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Original Article

Prediction of risk for secondary lower respiratory tract fungal infection during the acute exacerbation phase of COPD

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Abstract

Introduction: We aimed to investigate the risk factors for secondary lower respiratory tract fungal infection during acute exacerbation of chronic obstructive pulmonary disease (AECOPD).

Methodology: A total of 466 AECOPD patients diagnosed from March 2019 to November 2020 were divided into infection (n = 48) and non-infection (n = 418) groups. The risk factors for lower respiratory tract fungal infection were screened by logistic regression analysis, and a nomogram prediction model was established. The discriminability was validated by area under the receiver operating characteristic curve (AUC) and C-index, calibration was validated by GiViTI calibration belt and Hosmer-Lemeshow test, and clinical validity was assessed by decision curve analysis (DCA) curve.

Results: Thirty fungi strains were detected, including 18 strains of *Candida albicans*. Pulmonary heart disease, hypoalbuminemia, use of antibiotics within 3 months before admission, use time of antibiotics ≥ 14 d, invasive operation, blood glucose ≥ 11.10 mmol/L at admission, and procalcitonin (PCT) ≥ 0.5 ng/mL when diagnosed as fungal infection independent risk factors ($p < 0.05$). AUC was 0.891, indicating high discriminability of the model. The threshold probability in the DCA curve was set to 31.3%, suggesting that the model had clinical validity.

Conclusions: We identified the independent risk factors for lower respiratory tract fungal infection in AECOPD patients. The established model has high discriminability and calibration. Immediate intervention is beneficial when the predicted risk exceeds 31.3%.

Key words: pulmonary disease; chronic obstructive; respiratory tract; fungal infections; risk.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic airway inflammatory disease with lung parenchyma damage and lung small airway lesions as the main pathological characteristics, and progressive decline in pulmonary ventilation function as the clinical manifestation [1]. According to a survey, acute exacerbation of COPD (AECOPD) occurs 0.5-3.5 times in patients every year, and a higher frequency corresponds to a lower 5-year survival rate of patients [2]. Recurrent AECOPD is an important factor leading to death and hospitalization of COPD patients. The progression of AECOPD is affected by eosinophil proliferation, bacterial infection, fungal infection and non-inflammatory factors. At the same time, mechanical ventilation and use of glucocorticoids will reduce the body's immune function, which, combined with long-term use of antibiotics, will inevitably result in fungal infection. Therefore, AECOPD complicated with infection is more common in clinic. It is reported that 70-80% of AECOPD may be related to lower respiratory tract fungal infection [3]. Lower respiratory tract infection is a common respiratory tract infectious disease that causes death of critically ill patients, and it is of great significance to clarify its pathological characteristics and risk factors for reducing the risk of infection and improving the prognosis. Despite a large number of studies on the above issues in recent years, they primarily focus on drug resistance, and risk factors are rarely explored. In the present study, the risk factors for lower respiratory tract fungal infection in COPD patients were screened and a nomogram prediction model was established, so as to provide a theoretical basis for clinical prevention and treatment. The flow chart of all procedures is exhibited in Figure 1 [4].

Methodology

Subjects

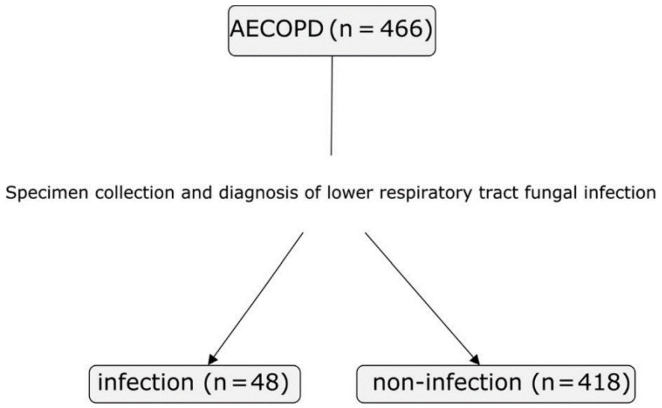
A total of 466 AECOPD patients admitted to and diagnosed in our hospital from March 2019 to

November 2020 were enrolled as the subjects. Inclusion criteria were as follows: (1) patients meeting the diagnostic criteria for AECOPD [5]: primary clinical manifestations (increased sputum, thick sputum, and dyspnea) and secondary clinical manifestations (cough, sore throat, runny nose, and sneezing), (2) those subjected to sputum fungus culture and normal sputum culture, (3) those with complete clinical data, (4) those without a history of upper respiratory tract infection within 28 d, and (5) those admitted to the hospital within 3 d after AECOPD. Exclusion criteria were as follows: (1) pregnant or lactating women, (2) patients complicated with tuberculosis, bronchial asthma, lung cancer or other respiratory diseases, (3) those who died before the diagnosis with fungal infection, or (4) those who gave up treatment during hospitalization, or were transferred to another hospital or discharged. This study was approved by the Ethics Committee of our hospital, and the patients or their families were informed of the study and signed the informed consent.

Collection of clinical data

The following data were collected: the patients' age, gender, body mass index (BMI), partial pressure of carbon dioxide ($PaCO_2$), partial pressure of oxygen (PaO_2), oxygenation index (PaO_2/FiO_2) and pH at admission, smoking or drinking status, course of COPD, grade of COPD, whether they were complicated with underlying diseases (diabetes, hypertension, pulmonary heart disease, chronic renal insufficiency, coronary heart disease, anemia, and hypoalbuminemia), whether AECOPD occurred ≥ 1 time in the past year, whether antibiotics or glucocorticoids were used within 3 months before admission, whether they underwent long-term home oxygen therapy, whether they were admitted to the hospital due to aggravation of disease within the past year, whether invasive operations were performed during hospitalization, whether carbapenem antibiotics were used during hospitalization, whether biphasic positive airway pressure (BiPAP) non-invasive assisted ventilation was given, duration of assisted ventilation, type of antibiotics used, use time of antibiotics, duration of hospitalization, serum procalcitonin (PCT) and C-reactive protein (CRP) levels at the time of diagnosis with fungal infection, and blood glucose level within 24 h after admission.

Figure 1. Flow chart of all procedures. AECOPD: Acute exacerbation of chronic obstructive pulmonary disease.



The risk factors for lower respiratory tract fungal infection were screened by logistic regression analysis, and a nomogram prediction model was established.

Positive fungal culture results included in determination criteria for infection

Sputum specimens were determined by microscopic examination as qualified at the leukocyte count of > 25/L and epithelial cell count of 10/L, or leukocyte/epithelial cell count ratio of > 2.5, or semi-quantitation (concentration of pathogenic or opportunistic pathogens) or relative quantitation of fungi +++ (≈ 106 CFU/mL) or fungus++++ (≥ 107 CFU/ml), and the culture results had clinical significance.

Determination criteria for fungal infection

(1) The body temperature was > 38 °C or < 37 °C, accompanied by underlying diseases, mechanical ventilation or long-term hormone therapy. (2) Imaging disclosed nodular or patch shadows. There were symptoms or signs of pulmonary infection (rale, cough, etc.), and persistent fever for 96 h. Antibiotic treatment was ineffective. The sputum specimens qualified for microbiological examination showed hyphae during direct microscopy, and the fungal culture results were positive in two tests. The bronchoalveolar lavage fluid was found to have hyphae by direct microscopy, and the fungal culture results were positive. The fungal cell wall component in blood specimens, 1,3-beta-D-glucan, was positive in two consecutive G tests [6].

Positive fungal culture results included in determination criteria for colonization

Specimens were unqualified, without clinical manifestations of fungal infection or with atypical clinical manifestations, without receiving clinical antifungal treatment or the treatment was ineffective.

Fungal culture method

The specimens were inoculated in Sabouraud dextrose agar (SDA) and Sabouraud-gentamicin-chloramphenicol (SGC) (Sigma-Aldrich, Beijing,

China), and then the media were sealed with plastic tapes. SDA was placed in an incubator at 35 °C, and SGC was placed in the other incubator at 28 °C. The fungi were observed daily, subcultured on Chromagar plates, and identified by ATBExpress automatic analyzer and fungus identification cards (bio-Mérieux, Lyon, France).

Serum G test

The serum of patients with suspected fungal infection was collected, and enzyme-linked immunosorbent assay was performed by miniVIDAS analyzer (bio-Mérieux, Lyon, France) to detect the fungal 1,3-beta-D-glucan content.

Statistical analysis

SPSS 20.0 software was used for statistical analysis, and R 3.6.2 software was used for plotting. Measurement data were expressed as ($\bar{\chi} \pm s$) and analyzed by the t test. Numerical data were expressed as frequency (percentage) and analyzed by the χ^2 test. The independent risk factors for lower respiratory tract fungal infection were screened by univariate and multivariate logistic regression analyses on population in the training set, and then incorporated to establish a nomogram prediction model. The discriminability, calibration and clinical validity of the model were validated. The discriminability was validated by the receiver operating characteristic (ROC) curve and C-index, the calibration was validated by GiViTI calibration belt and Hosmer-Lemeshow test, and the clinical validity was assessed by the cut-off value in the ROC curve combined with decision curve analysis (DCA) curve. $p < 0.05$ was considered to be statistically significant.

Results

Lower respiratory tract fungal infection in patients with AECOPD

Forty-eight AECOPD patients complicated with lower respiratory tract fungal infection were enrolled in the infection group, and the remaining 418 cases were enrolled in the non-infection group. In the infection group, all the patients had different degrees of cough, and coughed up thick and jelly-like sputum. Among them, 13 cases coughed up blood-stained sputum, 26 cases had fever, the peripheral blood leukocyte of > 10 × 10^9/L after fungal infection was found in 21 cases, pharyngeal, tongue or oral mucosa ulcers or leukoplakia occurred in 20 cases, and ≥ 75% neutrophils were detected in 32 cases. In terms of chest X-ray findings, 12 cases had thickening of lung marking, 27 cases had small patchy or punctate shadows on one or both lungs, and the remaining 9 cases showed consolidation shadow of lung lobes and segments.

Table 1. Types and composition of fungi in lower respiratory tract infection in patients with AECOPD.

Type of fungus	Number of strains	Composition ratio (%)
Aspergillus	1	3.33
Mucor	1	3.33
Candida krusei	2	6.66
Candida glabrata	2	6.66
Candida parapsilokis	2	6.66
Candida tropicalis	4	13.33
Candida albicans	18	60.00
Total	30	100.00

Types and composition of fungi in lower respiratory tract infection in patients with AECOPD

A total of 30 strains of fungi were detected, including 18 strains of *Candida albicans* and 4 strains of *Candida tropicalis* (Table 1).

General clinical data

According to the comparison results of the general clinical data between the two groups, the course of COPD was significantly longer, and the proportions of patients who had AECOPD ≥ 1 time in the past year, grade 3-4 COPD, pulmonary heart disease and hypoalbuminemia, used antibiotics within 3 months before admission, admitted due to aggravation of disease within the past year, underwent tracheal intubation, received assisted ventilation ≥ 14 d, used antibiotics ≥ 14 d, used ≥ 3 types of antibiotics, stayed in the hospital ≥ 21 d, had blood glucose ≥ 11.10 mmol/L at admission and PCT ≥ 0.5 ng/mL when diagnosed with fungal infection were significantly higher in infection group than those in non-infection group ($p < 0.05$) (Table 2).

Results of multivariate analysis on lower respiratory tract fungal infection

The related variables were assigned as follows. Pulmonary heart disease: yes = 1, no = 0; hypoalbuminemia: yes = 1, no = 0; use of antibiotics within 3 months before admission: yes = 1, no = 0; use time of antibiotics ≥ 14 d: yes= 1, no = 0; invasive operation: yes = 1, no = 0; blood glucose ≥ 11.10 mmol/L at admission: yes = 1, no = 0; PCT ≥ 0.5 ng/mL when diagnosed with fungal infection: yes = 1, no = 0.

Figure 2. Forest plot of multivariate analysis results influencing factors for lower respiratory tract fungal infection. AECOPD: Acute exacerbation of chronic obstructive pulmonary disease; COPD: chronic obstructive pulmonary disease.

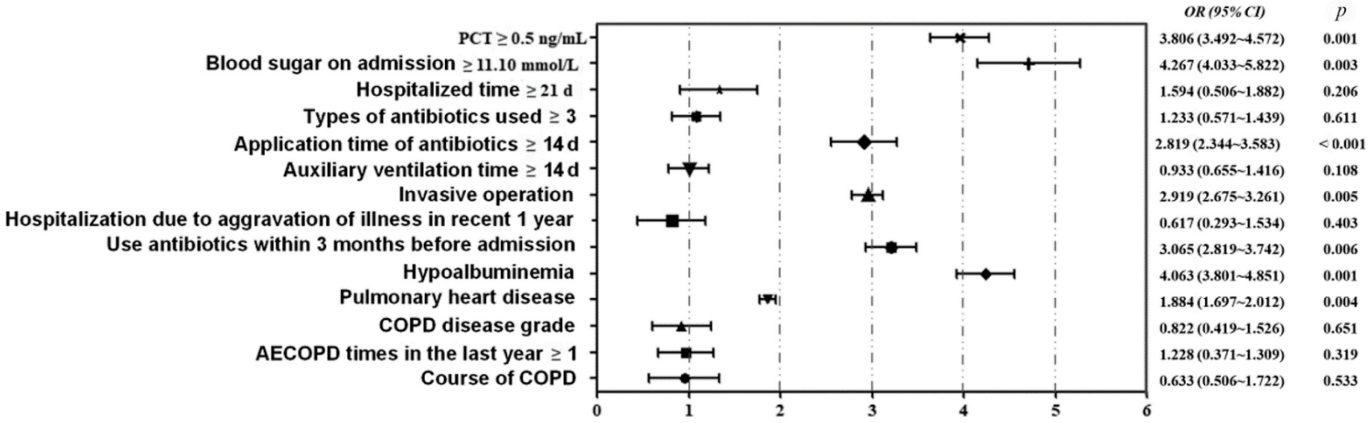


Table 2. General clinical data [$\bar{\chi} \pm s$, n (%)].

Clinical data	Infection group (n = 48)	Non-infection group (n = 418)	t/χ^2	*p*
Age (Y)	66.68 ± 10.51	64.27 ± 9.96	1.579	0.115
Gender	-	-	1.851	0.174
Male	30	218		
Female	18	200		
BMI (kg/m^2)	21.73 ± 3.15	22.36 ± 3.29	1.262	0.208
$PaCO_2$ (mmHg)	62.84 ± 8.33	61.65 ± 7.60	1.017	0.310
PaO_2 (mmHg)	51.13 ± 5.09	52.62 ± 6.02	1.648	0.100
PaO_2/FiO_2	287.49 ± 61.73	293.52 ± 70.43	0.569	0.570
pH	7.11 ± 0.07	7.12 ± 0.06	1.074	0.283
Course of COPD (Y)	8.12 ± 1.64	7.56 ± 1.48	2.455	0.014
AECOPD occurred ≥ 1 time in the past year	26	163	4.111	0.043
Grade of COPD	-	-	7.767	0.005
1-2	16	228		
3-4	32	190		
Drinking	17	134	0.222	0.638
Smoking	20	158	0.273	0.601
Underlying diseases complicated	-	-		
Diabetes	15	139	0.078	0.780
Hypertension	15	152	0.490	0.484
Pulmonary heart disease	21	111	6.270	0.012
Chronic renal insufficiency	5	19	3.038	0.081
Coronary heart disease	3	17	0.500	0.480
Anemia	7	48	0.398	0.528
Hypoalbuminemia	14	67	5.175	0.023
Treatment condition	-	-		
Use of antibiotics within 3 months before admission	31	193	5.847	0.016
Use of systemic glucocorticoids within 3 months before admission	18	118	1.790	0.181
Long-term home oxygen therapy	10	83	0.026	0.873
Admission to the hospital due to aggravation of disease within the past year	27	169	4.421	0.035
Invasive operation	29	186	4.391	0.036
BiPAP ventilation	33	265	0.535	0.464
Use of carbapenem antibiotics	8	61	0.147	0.702
Duration of assisted ventilation ≥ 14 d	25	155	4.088	0.043
Use time of antibiotics ≥ 14 d	20	113	4.520	0.033
Type of antibiotics used ≥ 3	14	64	5.931	0.015
Duration of hospitalization ≥ 21 d	31	172	9.618	0.002
Biochemical index	-	-		
Blood glucose ≥ 11.10 mmol/L at admission	13	55	6.699	0.010
PCT ≥ 0.5 ng/mL when diagnosed with fungal infection	35	234	5.061	0.024
CRP ≥ 10 mg/L when diagnosed with fungal infection	42	328	2.147	0.143

After assignment, the variables with statistically significant differences in both groups were incorporated into the multivariate logistic regression analysis, with the presence or absence of lower respiratory tract fungal infection in patients with AECOPD as the dependent variable (yes = 1, no = 0). The logistic regression equation was ln (P/1-P) = -4.503 + 0.385 × pulmonary heart disease + 1.437 × hypoalbuminemia + 1.169 × use of antibiotics within 3 months before admission + 1.351 × (use time of antibiotics ≥ 14 d) + 1.220 × invasive operation + 2.039 × (blood glucose ≥ 11.10 mmol/L at admission) + 1.040 × (PCT ≥ 0.5 ng/mL when diagnosed with fungal infection). The results of likelihood ratio test showed $\chi^2 = 12.597$ and $p < 0.01$, suggesting statistical significance of the model. The logistic regression analysis showed that pulmonary heart disease, hypoalbuminemia, use of antibiotics within 3 months before admission, use time of antibiotics ≥ 14 d, invasive operation, blood glucose ≥ 11.10 mmol/L at admission, and PCT ≥ 0.5 ng/mL when diagnosed with fungal infection were independent risk factors for lower respiratory tract fungal infection in patients with AECOPD ($p < 0.05$) (Figure 2).

Nomogram prediction model

The above 7 independent risk factors were incorporated into the prediction model to establish an individualized nomogram prediction model for the risk of lower respiratory tract fungal infection in AECOPD patients. The score corresponding to each predictive index could be obtained from this model, and then the total score was calculated. The prediction probability corresponding to the total score was the risk of lower respiratory tract fungal infection in AECOPD patients. According to the nomogram model, the scores of pulmonary heart disease, hypoalbuminemia, use of antibiotics within 3 months before admission, use time of antibiotics ≥ 14 d, invasive operation, blood glucose ≥ 11.10 mmol/L at admission, and PCT ≥ 0.5 ng/mL when diagnosed with fungal infection were 13.6 points, 36.7 points, 40.3 points, 36.1 points, 24.8 points, 16.8 points and 22.3 points, respectively, and the total score was 190.6 points. The probability of lower respiratory tract fungal infection corresponding to the total score was 9.51% (Figure 3).

Figure 3. Nomogram prediction model for the occurrence of lower respiratory tract fungal infection.

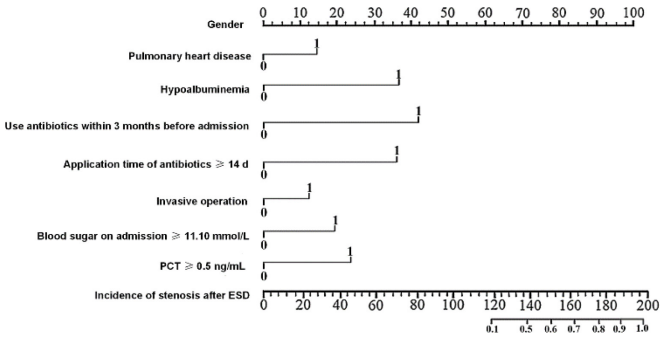
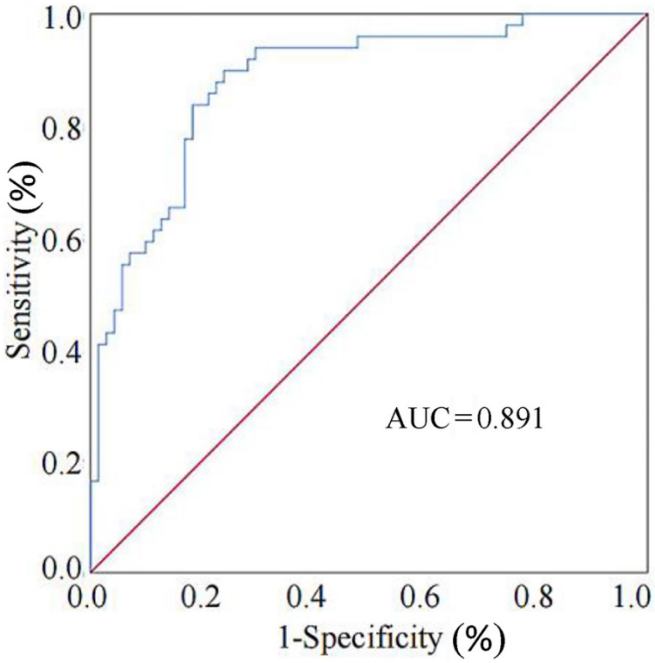


Figure 4. ROC curve of prediction model.



Validation of prediction model

It was found through ROC curve analysis that the AUC was 0.891 [95% confidence interval (CI): 0.835-0.962], the cut-off value was 31.3% ($p < 0.001$), and the C-index was > 0.75 (0.891) (Figure 4).

The 80-90% CI region on the GiViTI calibration belt did not cross the 45° angle bisector ($p > 0.05$). The Hosmer-Lemeshow goodness-of-fit test was performed on the prediction model, and it was found that $\chi^2 = 6.804$ and $p = 0.581$ (Figure 5).

On the DCA curve, when the threshold probability was 8-91% and 3-99%, the net benefit of patients was higher than that on the other two extreme curves [the horizontal line (None) indicated that the net benefit was 0 assuming that none of the patients had infection and underwent treatment, whereas the oblique line (All) indicated that the net benefit was a backslash with a negative slope assuming that all patients had infection and underwent treatment], in which case the model had clinical validity. The cut-off value (31.3%) obtained by ROC curve analysis was also within the range of

threshold probability of the DCA curve, confirming that the model had clinical validity. Furthermore, when the threshold probability of lower respiratory tract fungal infection and intervention measures was set to 31.3% in AECOPD patients, 31 out of 100 patients whose risk of fungal infection was predicted by this model could benefit from it without harming other people's interests (Figure 6).

Discussion

The incidence rate of deep fungal infection is increasing annually, dominated by pulmonary fungal infection accounting for 10-15% of hospital-acquired pneumonia, among which COPD ranks first [7]. It has been found in a clinical study that the respiratory tract is highly vulnerable to fungal infection [8]. The possible reason is that the non-specific inflammatory response of the respiratory tract in patients with COPD damages the respiratory mucosa and weakens the ability of the respiratory tract to resist pathogenic invasion, so that the respiratory tract is more prone to colonization of pathogens. In addition, Liu *et al.* confirmed that *Candida albicans* was the common pathogenic bacterium in the lower respiratory tract [9]. Ture *et al.* also found that *Candida albicans* was a common pathogenic bacterium of nosocomial infection [10]. Therefore, clinicians should pay more attention to the influencing factors for lower respiratory tract fungal infection in AECOPD patients, thereby more effectively guiding clinical prevention of lower respiratory tract fungal infection in AECOPD patients.

In the present study, it was found that the probability of lower respiratory tract fungal infection in AECOPD patients was 10.30%, and a total of 30 strains of fungi were detected, including 18 strains of *Candida albicans* constituting the largest proportion.

In this study, multivariate logistic regression analysis was conducted. The results revealed that pulmonary heart disease, hypoalbuminemia, use of antibiotics within 3 months before admission, use time of antibiotics ≥ 14 d, invasive operation, blood glucose ≥ 11.10 mmol/L at admission, and PCT ≥ 0.5 ng/mL when diagnosed with fungal infection were independent risk factors for lower respiratory tract fungal infection in patients with AECOPD. Pulmonary heart disease is one of the common underlying diseases of COPD, and favorable conditions are created for the proliferation of glucose-non-fermenting Gram-negative bacilli due to pulmonary hypertension, right ventricular dysfunction and congestion of pulmonary circulation [11]. Serum albumin is one of the important indices reflecting the visceral protein in the body, and also an important index for the body's nutritional status. It is reported [12] that hypoalbuminemia is more common in COPD, which reduces the ability of the urethral mucosa and respiratory tract to synthesize secretory IgA, and increases the risk of fungal infection [13]. Repeated infection frequently occurs in the respiratory tract of COPD patients, so antibiotics are often used repeatedly to control the disease. However, antibiotics will also affect the body's normal microflora and cause damage to the normal microbial structure while killing

Figure 5. Calibration of prediction model.

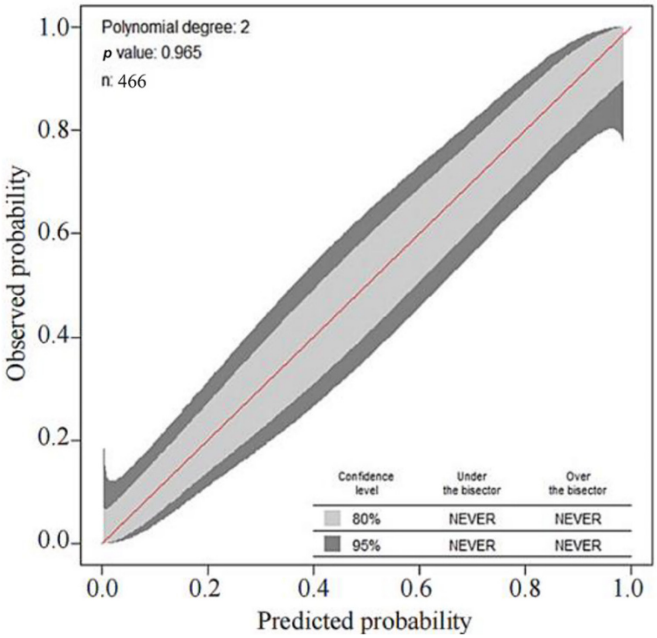
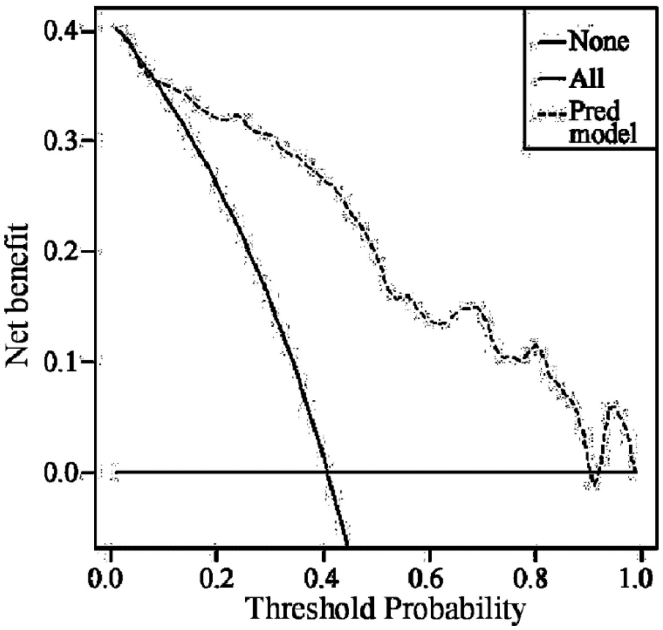


Figure 6. Analysis results of decision curve of prediction model.



pathogenic bacteria, so that the conditioned pathogens massively reproduce, leading to lower respiratory tract fungal infection [14]. In addition, long-term unreasonable combination of antibiotics is an independent risk factor for lower respiratory tract fungal infection and multi-drug resistance in bacterial strains [15]. In this study, it was also found that the proportion of patients who used antibiotics ≥ 14 d in infection group was significantly higher than that in non-infection group, and use time of antibiotics ≥ 14 d was an independent influencing factor for lower respiratory tract fungal infection in AECOPD patients. Urinary catheterization and tracheal intubation are common invasive operations that can damage the urinary tract mucosa and respiratory mucosa to a certain extent, and raise the risk of infection by pathogenic microorganism such as fungi [16]. It has been reported that blood glucose elevation is an independent influencing factor for the death of inpatients with COPD, and this was once again confirmed in this study [17]. Hyperglycemia frequently occurs in patients with AECOPD, which will weaken the body's immune function, lead to the imbalance of T lymphocyte subsets, and also damage the airway mucociliary function, thereby increasing the risk of fungal infection. An increased level of serum PCT can often indicate the worsening of both lung function and immune function in COPD patients, and an increased risk of death.

Currently, there has been no unified strategy regarding clinical prevention of lower respiratory tract fungal infection in patients with AECOPD. In this study, it can be seen based on the above influencing factors that standardizing the use of antibiotics, reducing invasive operations and adopting a reasonable diet can lower the risk of lower respiratory tract fungal infection in COPD patients. Which patients need early prevention is worth considering. In addition, there is a lack of clinical studies on the nomogram prediction model for the occurrence of lower respiratory tract fungal infection in AECOPD patients. In this study, a nomogram prediction model was established to predict the probability of lower respiratory tract fungal infection in patients with AECOPD based on the clinical data, providing theoretical references for individualized treatment. When the cut-off value 31.3% of the ROC curve was set as the threshold of the DCA curve, the patients' net benefit was higher than that of the two extreme cases (no intervention at all, and intervention in all patients), suggesting that when the risk of respiratory tract fungal infection in patients with AECOPD predicted by the model is higher than 31.3%, immediate intervention will provide clinical benefit for the patient, but the intervention can be temporarily delayed if the risk is lower than 31.3%. The above findings are helpful for developing clinical decision solutions for AECOPD patients.

Conclusions

In conclusion, pulmonary heart disease, hypoalbuminemia, use of antibiotics within 3 months before admission, use time of antibiotics ≥ 14 d, invasive operation, blood glucose ≥ 11.10 mmol/L at admission, and PCT ≥ 0.5 ng/mL when diagnosed with fungal infection are risk factors for lower respiratory tract fungal infection in patients with AECOPD. The nomogram prediction model established in this study has high discriminability and calibration. When the risk of lower respiratory tract fungal infection in patients with AECOPD predicted by the model is higher than 31.3%, immediate intervention will benefit the patient, but the intervention can be temporarily delayed if the risk is lower than 31.3%.

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