flavus* (n=3). A total of 50 patients with histologically confirmed lung cancer who completed first-line chemotherapy were included in the study.

Table 2. Fungal species identified from the sputum of lung cancer patients undergoing first-line chemotherapy at Persahabatan National Referral Hospital, Jakarta

Fungal Species	Number of Fungal Isolates	Percentage (%)
<i>Aspergillus fumigatus</i>	16	28.60%
<i>Aspergillus niger</i>	18	32.10%
<i>Aspergillus flavus</i>	3	5.40%
<i>Penicillium</i> sp.	1	1.80%
<i>Candida</i> sp.	27	48.20%
<i>Candida parapsilosis</i>	1	1.80%
<i>Candida tropicalis</i>	2	3.60%
<i>Candida albicans</i>	4	7.10%
Total	56	100.00%

Note: A single patient might have more than one fungal species isolated

Co-colonization involving *Aspergillus* spp. was frequently observed. The most common combinations were *A. fumigatus*+*Candida* sp. (10.6%) and *A. niger*+*Candida* sp. (6.4%). Multiple species

combinations, including *A. fumigatus*, *A. niger*, *A. flavus*, and *Penicillium* sp., were also detected in a smaller proportion of specimens.

Table 3. Diversity of *Aspergillus* spp. colonization in sputum samples (N=46)

Colonization Pattern	Number of Specimens	Percentage (%)
<i>A. fumigatus</i>	2	4.30%
<i>A. niger</i>	5	10.60%
<i>A. fumigatus</i> + <i>Candida</i> sp.	5	10.60%
<i>A. fumigatus</i> + <i>A. niger</i>	2	4.30%
<i>A. fumigatus</i> + <i>A. niger</i> + <i>A. flavus</i>	1	2.10%
<i>A. fumigatus</i> + <i>A. niger</i> + <i>Candida</i> sp.	2	4.30%
<i>A. fumigatus</i> + <i>Penicillium</i> sp.	1	2.10%
<i>A. fumigatus</i> + <i>A. niger</i> + <i>A. flavus</i> + <i>Candida</i> sp.	1	2.10%
<i>A. niger</i> + <i>Candida</i> sp.	3	6.40%
Total Samples with <i>Aspergillus</i> spp.	22	46.80%

Chest CT scans performed within one month before sample collection revealed that radiological abnormalities were present in 13 out of 50 patients (26%), while the majority (74%) had no radiological abnormalities. The most common radiologic finding was a fungal ball (aspergilloma) in 10 patients (20%), followed by cavitory lesions in 3 patients (6%), and pleural thickening in 3 patients (6%).

Bivariate analysis was conducted to evaluate associations between clinical variables and the presence of *Aspergillus* spp. infection. Among the variables tested, the Brinkman Index ($p=0.003$) was significantly associated with *Aspergillus* spp. detection. Other variables, such as age group ($p=0.421$), sex ($p=0.268$), BMI ($p=0.785$), cancer stage ($p=0.487$), and comorbidities ($p=0.801$), did not show statistically significant associations. Multivariate logistic regression analysis was then performed, incorporating the significant variables identified in the bivariate analysis. The Brinkman Index remained an independent predictor of *Aspergillus* spp. infection.

DISCUSSION

Although this study was designed as a descriptive investigation, it revealed an occurrence of fungal infections among patients with lung cancer undergoing first-line chemotherapy. A previous study underscored that IPA contributes significantly to morbidity and mortality in patients with malignancies.⁸ A study involving 2,543 patients with advanced-stage lung cancer reported that among 290 patients who underwent a galactomannan (GM) test, 34 (11.7%) were diagnosed with IPA.²

The risk of developing IPA was notably higher in those undergoing chemotherapy (hazard ratio/HR=4.02, $p=0.027$) and was also observed in patients receiving immunotherapy (HR=3.41, $p=0.076$).² Another meta-analysis including 20,138 lung cancer patients reported a pooled IPA incidence of 2.4% (95% confidence interval/CI: 1.5–3.2%) and identified several risk factors, including current or past smoking (odds ratio/OR 2.92, $p<0.001$) and male sex (OR 1.96, $p=0.008$).⁹ The descriptive findings of this study align

with these prior observations: among the 50 analyzed patients, 46 (92%) had positive sputum cultures for *Aspergillus* spp., and two (4%) demonstrated detectable serum IgG antibodies.

Patients with lung cancer in this study most commonly received carboplatin and paclitaxel (45 subjects), followed by cisplatin and pemetrexed (4 subjects), and carboplatin with etoposide (1 subject). These regimens are well-known for causing myelosuppression, particularly neutropenia, which critically impairs host defense against pathogens, including *Aspergillus* spp.

For instance, a Phase II trial of carboplatin-paclitaxel in advanced non-small cell lung cancer (NSCLC) reported grade 3-4 neutropenia in 29.9% of patients, with neutropenic fever in up to 4.5% of patients.¹⁰ Similarly, pemetrexed usage is associated with increased risk of severe infection in patients with NSCLC. A meta-analysis found febrile neutropenia in 1.3% and severe infection in 5.7% of cases (respiratory rate/RR 4.28, 95% CI 1.08-17.01; $p=0.04$).¹¹ Another study, using paclitaxel in conjunction with ifosfamide/carboplatin/etoposide (ICE) chemotherapy in patients with advanced lung cancer, found that 63% patients experienced grade 4 neutropenia.¹² In a Japanese study of 244 patients with lung cancer treated with etoposide plus platinum, febrile neutropenia affected 19.7% of patients, with grade 3-4 neutropenia in 85% of subjects.¹³

Different chemotherapy regimens, depending on the mechanism of action, can increase the susceptibility of patients with lung cancer to aspergillosis. A study by Yarsy, *et al.* (2023) highlighted the toxicity of various chemotherapy regimens, such as paclitaxel (18%), carboplatin and paclitaxel (23%), oxaliplatin and fluorouracil and leucovorin (23%), which cause neutropenia, thus increasing the risk of aspergillosis in patients with lung cancer.¹⁴ Shin, *et al.* (2020) found the use of chemotherapy and radiotherapy to be statistically significant factors in triggering aspergillosis.¹⁵ On its own, the incidence of chemotherapy-induced aspergillosis was not statistically significant (1.3%, $p=0.466$).¹⁵

This pattern of drug-induced neutropenia severely weakens mucosal barriers. It impairs phagocytic activity, thus facilitating fungal colonization and invasion easily.¹⁶ Neutropenia is recognized as one of the strongest risk factors for IPA across immunocompromised populations.^{10,12} Fungi are traditionally categorized as primary pathogens (e.g., *Histoplasma*, *Coccidioides*) that can infect healthy individuals, and opportunistic pathogens (e.g., *Aspergillus*, *Candida*, *Cryptococcus*) that predominantly cause disease in immunocompromised hosts. Opportunistic species can cause severe, invasive, and sometimes fatal infections when host defenses are impaired.¹⁷

Systemic fungal infections are increasingly observed in patients with weakened immunity, such as those undergoing chemotherapy, organ transplantation, or corticosteroid therapy. Fungi that typically act as commensals may become invasive under such conditions. Mucosal barrier damage (e.g., mucositis) and neutropenia create entry points for fungal invasion, as demonstrated in both clinical observations and experimental models.¹⁷

Interestingly, this study also revealed the occurrence of multi-species fungal colonization in several patients. Among 46 patients with positive fungal cultures, over 40% showed colonization by more than one fungal species, including combinations such as *Aspergillus fumigatus* with *Candida* sp., *A. niger*, and *Penicillium* sp. These findings suggest that the respiratory tract in patients with lung cancer may serve as a niche not only for pathogenic fungi but also for commensal organisms that become opportunistic under immunosuppressed conditions. This aligns with earlier evidence that polymicrobial fungal colonization can occur in immunocompromised individuals and may complicate diagnosis and management.¹⁸

In a study by Ali, *et al.* (2014), the prevalence of *Aspergillus* sp. colonization in patients with bronchogenic carcinoma showed that as many as 35.5% of patients with lung cancer experienced *Aspergillus* sp. colonization.¹⁹ From bronchoalveolar lavage (BAL) samples, only a portion of the colonized subjects showed positive results in galactomannan antigen examination, namely 58.3% in BAL and 47.2% in serum.¹⁹

In the multivariate analysis of this study, the Brinkman Index, a metric that integrates both duration and intensity of smoking, emerged as an independent predictor of *Aspergillus* spp. infection. This finding supports the critical role of cumulative smoking exposure in fungal colonization risk among patients with lung cancer undergoing chemotherapy. It aligns with accumulating evidence stating that smoking is a

significant risk factor for pulmonary fungal infections. Teng, *et al.* (2025) revealed that the risk factors for pulmonary aspergillosis in patients with lung cancer included current or past smoking (OR: 2.92; $p < 0.001$).⁹

Chronic tobacco exposure damages respiratory defenses through several mechanisms, including impaired mucociliary clearance, epithelial barrier disruption, and compromised innate immunity (e.g., dysfunction of alveolar macrophages and neutrophils). These changes increase the lung's susceptibility to colonization and invasion by airborne fungal spores such as *Aspergillus* spp., especially in the context of chemotherapy-induced immunosuppression.¹⁸

Supporting evidence also comes from a Japanese case series where all 19 patients with lung cancer with aspergillosis had prior smoking histories.¹⁷ A study of post-resection chronic aspergillosis found smoking was significantly more common in affected patients (83.9% vs. 60.3%, $p < 0.001$) along with other factors such as male sex, chronic obstructive pulmonary disease (COPD), interstitial lung disease (ILD), prior tuberculosis (TB), and major lung resections.^{9,20} The findings of this study, with the pooled evidence, support that smoking is a significant predisposing factor for fungal colonization in this high-risk patient group.

Given the elevated risk among heavy smokers, particularly those with high Brinkman Index scores, targeted screening for fungal colonization or infection should be considered in patients with lung cancer undergoing chemotherapy. Early detection using fungal cultures, antigen testing (e.g., galactomannan), or molecular diagnostics may facilitate prompt antifungal intervention and help prevent progression to invasive disease. Future studies are recommended to evaluate the cost-effectiveness, diagnostic yield, and clinical outcomes of incorporating routine fungal screening protocols into the management of high-risk patients.

CONCLUSION

This study revealed a high prevalence of *Aspergillus* spp. colonization among patients with lung cancer undergoing first-line chemotherapy at Persahabatan National Respiratory Referral Hospital, Jakarta, Indonesia, as identified through sputum cultures. *Aspergillus niger*, *A. fumigatus*, and *A. flavus* were the most frequently isolated species, often co-colonizing with *Candida* spp., highlighting a complex pattern of fungal colonization in immunocompromised airways. The use of chemotherapy likely contributes to fungal susceptibility through neutropenia and disruption of the mucosal barrier. Co-infection involving multiple fungal species was observed in culture-positive patients,

while chest CT findings, such as fungal balls and cavitary lesions, were present in a subset of cases. Importantly, multivariate analysis found that cumulative smoking exposure, identified with the Brinkman Index, was an independent risk factor for *Aspergillus* spp. infection. These findings emphasize the need for targeted fungal screening in high-risk individuals, particularly heavy smokers, to enable early detection.

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Conflict of Interest

The authors declared there is no conflict of interest.

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Authors' Contributions

Conceptualization: HKPF, AA, JZ, AR. Data curation: HKPF, AA. Methodology: HKPF, AA, JZ, AR. Writing the manuscript: HKPF, AA, IADP, JZ, AR. Visualization: HKPF, AA, AAH, JZ, AR.

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