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ORIGINAL RESEARCH

Independent Risk Factors and Nomogram-Based Prediction of Pulmonary Fungal Infection in Lung Cancer Inpatients: A Single-Center Retrospective Study

Yanran Xu[1,2], Yan Chen[1,2]

[1]Department of Respiratory and Critical Care Medicine, The Second Clinical Medical College of North Sichuan Medical College, Nanchong, Sichuan, 637000, People's Republic of China; [2]Department of Respiratory and Critical Care Medicine, Beijing Anzhen Nanchong Hospital of Capital Medical University & Nanchong Central Hospital, Nanchong, Sichuan, 637000, People's Republic of China

Correspondence: Yan Chen, Email 13990829946@163.com

Purpose: To investigate independent risk factors and construct an internally validated risk prediction model for invasive pulmonary fungal infection (IPFI) in patients with lung cancer.

Patients and Methods: Clinical data from 250 consecutive lung cancer inpatients admitted to Nanchong Central Hospital between February 2022 and March 2025 were retrospectively analyzed; 41 patients developed IPFI and 209 did not. Patients were randomly assigned to a training set (n=175) and a validation set (n=75) at a 7:3 ratio. Candidate predictors were screened by univariate logistic regression, reduced using least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation, and entered into multivariable logistic regression to construct a nomogram. Model performance was evaluated using bootstrap internal validation (1000 resamples), calibration curves and goodness-of-fit testing, receiver operating characteristic analysis, and decision curve analysis.

Results: Diabetes mellitus, invasive procedures, systemic glucocorticoid use, lower CD4+ T-cell count, and length of hospital stay >14 days were associated with IPFI and were retained as independent predictors in the final model. The model showed good discrimination, with an area under the curve of 0.876 (95% CI: 0.809–0.944) in the training set and 0.861 (95% CI: 0.750–0.973) in the validation set, and demonstrated clinical net benefit across threshold probability ranges of 0.03–0.90 (training) and 0.04–0.78 (validation).

Conclusion: This nomogram may support early risk stratification for IPFI among lung cancer inpatients, while confirmation in external, multi-center cohorts is needed before broader clinical application.

Keywords: lung cancer, invasive pulmonary fungal infection, risk factors, nomogram, prediction model

Introduction

According to the *Global Cancer Statistics 2022* released by the International Agency for Research on Cancer (IARC),[1] Lung cancer has become the malignancy with the highest global incidence and mortality rates. The expanding population of treated survivors increases the number of patients exposed to prolonged hospitalization, repeated procedures, and therapy-associated immune dysfunction that can predispose to opportunistic pulmonary infections. In this context, invasive pulmonary fungal infection is clinically consequential because delayed recognition is common, respiratory signs can overlap with tumor progression or treatment toxicity, and diagnostic pathways often require integration of imaging with microbiologic or biomarker evidence to avoid missed or late diagnoses.[2] A focused inpatient risk-stratification framework is therefore clinically motivated, particularly in respiratory and oncology wards where triage decisions must often be made before definitive mycologic confirmation.

Over recent decades, advancements in diagnostic techniques and therapeutic modalities have contributed to a decline in overall mortality among lung cancer patients.[3] With prolonged survival, however, patients exhibit significantly compromised immune function due to the combined effects of the tumor itself, radiotherapy, chemotherapy, surgical

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interventions, and other treatments, rendering them highly susceptible to opportunistic infections.[4] Fungi predominantly act as opportunistic pathogens that can cause invasive infections in immunocompromised hosts.[5] Across studies of invasive fungal disease, comparability is strongly influenced by how cases are defined, because host factors, compatible clinical features, and supporting mycologic evidence are variably operationalized in retrospective datasets.[6] A recent systematic synthesis in lung cancer populations further indicates that different pulmonary fungal syndromes concentrate in distinct risk pathways, with chronic pulmonary aspergillosis linked to pre-existing lung structural disease and Pneumocystis pneumonia showing strong associations with high-dose systemic corticosteroids, supporting the need to specify syndrome definitions when framing prediction endpoints.[7] For model development and interpretation, explicit diagnostic criteria and transparent variable definitions are essential to enable clinically meaningful benchmarking and reduce ambiguity in how "pulmonary fungal infection" is captured across centers.

Studies indicate that pulmonary infections account for 20% to 68% of mortality causes in lung cancer patients, with fungal infections responsible for approximately 20% of such cases.[8] Epidemiological data reveal an increasing incidence of Invasive Pulmonary Fungal Infection (IPFI), with mortality rates persistently reaching 35.7%.[9] Epidemiologic summaries focused on pulmonary aspergillosis in lung cancer suggest a measurable but heterogeneous burden, emphasizing the need for pragmatic prediction tools that can function with routinely captured variables. A meta-analysis of retrospective cohorts reported an overall pulmonary aspergillosis incidence around a few percent in lung cancer, and highlighted consistent associations with smoking and chronic lung disease that may act through airway remodeling and impaired local defenses.[10] Long-term follow-up after curative-intent surgery also indicates that chronic pulmonary aspergillosis can emerge years later and increase cumulatively, with risks associated with postoperative pulmonary complications and combined chemo-radiotherapy exposure.[11] Together, these patterns support inpatient screening logic that integrates comorbidity, exposure, and immune status.

Concurrent IPFI in lung cancer patients not only exacerbates disease severity and elevates mortality risk but also delays oncological treatment, thereby significantly impairing prognosis.[12–15] Clinical cohorts in routine practice also demonstrate that pulmonary fungal infection in lung cancer is not pathogen-monolithic, and that comorbidity clustering and care intensity can shape observed case mixes. In a large retrospective cohort of proven/probable invasive pulmonary fungal disease in lung cancer, Candida and Aspergillus dominated the pathogen spectrum, and risks concentrated in patients with chronic respiratory disease, bone marrow suppression, multiple comorbidities, and smoking-related profiles, indicating that both systemic vulnerability and airway-lung substrate matter for case accrual.[16] In advanced disease settings, treatment era effects are also clinically relevant; propensity-matched analyses have linked invasive pulmonary aspergillosis to poorer survival and suggested that chemotherapy and immune checkpoint inhibitor exposure may track higher risk, reinforcing the value of early identification pathways.[17]

Current research on pulmonary fungal infections in lung cancer populations primarily focuses on characterizing infection patterns, while studies developing predictive models for fungal infection risk remain scarce.[18,19] Prediction modeling for pulmonary fungal infection in lung cancer has recently been operationalized with nomograms, providing a direct methodological foundation for structured risk scoring in hospitalized cohorts. A recent study constructed a logistic-regression nomogram with internal validation, using routine clinical predictors such as diabetes, glucocorticoid exposure, invasive procedures, antimicrobial exposure, and length of stay, demonstrating strong discrimination within a single-center split-sample design and establishing a benchmark for model positioning and comparability.[20] Thus, direct benchmarking across studies requires transparent case-definition criteria and harmonized variable operationalization, because differences in diagnostic thresholds and host-factor coding can change apparent predictor effects and model transportability. Clinical urgency is underscored by outcome data from lung cancer patients with invasive pulmonary aspergillosis, where short-term mortality can be high and is associated with frailty and inflammatory markers, supporting the clinical utility of front-loaded risk stratification to prompt targeted diagnostic work-up and preventive attention.[21]

Outcome definitions and target populations vary across available nomograms; for example, Lai et al[20] modeled pulmonary fungal infection risk using routine inpatient predictors, whereas the present framework centers invasive pulmonary fungal infection (IPFI) risk stratification in consecutively hospitalized lung cancer patients, incorporating cellular immune status alongside exposure and care-intensity indicators to support earlier triage. Accordingly, the study prioritizes predictors available at admission and during early inpatient care, including immune-cell depletion signals and

prolonged hospitalization markers, to align risk scoring with actionable timing for diagnostic escalation and preventive management in routine lung cancer wards.

Therefore, this study aims to systematically identify risk factors for secondary pulmonary fungal infections in lung cancer patients through retrospective analysis of clinical data, develop a predictive model based on these factors, conduct comprehensive model validation, and provide a reference tool for early clinical risk stratification and therapeutic decision-making.

Materials and Methods

Study Population

A single-center, retrospective cohort design was applied using the electronic medical record (EMR) system of Nanchong Central Hospital. The study window spanned February 2022 to March 2025, and consecutive admissions meeting eligibility criteria were screened to minimize selection bias. The final cohort size was fixed by case availability within the prespecified timeframe and data completeness for the prespecified candidate predictors and outcome status.

A total of 250 consecutive lung cancer patients admitted to Nanchong Central Hospital between February 2022 and March 2025 were retrospectively enrolled. Participants were stratified into two cohorts based on IPFI occurrence: an infection group (n = 41) and a non-infection group (n = 209).

Inclusion criteria: (1) Histologically or cytologically confirmed lung cancer;[18] (2) Meeting diagnostic criteria for pulmonary fungal infection per the Expert Consensus on Diagnosis and Treatment of Pulmonary Mycosis;[19] (3) Complete clinical documentation. No exclusion was applied based on tumor stage; TNM stages I–IV were eligible and staging was abstracted from the EMR according to the contemporaneous lung cancer guideline used in routine care.

Exclusion criteria: (1) Concomitant immunocompromising conditions (eg, solid organ transplantation, HIV infection); (2) Coexisting active infections; (3) History of other malignancies; (4) Severe cardiac, hepatic, or renal dysfunction.

This study received ethical approval from the Institutional Review Board of our hospital (Approval No.: 2025-121).

Definition of Pulmonary Fungal Infection (IPFI)

Pulmonary fungal infection status was defined according to the Expert Consensus on Diagnosis and Treatment of Pulmonary Mycosis and operationalized for retrospective ascertainment from EMR documentation. IPFI was coded when the medical record documented (i) compatible clinical features prompting antifungal evaluation (respiratory symptoms such as cough, dyspnea, fever, hemoptysis, or refractory pulmonary symptoms), and (ii) chest imaging consistent with pulmonary fungal disease (new or progressive infiltrates, nodules, consolidation, cavitation, or other clinician-documented fungal-suspected CT findings), together with (iii) mycological evidence recorded in the chart from at least one source: direct microscopy or culture from lower-respiratory specimens (sputum, endotracheal aspirate, or bronchoalveolar lavage fluid), histopathology/cytology demonstrating fungal elements in respiratory specimens, or fungal biomarker positivity documented in the record (eg, galactomannan and/or 1,3-β-D-glucan) in the setting of compatible imaging. Patients not meeting the above documentation-based criteria during the index hospitalization were classified as non-IPFI.

Data Collection

Patient data were systematically extracted from the hospital electronic medical record (EMR) system in strict accordance with predefined inclusion and exclusion criteria. The collected parameters encompassed: (1) Demographic and Clinical Characteristics: Gender, age, BMI, smoking history, comorbidities, Pathological type, TNM stage, Recent anticancer treatments within 30 days (radiotherapy, chemotherapy, immunotherapy), Invasive procedures, Prolonged antibiotic use (>7 days), systemic corticosteroid administration, Length of hospital stay. (2) Laboratory Parameters: Complete blood count, Inflammatory biomarkers (hs-CRP, PCT), ALB, T-cell immunity profiles.

For baseline laboratory indices (complete blood count, hs-CRP, PCT, albumin, and T-cell immunity profiles), the primary value was defined as the first recorded result after admission for the index hospitalization; when multiple results were available, the earliest measurement prior to documented IPFI diagnosis (infection group) or prior to discharge (non-IPFI group) was used. “Recent anticancer treatment within 30 days” was abstracted as any record of chemotherapy, radiotherapy, or immunotherapy administered within the 30 days preceding admission. “Prolonged antibiotic use” was coded as systemic antibacterial therapy documented for >7 consecutive days during the index hospitalization. “Systemic

corticosteroid administration" was coded as any systemic (oral or intravenous) glucocorticoid exposure during the index hospitalization. "Invasive procedures" were abstracted as any EMR-documented invasive respiratory or vascular procedure (eg, bronchoscopy, central venous catheterization, endotracheal intubation, or mechanical ventilation) performed during hospitalization.

Statistical Analysis

Data processing and analysis were conducted using R language (version 4.4.1). For continuous variables, if they conformed to a normal distribution, mean ± standard deviation was used for statistical description, and independent sample *t*-test was applied for inter-group comparison. If they did not conform to a normal distribution, median [P25, P75] was used for description, and rank sum test was applied for inter-group comparison. For count data, number of cases (%) was used for description, and chi-square test was applied for inter-group comparison. Fisher's exact probability was used when chi-square test was not applicable. For a small number of missing values, multiple imputation was performed using the "missRanger" package in R language.

All data were randomly divided into a training set (70%) and a validation set (30%) at a ratio of 7:3. To ensure reproducibility, a fixed random seed was set prior to dataset partitioning and resampling procedures. Missing data were imputed using the missRanger package with predictive mean matching (pmm.k = 5) and ranger-based imputation under default iteration settings (maxiter = 10; num.trees = 100) unless otherwise specified by the package defaults in the analysis environment. Feature selection was implemented using LASSO logistic regression in the glmnet framework (family = "binomial", $\alpha = 1$), with predictor standardization enabled (standardize = TRUE). Ten-fold cross-validation was conducted (nfolds = 10) using deviance as the optimization criterion (type.measure = "deviance"). The penalization parameter was selected using the one-standard-error rule (lambda.1se; $\lambda = 0.057$ in the cross-validation profile), and variables with non-zero coefficients at lambda.1se were retained for downstream multivariable modeling.

The training set was used for model training, and the validation set was used for model validation. The steps for constructing the predictive model were as follows: Firstly, based on univariate logistic regression analysis, potential predictors of the outcome event were screened out ($P < 0.1$). Further, for the selected variables, the least absolute shrinkage and selection operator (LASSO) logistic regression algorithm was used to select significant features (non-zero coefficients), and 10-fold cross-validation was used to determine the optimal parameter configuration. The lambda value corresponding to the minimum mean squared error (min) was used to determine the coefficients, and variables with non-zero coefficients were selected.

For the selected variables, multivariate logistic regression analysis (stepwise method, bidirectional) was conducted. A nomogram for the predictive model was constructed based on the variables with $P < 0.05$ in the stepwise method. The constructed nomogram was verified by 1000 bootstrap samples, and calibration curves were drawn to evaluate the model's calibration. The Hosmer-Lemeshow (HL) test was used to assess the model's goodness of fit. Further, the receiver operating characteristic (ROC) curve analysis was conducted to calculate the area under the curve (AUC), sensitivity, specificity, and other indicators to evaluate the model's discriminatory power. A clinical decision curve (DCA) was constructed to evaluate the clinical application value of the model and quantify the net benefit within the threshold probability range. Finally, the constructed model was validated in the validation set. A two-sided test with $P < 0.05$ was considered statistically significant.

Results

Baseline Characteristics of Training and Validation Sets

The cohort of 250 lung cancer patients was randomly partitioned into a training set (n = 175, 70%) and a validation set (n = 75, 30%). Baseline characteristics of the training and validation sets are summarized in Table 1 together with absolute standardized mean differences (|SMD|) for each variable.

The largest |SMD| values were observed for lymphocyte count (|SMD|=0.417), CD4+ T-cell count (|SMD|=0.270), and invasive procedures (|SMD|=0.250), while other variables showed smaller between-set differences (Table 1).

Table 1 Baseline Characteristics of Training and Validation Sets

Variable	Total (n=250)	Training (n=175)	Validation (n=75)	|SMD|
Women	64 (25.6%)	47 (26.9%)	17 (22.7%)	0.096
Age ≤60 years	90 (36.0%)	63 (36.0%)	27 (36.0%)	0.000
BMI (kg/m^2), mean±SD	22.49 ± 3.40	22.61 ± 3.35	22.19 ± 3.53	0.123
Smoking history: Yes	107 (42.8%)	71 (40.6%)	36 (48.0%)	0.150
Respiratory diseases: Yes	76 (30.4%)	54 (30.9%)	22 (29.3%)	0.035
Cardiovascular disease: Yes	71 (28.4%)	54 (30.9%)	17 (22.7%)	0.184
Diabetes mellitus: Yes	38 (15.2%)	30 (17.1%)	8 (10.7%)	0.185
Pathology: Small cell lung cancer	23 (9.2%)	19 (10.9%)	4 (5.3%)	0.204
TNM stage III–IV	212 (84.8%)	148 (84.6%)	64 (85.3%)	0.019
Recent chemotherapy: Yes	102 (40.8%)	69 (39.4%)	33 (44.0%)	0.093
Recent radiotherapy: Yes	28 (11.2%)	18 (10.3%)	10 (13.3%)	0.095
Recent immunotherapy: Yes	62 (24.8%)	41 (23.4%)	21 (28.0%)	0.105
Invasive procedures: Yes	98 (39.2%)	75 (42.9%)	23 (30.7%)	0.250
Prolonged antibiotic use (>7 d): Yes	101 (40.4%)	66 (37.7%)	35 (46.7%)	0.182
Systemic glucocorticoids: Yes	47 (18.8%)	35 (20.0%)	12 (16.0%)	0.104
Length of stay >14 d	69 (27.6%)	50 (28.6%)	19 (25.3%)	0.073
WBC (×10^9/L), median (IQR)	6.71 (5.04, 9.56)	6.84 (5.52, 9.97)	6.39 (4.27, 8.77)	0.136
Lymphocytes (×10^9/L), median (IQR)	1.12 (0.70, 1.58)	1.20 (0.79, 1.61)	0.96 (0.58, 1.31)	0.417
PCT (ng/mL), median (IQR)	0.03 (0.02, 0.07)	0.03 (0.02, 0.06)	0.03 (0.02, 0.10)	0.000
hs-CRP (mg/L), median (IQR)	10.06 (2.07, 65.24)	11.69 (1.80, 76.85)	6.20 (2.55, 42.47)	0.123
Albumin (g/L), median (IQR)	40.20 (35.52, 43.75)	40.20 (35.85, 43.87)	40.20 (35.45, 43.50)	0.000
CD4+ T cell count (cells/μL), median (IQR)	330.00 (211.75, 494.75)	347.00 (237.00, 512.50)	294.00 (182.52, 436.00)	0.270
CD4+/CD8+, median (IQR)	1.23 (0.93, 1.81)	1.21 (0.94, 1.75)	1.31 (0.92, 1.89)	0.151

Outcome-Stratified Baseline Features in Training Set

Within the training set, patients with secondary fungal infection (infection group) exhibited significant differences ($P < 0.05$) versus the non-infection group in: BMI, invasive procedures, prolonged antibiotic use, corticosteroid administration, WBC, L, PCT, hs-CRP, ALB, CD4+ T-cell count, CD4+/CD8+, and length of hospital stay. The combined fungal infection group had lower BMI, L, CD4+ T cell count, and CD4+/CD8+, higher proportions of invasive procedures, prolonged antibiotics, corticosteroids, and hospitalization duration (greater than 14 days), and relatively higher WBC, PCT, and hs-CRP levels. There were no statistically significant differences in the distribution of other variables between the two groups ($P > 0.05$) (Table 2). Within the training set, the infection group had higher frequencies of invasive procedures (75.9% vs 36.3%), prolonged antibiotic use (65.5% vs 32.2%), systemic glucocorticoid exposure (55.2% vs 13.0%), and length of stay >14 days (48.3% vs 24.7%), alongside lower median CD4+ T-cell count (233.00 vs 370.00 cells/μL) and lower CD4+/CD8 + ratio (0.99 vs 1.24) than the non-infection group (Table 2).

Table 2 Baseline Table for Training Set Outcome Grouping

Variables	Non-Coinfected (n =146)	Coinfected (n = 29)	Statistic	p
Gender			1.636	0.201
Women	42 (28.8)	5 (17.2)		
Men	104 (71.2)	24 (82.8)		
Age, y			0.035	0.852
≤60.0	53 (36.3)	10 (34.5)		
>60.0	93 (63.7)	19 (65.5)		
BMI (kg/m^2)	22.82 ± 3.49	21.57 ± 2.30	2.422	0.019

(*Continued*)

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Table 2 (Continued).

Variables	Non-Coinfected (n =146)	Coinfected (n = 29)	Statistic	p
Smoking history			1.793	0.181
No	90 (61.6)	14 (48.3)		
Yes	56 (38.4)	15 (51.7)		
Respiratory diseases			1.804	0.179
No	104 (71.2)	17 (58.6)		
Yes	42 (28.8)	12 (41.4)		
Cardiovascular disease			1.804	0.179
No	104 (71.2)	17 (58.6)		
Yes	42 (28.8)	12 (41.4)		
Diabetes			Fisher	0.055
No	125 (85.6)	20 (69.0)		
Yes	21 (14.4)	9 (31.0)		
Pathological type			Fisher	0.095
Non-small cell lung cancer	133 (91.1)	23 (79.3)		
Small cell lung cancer	13 (8.9)	6 (20.7)		
TNM			Fisher	0.165
I–II	20 (13.7)	7 (24.1)		
III–IV	126 (86.3)	22 (75.9)		
Recent chemotherapy			2.041	0.153
No	85 (58.2)	21 (72.4)		
Yes	61 (41.8)	8 (27.6)		
Recent radiotherapy			Fisher	0.315
No	129 (88.4)	28 (96.6)		
Yes	17 (11.6)	1 (3.4)		
Recent immunotherapy			0.742	0.389
No	110 (75.3)	24 (82.8)		
Yes	36 (24.7)	5 (17.2)		
Invasive procedures			15.462	<0.001
No	93 (63.7)	7 (24.1)		
Yes	53 (36.3)	22 (75.9)		
Prolonged antibiotic use			11.439	<0.001
No	99 (67.8)	10 (34.5)		
Yes	47 (32.2)	19 (65.5)		
Use of glucocorticoids			26.876	<0.001
No	127 (87.0)	13 (44.8)		
Yes	19 (13.0)	16 (55.2)		
WBC ($\times 10^9$/L)	6.72 (5.48, 9.15)	9.55 (5.89, 12.38)	−2.165	0.030
NEU (%)	70.55 (64.50, 78.72)	77.70 (67.60, 85.90)	−1.836	0.066
Lymphocytes ($\times 10^9$/L)	1.22 (0.85, 1.62)	0.85 (0.47, 1.58)	2.344	0.019
PCT (ng/mL)	0.03 (0.02, 0.05)	0.08 (0.03, 0.30)	−3.352	<0.001
hs-CRP (mg/L)	6.60 (1.30, 59.94)	54.30 (22.00, 102.83)	−3.975	<0.001
Albumin (g/L)	40.25 ± 5.45	36.76 ± 6.49	2.717	0.010
CD4+T cell count (cells/μL)	370.00 (257.25, 527.00)	233.00 (66.00, 290.84)	3.967	<0.001
$CD4^+/CD8^+$	1.24 (0.99, 1.78)	0.99 (0.45, 1.37)	2.885	0.004
Length of hospital stay (days)			6.613	0.010
≤14.0	110 (75.3)	15 (51.7)		
>14.0	36 (24.7)	14 (48.3)		

Univariate Logistic Regression Analysis

Univariate analysis identified the following predictors of fungal infection ($P < 0.1$): BMI, diabetes, pathological type, invasive procedures, prolonged antibiotic use, corticosteroid administration, WBC, L, hs-CRP, ALB, CD4+ T-cell count, CD4+/CD8+, and Length of hospital stay (Table 3).

Table 3 Training Set Single-Factor Logistic Regression Results

Variable	β	SE	z	OR (95% CI)	p
Gender					
Women	0.000			Reference	
Men	0.662	0.524	1.262	1.938 (0.744, 6.055)	0.207
Age, y					
≤60.0	0.000			Reference	
>60.0	0.080	0.427	0.186	1.083 (0.477, 2.584)	0.852
BMI (kg/m^2)	−0.123	0.067	−1.838	0.884 (0.771, 1.004)	0.066
Smoking history					
No	0.000			Reference	
Yes	0.543	0.409	1.330	1.722 (0.771, 3.873)	0.184
Respiratory diseases					
No	0.000			Reference	
Yes	0.558	0.419	1.333	1.748 (0.755, 3.955)	0.183
Cardiovascular disease					
No	0.000			Reference	
Yes	0.558	0.419	1.333	1.748 (0.755, 3.955)	0.183
Diabetes					
No	0.000			Reference	
Yes	0.985	0.466	2.116	2.679 (1.041, 6.575)	0.034
Pathological type					
Non-small cell lung cancer	0.000			Reference	
Small cell lung cancer	0.982	0.543	1.809	2.669 (0.866, 7.516)	0.071
TNM					
I–II	0.000			Reference	
III–IV	−0.695	0.496	−1.401	0.499 (0.194, 1.395)	0.161
Recent chemotherapy					
No	0.000			Reference	
Yes	−0.633	0.448	−1.413	0.531 (0.209, 1.236)	0.158
Recent radiotherapy					
No	0.000			Reference	
Yes	−1.306	1.050	−1.244	0.271 (0.015, 1.407)	0.214
Recent immunotherapy					
No	0.000			Reference	
Yes	−0.452	0.528	−0.856	0.637 (0.203, 1.672)	0.392
Invasive procedures					
No	0.000			Reference	
Yes	1.707	0.467	3.658	5.515 (2.307, 14.741)	<0.001
Prolonged antibiotic use					
No	0.000			Reference	
Yes	1.387	0.429	3.233	4.002 (1.760, 9.603)	0.001
Use of glucocorticoids					
No	0.000			Reference	
Yes	2.107	0.447	4.713	8.227 (3.458, 20.172)	<0.001
WBC (×10^9/L)	0.124	0.050	2.453	1.132 (1.024, 1.251)	0.014

(*Continued*)

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Table 3 (Continued).

Variable	β	SE	z	OR (95% CI)	p
NEU (%)	0.016	0.016	1.030	1.016 (0.987, 1.050)	0.303
Lymphocytes (×10^9/L)	−0.666	0.372	−1.790	0.514 (0.238, 0.947)	0.074
PCT (ng/mL)	0.007	0.093	0.075	1.007 (0.714, 1.180)	0.940
hs-CRP (mg/L)	0.007	0.002	2.748	1.007 (1.002, 1.012)	0.006
Albumin (g/L)	−0.107	0.037	−2.888	0.898 (0.833, 0.964)	0.004
CD4+ T cell count (cells/μL)	−0.005	0.001	−3.685	0.995 (0.992, 0.998)	<0.001
$CD4^+/CD8^+$	−1.077	0.405	−2.657	0.341 (0.143, 0.701)	0.008
Length of hospital stay (days)					
≤14.0	0.000			Reference	
>14.0	1.048	0.418	2.505	2.852 (1.249, 6.512)	0.012

Feature Selection via LASSO Regression

To address multicollinearity, variables with $P < 0.1$ from univariate analysis underwent LASSO regression. Six predictors retained non-zero coefficients: diabetes mellitus, invasive procedures, prolonged antibiotic use, corticosteroid administration, CD4+ T-cell count, and Length of hospital stay (Figure 1A and B).

Multivariable Logistic Regression Analysis

In the complete multivariable model including all LASSO-selected predictors, diabetes mellitus (adjusted OR 3.707, 95% CI 1.132–12.141), invasive procedures (adjusted OR 5.613, 95% CI 1.766–17.847), systemic glucocorticoid exposure (adjusted OR 4.288, 95% CI 1.468–12.523), and length of stay >14 days (adjusted OR 2.719, 95% CI 1.011–7.317) were associated with higher odds of IPFI, whereas higher CD4+ T-cell count was protective (adjusted OR 0.995 per 1 cell/μL, 95% CI 0.992–0.998) (Table 4). Prolonged antibiotic use did not retain an independent association after adjustment (adjusted OR 1.620, 95% CI 0.673–3.899) (Table 4).

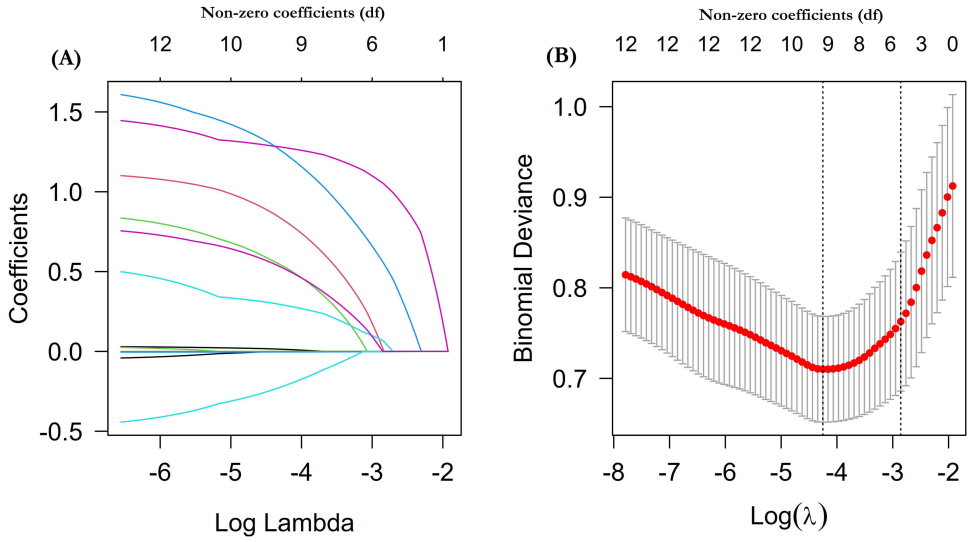

Figure 1 The LASSO variable selection process. (**A**) Coefficient path plot showing the shrinkage of predictor coefficients versus log(λ). (**B**) Ten-fold cross-validation curve (binomial deviance versus log(λ)). The left and right vertical dashed lines represent the lambda.min and lambda.1se criteria, respectively. In this study, the lambda.1se criterion (λ= 0.057) was applied, resulting in the selection of six non-zero coefficients.

Table 4 Multivariable Logistic Regression Including All LASSO-Selected Predictors

Complete Model					
Predictor	**β**	**SE**	**z**	**Adjusted OR (95% CI)**	**p**
Diabetes mellitus (Yes vs No)	1.310	0.605	2.165	3.707 (1.132, 12.141)	0.030
Invasive procedures (Yes vs No)	1.725	0.590	2.924	5.613 (1.766, 17.847)	0.003
Prolonged antibiotic use >7 d (Yes vs No)	0.482	0.448	1.077	1.620 (0.673, 3.899)	0.281
Systemic glucocorticoids (Yes vs No)	1.456	0.548	2.657	4.288 (1.468, 12.523)	0.008
CD4+ T cell count (per 1 cell/μL)	−0.0051	0.0016	−3.188	0.995 (0.992, 0.998)	0.001
Length of stay >14 d (Yes vs ≤14 d)	1.000	0.505	1.980	2.719 (1.011, 7.317)	0.048
Intercept	−3.200	0.920	−3.478	0.041 (0.007, 0.246)	<0.001
Final Nomogram Predictors (internally validated model)					
Predictor	**β**	**SE**	**z**	**Adjusted OR (95% CI)**	**p**
Diabetes mellitus (Yes vs No)	1.335	0.594	2.246	3.801 (1.184, 12.519)	0.025
Invasive procedures (Yes vs No)	1.771	0.572	3.094	5.875 (2.011, 19.481)	0.002
Systemic glucocorticoids (Yes vs No)	1.507	0.533	2.829	4.515 (1.590, 13.035)	0.005
CD4+ T cell count (per 1 cell/μL)	−0.005	0.002	−3.392	0.995 (0.991, 0.997)	0.001
Length of stay >14 d (Yes vs ≤14 d)	1.021	0.517	1.976	2.777 (1.015, 7.866)	0.048

Nomogram Construction

A clinical nomogram was developed using the five independent predictors. Points are assigned per predictor by vertical projection to the "Points" axis. Summing these yields a total score, which is projected downward to estimate infection probability (Figure 2; Table 5). A risk list summarizing predictor operational definitions and adjusted effect estimates corresponding to the nomogram is provided in Table 5.

Calibration Curve

The constructed nomogram model underwent internal validation using the bootstrap method with 1000 resamples. Calibration curves were plotted for both the training set and the validation set. The results demonstrated close agreement between the model-predicted probabilities and the actual observed event rates in both the training set and the validation set. The mean absolute errors were low, at 0.029 and 0.033 for the training and validation sets, respectively, indicating good model accuracy.

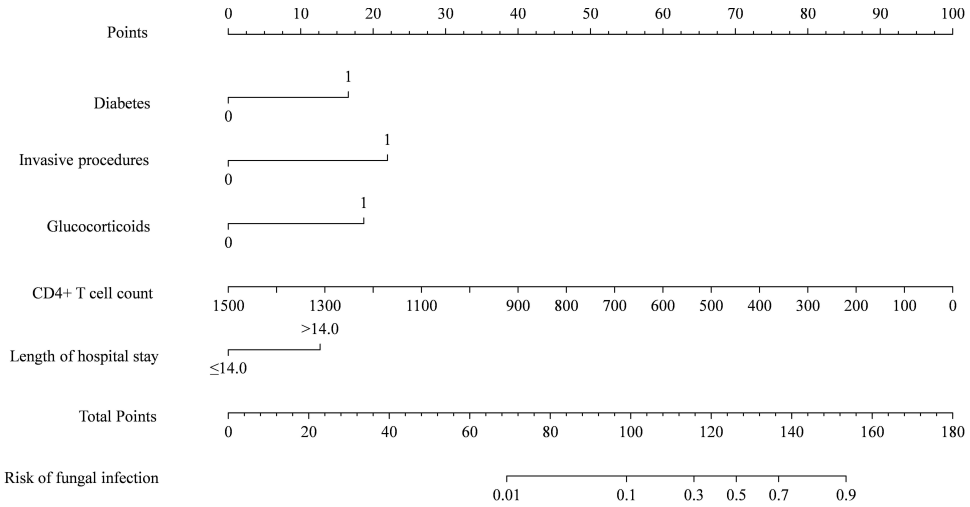

Figure 2 Risk factor prediction curve for lung cancer combined with pulmonary fungal infection.

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Table 5 Risk List for IPFI in Lung Cancer Inpatients (Final Model Predictors)

Predictor	Operational Definition	Adjusted OR (95% CI)	p	Direction/Interpretation
Diabetes mellitus	History of diabetes documented in EMR at admission (Yes/No).	3.801 (1.184, 12.519)	0.025	Risk factor
Invasive procedures	Any EMR-documented invasive respiratory/vascular procedure during index admission (Yes/No).	5.875 (2.011, 19.481)	0.002	Risk factor
Systemic glucocorticoids	Any systemic (oral/IV) glucocorticoid exposure during index admission (Yes/No).	4.515 (1.590, 13.035)	0.005	Risk factor
CD4+ T-cell count	First CD4+ T-cell count after admission; modeled per 1 cell/μL increase.	0.995 (0.991, 0.997)	0.001	Protective (per +100 cells/μL: OR≈0.607; per −100: OR≈1.649)
Length of stay >14 days	Index hospitalization length of stay dichotomized as >14 vs ≤14 days.	2.777 (1.015, 7.866)	0.048	Risk factor

Furthermore, the Hosmer-Lemeshow goodness-of-fit test yielded non-significant results (P > 0.05) for both the training and validation sets, suggesting adequate model fit (Figure 3A and B).

ROC Curve Analysis

Receiver operating characteristic (ROC) curve analysis was performed to evaluate the constructed model. The results demonstrated good discriminatory ability: the area under the ROC curve (AUC) was 0.876 (95% CI: 0.809, 0.944) for the training set and 0.861 (95% CI: 0.750, 0.973) for the validation set. Sensitivity was 0.724 (95% CI: 0.561, 0.887) in the training set and 0.750 (95% CI: 0.505, 0.995) in the validation set. Specificity was 0.925 (95% CI: 0.882, 0.967) in the training set and 0.857 (95% CI: 0.771, 0.944) in the validation set. Accuracy was 0.891 (95% CI: 0.890, 0.893) in the training set and 0.840 (95% CI: 0.836, 0.844) in the validation set (Figure 4A and B).

Clinical Decision Curve Analysis

Clinical decision curve analysis (DCA) was conducted to assess the clinical utility of the constructed model. The DCA results indicated that the model provided net benefit over the threshold probability ranges of 0.03 to 0.90 in the training set and 0.04 to 0.78 in the validation set. Within these ranges, the net benefit derived from using the model to guide interventions was higher than both the strategies of intervening on all patients or intervening on no patients. This finding suggests favorable clinical applicability of the model (Figure 5A and B; Table 6).

Discrimination, calibration, and decision-curve results for the training and validation sets are summarized in Table 6.

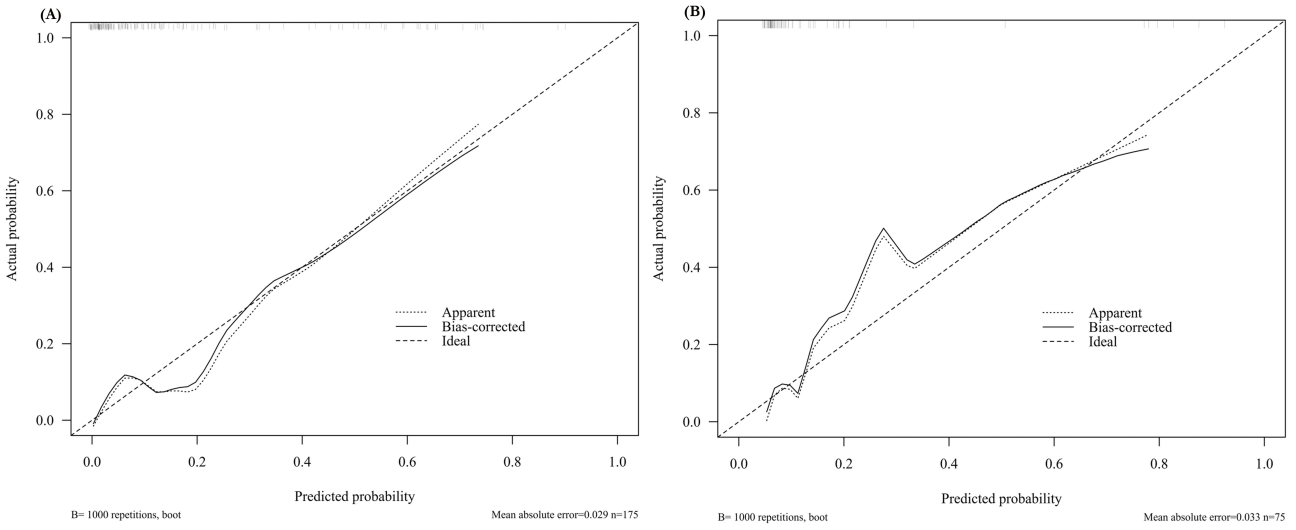

Figure 3 Bootstrap sampling validation calibration curve. (**A**) Training Set and (**B**) Validation Set.

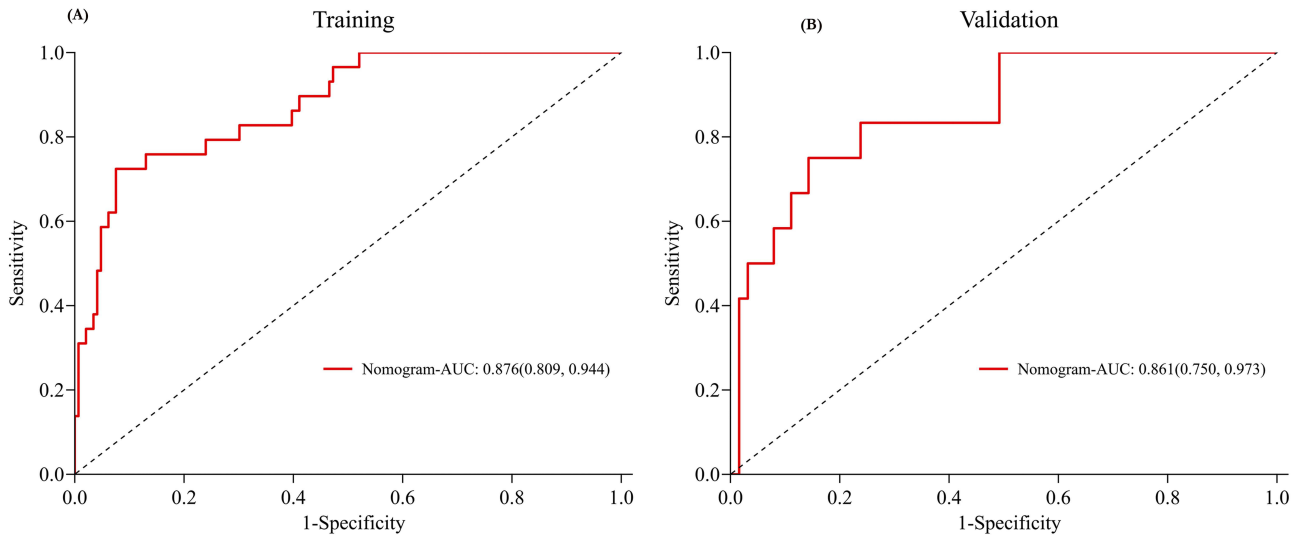

Figure 4 Receiver operating characteristic curves for the nomogram. (**A**) In the training and (**B**) Validation sets.

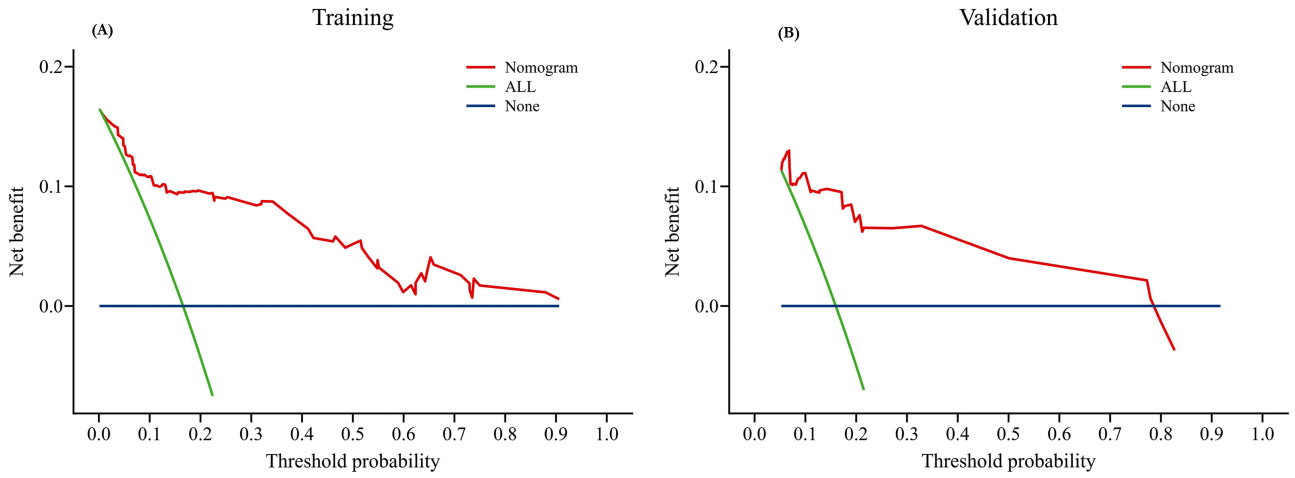

Figure 5 Decision curve analysis of the prediction of pulmonary fungal infection in lung cancer. (**A**) Training set, and (**B**) Validation Set.

Discussion

Due to aberrant inflammatory responses, lung cancer patients often present with atypical clinical symptoms upon pathogenic infection, which can easily lead to missed or delayed diagnosis and treatment.[22] Studies have shown that improving early diagnosis and timely intervention for fungal infections in the lungs can effectively curb the spread of pathogens, reduce the incidence of multi-organ failure, and significantly improve patient survival rates.[23] This study analyzed the clinical data from a cohort of 250 lung cancer patients to construct a predictive model for risk factors, aiming

Table 6 Discrimination, Calibration, and Decision-Curve Summary (Internal Validation)

Dataset	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	Accuracy (95% CI)	Calibration MAE	HL test p	DCA Net-Benefit Threshold Range
Training set	0.876 (0.809, 0.944)	0.724 (0.561, 0.887)	0.925 (0.882, 0.967)	0.891 (0.890, 0.893)	0.029	>0.05	0.03–0.90
Validation set	0.861 (0.750, 0.973)	0.750 (0.505, 0.995)	0.857 (0.771, 0.944)	0.840 (0.836, 0.844)	0.033	>0.05	0.04–0.78

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to maximally mitigate the risk of fungal infection and enhance clinical outcomes for this patient population. Clinical impact is shaped by the combination of diagnostic delay and rapid clinical deterioration once invasive disease is established, which helps explain why early inpatient triage has practical value beyond etiologic description.[2] Short-term outcomes in lung cancer–associated invasive pulmonary aspergillosis can be poor in real-world series, supporting an approach that prioritizes early risk recognition and faster escalation of diagnostic work-up in high-risk admissions.[21]

The results of this study indicate that diabetes is a risk factor for pulmonary fungal infections in lung cancer patients. Chronic hyperglycemia in diabetic patients provides ample nutrients for fungi, promoting their metabolism and proliferation.[24] Additionally, impaired autonomic nervous system function and immune function in diabetes patients reduce the body's ability to defend against and clear fungi, thereby increasing the risk of infection.[25,26] Jeong et al[27] found that patients with diabetes are more susceptible to infection by Mucor fungi. The immune system serves as the body's primary defense against external pathogens, eliminating pathogens through cellular and humoral immunity. T lymphocytes are major components of the immune system, primarily comprising $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells. $CD4^+$ T cells activate and coordinate other immune cells by recognizing pathogen antigens, thereby leading the immune response. $CD8^+$ T cells primarily recognize and eliminate infected cells. These two T cell subsets mutually regulate and cooperate to maintain immune balance.[28]

In lung cancer patients, the immune system's function is suppressed to some extent due to the tumor's own consumption and the presence of an immunosuppressive microenvironment.[29,30] Additionally, certain fungi and their metabolic products can directly damage $CD4^+$ T lymphocytes, leading to a reduction in cell numbers and functional suppression, thereby weakening the body's defensive capabilities and increasing the risk of IPFI.[31] Roblot et al[32] proposed that Pneumocystis jirovecii infection is commonly observed in patients with significantly reduced $CD4^+$ T lymphocyte counts. Therefore, infection prevention and control should be prioritized in patients with low $CD4^+$ T cell counts.

Glucocorticoids (GCs), known for their anti-inflammatory and immunosuppressive effects, effectively inhibit the production of reactive oxygen intermediates and mitigate pulmonary oxidative stress.[33] They are widely used in pretreatment for chemotherapy, management of complications, and treatment of immune-related adverse events (irAEs) in cancer patients.[34] However, many biological effects induced by glucocorticoids significantly increase susceptibility to invasive fungal infections (such as aspergillosis and candidiasis).[35] GCs reduce the host's defense against fungi by inhibiting neutrophil chemotaxis, decreasing alveolar macrophage phagocytic function, and suppressing T lymphocyte activity.[36–39] Additionally, long-term use of glucocorticoids can disrupt the normal flora and ecological balance of the microbiome, further increasing the risk of IPFI.[40,41] Risk linked to anticancer treatment is heterogeneous and often depends on downstream immune effects and supportive-care decisions rather than drug class labels alone. In advanced lung cancer settings, invasive aspergillosis patterns have been reported to vary across chemotherapy- and immunotherapy-exposed groups even after adjustment, consistent with treatment-modulated susceptibility that is clinically consequential.[17] Because immune checkpoint inhibitor–associated pneumonitis and other immune toxicities are frequently managed with systemic corticosteroids, fungal risk can increase indirectly through the intensity and duration of immunosuppression.

Due to factors such as the continued progression of tumors, immune damage caused by periodic anticancer treatments, and combined drug therapy, patients' hospital stays are prolonged.[12,13] Reduced mobility during extended hospital stays weakens the respiratory clearance mechanisms, thereby increasing the risk of pulmonary infections.[42–44] Depending on clinical needs, lung cancer patients may undergo various invasive procedures, such as central venous catheterization, endotracheal intubation, and mechanical ventilation. Invasive procedures directly compromise the integrity of the respiratory tract or skin mucosal barriers, and the surfaces of catheters or devices are prone to fungal contamination, providing a pathway for fungal invasion.[20,29] Moreover, invasive procedures are often accompanied by a certain degree of stress response, which can further suppress immune function and disrupt local defense mechanisms, thereby creating favorable conditions for fungal colonization and invasion, and increasing infection risk.[45]

Observed associations with prolonged inpatient care can reflect cumulative exposure to devices, airway instrumentation, and hospital microecology, which can shift the pathogen spectrum away from a single-organism model of pulmonary mycosis. In routine cohorts of proven/probable invasive pulmonary fungal disease in lung cancer, Candida

and Aspergillus commonly co-dominate, supporting clinical vigilance for multiple syndromes and not only aspergillosis when deterioration occurs during intensive inpatient care.[16] Structural lung injury also shapes fungal vulnerability over longer horizons; post-treatment lung remodeling and postoperative pulmonary complications have been linked to later chronic pulmonary aspergillosis, indicating that "susceptibility" can persist beyond the index admission in selected phenotypes.[11]

Nomograms have become an essential component of modern medical decision-making, enabling visual and quantitative assessment of individualized clinical event risks by integrating key predictive variables.[42,44,46] Validation results of the predictive model developed in this study demonstrated strong performance: the calibration curve indicated high consistency between the predicted and actual incidence of pulmonary fungal infection in lung cancer patients; the ROC curve confirmed its excellent discriminative ability; and decision curve analysis (DCA) showed that the model provides stable net benefit across a reasonable range of clinical threshold probabilities, underscoring its significant clinical utility. However, we found that some risk factors identified in previous studies were not reflected in the model, such as long-term use of broad-spectrum antibiotics and hypoalbuminemia.

Interpretation of predictors that attenuate after adjustment depends on harmonized variable definitions, since invasive fungal disease comparability is sensitive to how host factors, clinical features, and mycological evidence are operationalized in retrospective datasets.[6] Antibiotic exposure is especially definition-dependent because duration thresholds, spectrum, combination therapy, and timing relative to fungal evaluation vary across cohorts, which can shift whether antibiotic use behaves as an independent driver or as a marker of illness severity captured by other covariates; this definitional variability complicates direct benchmarking across nomograms developed in different hospitals.[20]

In the LASSO regression analysis of this study, long-term use of antibiotics was identified as a potential predictive factor. Previous literature has reported that broad-spectrum antibiotics can disrupt the body's microbial balance and increase susceptibility to fungal infections.[9,24,35] In this study, we observed a high proportion of patients with long-term antibiotic use, but it did not become an independent predictive factor. This discrepancy may be attributed to differences in how long-term antibiotic use was defined or classified in terms of drug types compared to prior studies. Additionally, cancer patients often present with hypoalbuminemia due to tumor-related catabolism and malnutrition, which can compromise immune defenses and elevate fungal infection risk.[47–50] Nonetheless, in our cohort, albumin levels did not show a statistically significant association with fungal infection risk, possibly due to relatively stable nutritional status in the study population or variations in the timing of albumin measurement. Therefore, future studies should aim to optimize research design by enlarging the sample size, refining variable assessments, and accounting for potential multifactor interactions.

In summary, diabetes, invasive procedures, glucocorticoid use, $CD4^+$ T cell levels, and length of hospitalization were identified as independent risk factors for secondary pulmonary fungal infections in lung cancer patients. The predictive model constructed based on these factors demonstrated preliminary predictive performance, providing a potential tool for the early prevention and management of invasive pulmonary fungal infection (IPFI). Nevertheless, this study has several limitations. First, as a single-center retrospective study with a limited sample size composed predominantly of patient s from the Sichuan region, the absence of external validation may affect the generalizability of the results and introduce potential bias.

Additional constraints include outcome ascertainment driven by clinician suspicion and testing availability, which can miss subclinical or untested cases and can also misclassify colonization as infection when mycology is interpreted without standardized adjudication. Event counts limit stable estimation for therapy-granular effects, including specific targeted agents, ADC payloads, monoclonal subclasses, radiotherapy field/dose, and immunotherapy-toxicity management pathways, which are clinically relevant for distinguishing risk trajectories by treatment phenotype. External validation across centers with harmonized diagnostic work-up and therapy-level recording is needed to define transportability and to support threshold selection for implementation in routine lung cancer wards.

Furthermore, the variables collected were relatively limited; indicators such as surgical history, duration of glucocorticoid use, and detailed disease course were not included, which may have influenced the findings. Therefore, subsequent studies should aim to expand the sample size and incorporate multi-center clinical data to enhance the accuracy and clinical applicability of the model through prospective validation.

Diabetes mellitus, invasive procedures, systemic glucocorticoid exposure, prolonged hospitalization, and lower CD4+ T-cell count were the most informative predictors of invasive pulmonary fungal infection among hospitalized lung cancer patients, indicating that metabolic comorbidity, care intensity, iatrogenic immunosuppression, and cellular immune depletion jointly shape inpatient susceptibility. The resulting nomogram provides a practical approach to quantify individual risk using routinely available variables and can be used to prioritize earlier fungal-focused diagnostic evaluation, closer monitoring, and timely preventive or therapeutic decision-making for patients flagged as higher risk during inpatient care.

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Disclosure

The authors declare no conflict of interest. This paper has been uploaded to Research Square as a preprint: https://doi.org/10.21203/rs.3.rs-7525008/v1.

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