Establishment of a risk classifier to predict the in-hospital death risk of nosocomial infections caused by fungi in cancer patients

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Research Article

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Abstract

(1) Background:

Patients with malignancy are more vulnerable to developing nosocomial infections. Limited studies investigated cancer patients' clinical features and prognostic factors of fungi infections. Herein, this study was performed to explore the clinical characteristics of nosocomial infections due to fungi and develop a nomogram to predict the in-hospital death risk of these patients.

(2) Methods: This retrospective observational study analyzed cancer patients with nosocomial infections caused by fungi from September 2013 to September 2021. The univariate and multivariate logistics regression analyses were utilized to identify the influencing factors of in-hospital death risk of nosocomial infections caused by fungi. A nomogram was developed to predict the in-hospital death risk of these individuals, with the receiver operating characteristics curve (ROC), calibration curve, and decision curve being generated to evaluate its performance.

(3) Results: 216 patients with solid tumors developed fungal infections during hospitalization, of which 57 experienced in-hospital death. C.albicans is the most common fungal species(68.0%). The respiratory system was the most common site of infection(59.0%), followed by intra-abdominal infection (8.8%). The multivariate regression analysis revealed that ECOG-PS 3–4, pulmonary metastases, thrombocytopenia, hypoalbuminemia, and mechanical ventilation were independent risk factors of in-hospital death risk. A nomogram was constructed based on the identified risk factors to predict the in-hospital death risk of these patients.

(4) Conclusions: Fungi-related nosocomial infections are common in solid tumors and have a bleak prognosis. The constructed nomogram could help oncologists make a timely and appropriate clinical decision with significant net clinical benefit to patients.

1. Introduction

Cancer patients are predisposed to developing nosocomial infections due to immunosuppressive caused by malignancy and long-term antitumor treatment. [1, 2]. Besides, routine diagnostic and therapeutic procedures, especially invasive operations such as tissue biopsy and catheter placement, significantly increase the risk of nosocomial infections in cancer patients[3]. It is reported that surgery is closely related to the occurrence of nosocomial infections in these individuals[4]. Therefore, nosocomial infections have become one of the most common complications in patients with tumors. Once a severe infection occurs, it will undoubtedly affect the initiation of antitumor treatment, prolong the length of hospitalization, increase healthcare-related costs, and lead to the death of patients in severe cases. As a result, infection has become the leading non-cancer cause of death in cancer patients[5, 6]

The clinical features, microbiological distribution, and prognostic factors of nosocomial infections caused by bacteria are well documented[1, 2, 7–11]. Most importantly, relevant guidelines are also published to guide the diagnosing and treatment of nosocomial infections caused by bacteria in patients with malignancy[12–14]. Unlike bacterial pathogens, fungi usually do not produce endotoxins and exotoxins. The pathogenicity caused by fungi may be related to mechanical damage caused by their reproduction in the body, as well as the type of enzyme production and acidic metabolites[15]. Patients with malignant tumors are at high risk of fungal infections due to impaired immune function. In this context, invasive fungal disease (IFD) will occur in severe cases [16]. Furthermore, the subsequent long-course intervention of antifungal therapy malnutrition, and secondary infections will further increase the risk of in-hospital death of these patients [17].

However, in actual clinical work, there are still tumor patients with a fungal infection, but the degree of infection is not up to the diagnostic criteria for IFD. There is insufficient statistical evidence and relevant guidelines for these patients' infection characteristics, treatment modes, and prognostic factors. Therefore, it is vital for clinical practice to understand the clinical features and epidemiological characteristics of solid tumors complicated with fungal infections in hospitals. Meanwhile, there is no available risk model to predict these patients' prognoses robustly. Therefore, we conducted this retrospective study to explore the clinical characteristics and prognostic factors of nosocomial infections caused by fungi in cancer patients and to develop a nomogram to predict the in-hospital mortality of these patients.

2. Methods

2.1 Study population and design

We conducted this single-center retrospective observational cohort study at the First Affiliated Hospital of Xi'an Jiaotong University in the Northwest of China. Searching for ICD-10 coded diagnoses included patients with solid tumors with in-hospital fungal infections who received medical care during their hospitalization from September 2013 to September 2021. This study included patients who met all the following criteria: 1) age ≥ 18 years; 2) laboratory confirmed diagnosis of infection caused by fungi; 3) a solid tumor was confirmed by histological pathology or cytological pathology; and 4) patients hospitalized during the study period with complete electronic medical records (EMR). Patients under 18 years old or without total medical records were excluded. The study was approved by the ethics committee of the First Affiliated Hospital of Xi'an Jiaotong University (No: XJTU1AF2020LSK-049). Waiving of informed consent was obtained due to the retrospective noninterventional study design.

2.2 Data collection

All data were manually extracted from the EMR and recorded in the Excel of Microsoft. The extracted data included age, gender, smoking history, Eastern Cooperative Oncology Group (ECOG) Performance Status, TNM staging, tumor type, and records of distant metastases. Information related to the infection was

collected simultaneously, including the primary site of infection, the fungal species, whether combined with bacterial infection and time and types of intravenous antifungal drugs. Other information was also collected, such as fever, antitumor therapy within 30 days (including but not limited to surgery, chemotherapy, immune checkpoint inhibitor therapy, and radiotherapy), corticosteroid therapy in the past 30 days, Granulocyte colony-stimulating factor (G-CSF) usage within 30 days, antibiotic therapy within 30 days, invasive procedures in the last 30 days, intensive care unit (ICU) admission during hospitalization, the experience of septic shock, mechanical ventilation, and outcome after fungi infection (death or discharge). The worst values of laboratory parameters before infection diagnosis, including blood routine results (hemoglobin counts, platelet counts, and the white blood cell and differential count), serum albumin, and electrolyte levels were collected in terms of laboratory indicators.

2.3 Definition

Nosocomial infection caused by fungi was considered if the patient had the following criteria: (a) on the premise of excluding contamination of clinical specimens, the results of fungi culture indicated that at least one pathogen was positive (> 48h after hospital admission); (b) there were corresponding clinical manifestations, laboratory examination results, or radiological results recorded which is in electronic medical records; or (c) a clear infection type record that was acquired from the electronic medical records. Otherwise, the case is considered community-onset [18–20]. Clinical samples such as sputum, urine, blood culture, stool, wounds secreta, ascites, pleural, drainage fluid postoperation, and other samples were collected once patients were suspected of fungal infection. Fever was considered an axillary temperature of 38.3°C on one occasion or a temperature of > 38.0°C on two or more occasions during 12h [21]. The shock was referred to as systolic blood pressure 90mmHg, and fluid therapy and/or vasoactive medications have no improvement in this condition[20].

2.3 Study outcomes

This study aimed to characterize the clinical features, microbial profile, and prognostic factors of nosocomial infections caused by fungi in patients with solid tumors and to develop a predictive model to predict their in-hospital death risk. Thus, in-hospital mortality was the primary outcome of this study. It is worth noting that only death cases caused by nosocomial infections during hospitalization were selected for in-hospital mortality calculation.

2.4 Statistical analysis

The extracted clinical data were recorded in a standardized form and compared according to the patient's survival status after infection during hospitalization. As appropriate, continuous variables were summarized as means and standard deviation (SD) or median and interquartile range (IQR). Categorical variables were expressed as frequency and percentage. Continuous variables were analyzed by an independent-sample t-test or a Mann-Whitney U-test. Categorical variables were analyzed by Chi-Square Test or Fisher's Exact Test. Univariate and multivariate logistic regression analyses were adopted to investigate the independent risk factors for in-hospital mortality of nosocomial infections. Variables for the p-value < 0.05 for the univariate analysis were included in the multivariable logistic regression

analysis. A two-sided p-value < 0.05 was considered statistically significant. The nomogram was constructed based on independent factors identified in the multivariate analysis to predict the probability of in-hospital death after nosocomial fungal infection. Besides, the receiver operating characteristics curve (ROC), calibration curve, and decision curve were employed to evaluate its performance. All statistical analyses were performed in R software (version 4.1.3) for windows 64.0.

3. Results

3.1 The essential characteristics of the participants

A total of 216 patients with solid tumors were diagnosed with nosocomial infections and received complementary treatment in the First Affiliated Hospital of Xi'an Jiaotong University during the eight years of the study period (Fig. 1). Among them, 138 were males (64%), and 78 were females (36%). The median age was 65-year-old. 90% of patients had an ECOG-PS 0–2, and 74% had a TNM stage of III-IV. The common diagnoses were respiratory tumors (34%), gastrointestinal tumors (24%), and hepatobiliary and pancreatic tumors (24%). Regarding the detailed antitumor therapy, 72 patients (33.6%) underwent surgery, 62 patients (29%) received chemotherapy, and 13 patients (6%) received immune checkpoint blockade (ICB) treatment within 30 days, respectively. A total of 69 patients (32%) received glucocorticoids within 30 days. In the past 30 days, 78 patients (36%) received simultaneous antibacterial therapy (Table 1).

Table 1
The general characteristics of solid patients with fungal infection

Variable	Overall, N = 216[1]	Survival, N = 159[1]	Death, N = 57[1]	p-value[2]
Demographic data				
Age (years)	65 (58, 71)	65 (59, 71)	65 (58, 71)	> 0.900
Gender				0.200
male	138 (64%)	98 (62%)	40 (70%)	
female	78 (36%)	61 (38%)	17 (30%)	
Smoking history (Yes)	97 (45%)	66 (42%)	31 (54%)	0.094
Days of hospitalization(days)	17 (9, 27)	17 (10, 27)	16 (8, 26)	0.400
ECOG-performance status				< 0.001
0,1,2	194 (90%)	153 (96%)	41 (72%)	
3,4	22 (10%)	6 (3.8%)	16 (28%)	
TNM stage				0.014
Stage I-II	57 (26%)	49 (31%)	8 (14%)	
Stage III-IV	159 (74%)	110 (69%)	49 (86%)	
Underlying cancer type				
Head and neck cancer	7 (3.2%)	6 (3.8%)	1 (1.8%)	
Lung cancer	73 (34%)	50 (31%)	23 (40%)	
Esophago-gastrointestinal cancer	35 (16%)	26 (16%)	9 (16%)	
Colon and rectal cancer	17 (7.9%)	10 (6.3%)	7 (12%)	
Hepatobiliary and pancreatic cancer	52 (24%)	42 (26%)	10 (18%)	
Breast cancer	6 (2.8%)	5 (3.1%)	1 (1.8%)	
Genitourinary cancer	8 (3.7%)	4 (2.5%)	4 (7.0%)	
Gynecological cancer	10 (4.6%)	9 (5.7%)	1 (1.8%)	
Lymphoma	4 (1.9%)	4 (2.5%)	0 (0%)	
Others	4 (1.9%)	3 (1.9%)	1 (1.8%)	

Variable	Overall, N = 216[1]	Survival, N = 159[1]	Death, N = 57[1]	p-value[2]
Distant metastasis				
Liver metastasis	32 (15%)	26 (16%)	6 (11%)	0.300
Lung metastasis	31 (14%)	18 (11%)	13 (23%)	0.034
Brain metastasis	10 (4.6%)	5 (3.1%)	5 (8.8%)	0.130
Bone metastasis	40 (19%)	24 (15%)	16 (28%)	0.030
Other metastasis	41 (19%)	29 (18%)	12 (21%)	0.600
CCI score				0.012
0–3	207 (96%)	156 (98%)	51 (89%)	
> 3	9 (4.2%)	3 (1.9%)	6 (11%)	
Operation type (within 30 days)				0.017
Unoperated	144 (67%)	99 (62%)	45 (79%)	
Curative operation	60 (28%)	52 (33%)	8 (14%)	
Palliative operation	12 (5.6%)	8 (5.0%)	4 (7.0%)	
Prior treatment (within 30 days)				
Chemotherapy	62 (29%)	47 (30%)	15 (26%)	0.600
Radiotherapy	20 (9.3%)	14 (8.8%)	6 (11%)	0.700
Concurrent chemoradiotherapy	11 (5.1%)	8 (5.0%)	3 (5.3%)	> 0.900
Perfusion therapy	11 (5.1%)	10 (6.3%)	1 (1.8%)	0.300
Immunotherapy	13 (6.0%)	7 (4.4%)	6 (11%)	0.110
Targeted therapy	15 (6.9%)	8 (5.0%)	7 (12%)	0.075
Glucocorticoid therapy	69 (32%)	53 (33%)	16 (28%)	0.500
G-CSF usage	47 (22%)	35 (22%)	12 (21%)	0.900
Antibiotic usage	78 (36%)	52 (33%)	26 (46%)	0.082
Laboratory indexes				
Hemoglobin(g/L)	103 (90, 120)	106 (93, 120)	98 (85, 115)	0.041
< 110	131 (61%)	94 (59%)	37 (65%)	0.400

Variable	Overall, N = 216[1]	Survival, N = 159[1]	Death, N = 57[1]	p-value[2]
Platelet count (×10^9/L)	176 (111, 252)	197 (132, 266)	117 (58, 210)	< 0.001
< 100	50 (23%)	26 (16%)	24 (42%)	< 0.001
Leucocyte count (×10^9/L)	8.0 (5.4, 11.2)	8.1 (5.4, 11.1)	7.9 (5.1, 11.9)	0.700
< 4.0	33 (15%)	26 (16%)	7 (12%)	0.500
Neutrophils(×10^9/L)	6.4 (3.7, 9.3)	6.3 (3.5, 9.2)	6.8 (4.3, 10.8)	0.300
Lymphocyte(×10^9/L)	0.82 (0.52, 1.11)	0.84 (0.52, 1.14)	0.71 (0.48, 1.06)	0.140
Monocyte(×10^9/L)	0.42 (0.25, 0.71)	0.42 (0.25, 0.72)	0.40 (0.23, 0.68)	0.800
Albumin(g/L)	30.9 (28.2, 35.0)	31.8 (28.8, 36.0)	29.0 (25.8, 31.2)	< 0.001
< 30	90 (42%)	55 (35%)	35 (61%)	< 0.001
Serum calcium(mmol/L)	2.06 (1.95, 2.20)	2.09 (1.98, 2.21)	2.01 (1.89, 2.12)	0.006
< 2.0	144 (67%)	114 (72%)	30 (53%)	0.009
Serum corrected calcium(mmol/L)	2.28 (2.20, 2.38)	2.28 (2.21, 2.38)	2.27 (2.18, 2.40)	0.800
Serum sodium(mmol/L)	138.0(134.0,140.1)	138.4(135.6, 141.0)	135.3(131.0,139.0)	0.020
< 130	61 (28%)	36 (23%)	25 (44%)	0.002
Abbreviations: ECOG Eastern Cooperative Oncology Group, CCI Charlson Co-morbidity Index score, G-CSF granulocyte colony-stimulating factor				
[1]n (%); Median (IQR),[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test				

3.2 Data on infection in cancer patients with nosocomial infections caused by fungi

We reviewed all clinical data on nosocomial infections caused by fungi of the participants. Thirty-four patients (16%) had a history of previously known infection within 30 days. Respiratory tract infection was the most predominant primary infection type, accounting for 59% of cases, followed by celiac infections (8.8%). During hospitalization, 140 patients (65%) received intravenous antifungal therapy. Of these people, 122 patients (56%) received triazole antifungal drugs, followed by echinocandin antifungal drugs

(5.1%). At the same time, 3.2% of patients received two or more intravenous antifungal drugs. C. Albicans were the predominant pathogens (68%), followed by other Candida species (19%). Two patients (0.9%) were complicated with two or more fungal infections. Of all patients, 135 patients have undergone invasive procedures in the last 30 days, with indwelling catheterization being the most common (28%). In addition, 43 patients (20%) were admitted to the ICU, and 29 (13%) were mechanically ventilated.

3.3 Comparison of clinical and infection-related characteristics in the study population based on the survival status of patients during hospitalization

We used data on nosocomial mortality to assess the primary clinical outcomes of nosocomial infections caused by fungi in patients with solid tumors. The study participants' overall fatality rate was 26.4% (57/216). We also analyzed the relationship between these patients' prognoses and clinical features. The results showed that ECOG-PS, TNM stage, pulmonary metastases, liver metastases, CCI, surgery or chemotherapy within 30 days, laboratory results (platelet count, serum albumin level, serum calcium, and serum sodium levels) were varied ($p < 0.05$; Table 1). Meanwhile, the two groups' body temperature, antifungal therapy, immunoglobulin therapy, admission to ICU, mechanical ventilation, and type of sepsis varied ($p < 0.05$; Table 2).

Table 2
The Infection-related characteristics of solid patients with fungal infection

Variable	Overall, N = 216[1]	Survival, N = 159[1]	Death, N = 57[1]	p-value[2]
Primary sites of infection				0.500
Respiratory tract	128 (59%)	93 (58%)	35 (61%)	
Digestive tract	15 (6.9%)	11 (6.9%)	4 (7.0%)	
Urinary tract	11 (5.1%)	7 (4.4%)	4 (7.0%)	
Thoracic cavity	5 (2.3%)	5 (3.1%)	0 (0%)	
Enterocoelia	19 (8.8%)	16 (10%)	3 (5.3%)	
Temperature(≥ 38°C)	68 (31%)	43 (27%)	25 (44%)	0.019
Infection history (within 30 days)	34 (16%)	23 (14%)	11 (19%)	0.400
FN history (within 30 days)	3 (1.4%)	2 (1.3%)	1 (1.8%)	> 0.900
Invasive procedure (within 30 days)	135 (62%)	104 (65%)	31 (54%)	0.140
Biliary stent implantation	7 (3.2%)	7 (4.4%)	0 (0%)	0.200
Ureteral stent implantation	3 (1.4%)	2 (1.3%)	1 (1.8%)	> 0.900
Indwelling urinary catheter	60 (28%)	46 (29%)	14 (25%)	0.500
PICC	16 (7.4%)	12 (7.5%)	4 (7.0%)	> 0.900
Infusion port implantation	3 (1.4%)	3 (1.9%)	0 (0%)	0.600
Thoracic puncture catheter drainage	34 (16%)	25 (16%)	9 (16%)	> 0.900
Abdominal catheterization	19 (8.8%)	15 (9.4%)	4 (7.0%)	0.600
Arterial catheterization	5 (2.3%)	1 (0.6%)	4 (7.0%)	0.018
Central venous pressure apparatus	11 (5.1%)	8 (5.0%)	3 (5.3%)	> 0.900
Postoperative drainage	59 (27%)	50 (31%)	9 (16%)	0.023
Indwelling gastric tube	49 (23%)	37 (23%)	12 (21%)	0.700
Fungi types				0.200
Candida albicans	146 (68%)	114 (72%)	32 (56%)	
Mycotoruloides	41 (19%)	26 (16%)	15 (26%)	
Aspergillus flavus	6 (2.8%)	4 (2.5%)	2 (3.5%)	

Variable	Overall, N = 216[1]	Survival, N = 159[1]	Death, N = 57[1]	p-value[2]
Aspergillus	18 (8.3%)	11 (6.9%)	7 (12%)	
Penicillium	1 (0.5%)	1 (0.6%)	0 (0%)	
Coinfection	2 (0.9%)	1 (0.6%)	1 (1.8%)	
Others	2 (0.9%)	2 (1.3%)	0 (0%)	
Types of antifungal drugs				0.005
Unantifungal treatment	76 (35%)	63 (40%)	13 (23%)	
Triazole antifungal agent	122 (56%)	88 (55%)	34 (60%)	
Echinocandin antifungal agent	11 (5.1%)	6 (3.8%)	5 (8.8%)	
Combination therapy	7 (3.2%)	2 (1.3%)	5 (8.8%)	
Length of antifungal treatment (days)	4 (0, 8)	3 (0, 8)	5 (1, 9)	0.110
Combined with bacterial infection	54 (25%)	37 (23%)	17 (30%)	0.300
Immunoglobulin use	40 (19%)	23 (14%)	17 (30%)	0.010
ICU admission	43 (20%)	26 (16%)	17 (30%)	0.029
Mechanical ventilation	29 (13%)	14 (8.8%)	15 (26%)	< 0.001
Cardiac arrest	12 (5.6%)	0 (0%)	12 (21%)	< 0.001
Sepsis classification				< 0.001
None	176 (81%)	140 (88%)	36 (63%)	
Sepsis	21 (9.8%)	15 (9.5%)	6 (11%)	
Severe sepsis	5 (2.3%)	3 (1.9%)	2 (3.5%)	
Septic shock	14 (6.5%)	1 (0.6%)	13 (23%)	
Abbreviations: PICC peripherally inserted central catheter, ICU Intensive Care Unit				
[1]n (%); Median (IQR),[2]Pearson's Chi-squared test; Wilcoxon rank sum test; Fisher's exact test				

3.4 Risk factors for nosocomial death

In this study, univariate analysis results showed: ECOG-PS 3–4, TNM stage III-IV, lung metastasis, bone metastasis, radical surgery with 30 days, CCI, admission to the ICU, mechanical ventilation, hypoproteinemia, thrombocytopenia, and hyponatremia were significantly associated with in-hospital mortality. The multivariate analysis determined that ECOG-PS 3–4 (OR = 6.08, 95%CI: 2.04–18.12, p

= .001), pulmonary metastases (OR = 2.76, 95%CI: 1.11–6.848, p = .029), thrombocytopenia (OR = 2.58, 95%CI: 1.21–5.47, p = .014), hypoalbuminemia (OR = 2.44, 95%CI: 1.22–4.90, p = .012), and mechanical ventilation (OR = 2.64, 95%CI: 1.03–6.73, p = 0.42) were independent influencing factors of nosocomial death in tumor patients with nosocomial infections caused by fungi (Table 3).

Table 3
Logistic regression analysis of in-hospital death in solid patients with fungal infection

Variable		OR (univariable)	OR (multivariable)
ECOG-PS	0,1,2	REF (1.00)	REF (1.00)
	3,4	9.95 (3.66–27.04, p < .001)	6.08 (2.04–18.12, p = .001)
TNM stage	I-II	REF (1.00)	
	III-IV	2.73 (1.20–6.19, p = .016)	
Pulmonary metastasis	Yes	2.31 (1.05–5.10, p = .037)	2.76 (1.11–6.848, p = .029)
Bone metastasis	Yes	2.20 (1.07–4.52, p = .033)	
Operation type	Unoperated	REF (1.00)	
	Radical operation	0.34 (0.15–0.77, p = .010)	
	Palliative operation	1.10 (0.31–3.84, p = .881)	
ICU admission	Yes	2.17 (1.07–4.40, p = .031)	
CCI	≤ 3	REF (1.00)	
	> 3	2.69 (1.13–6.40, p = .026)	
Platelet count ($\times 10^9$/L)	< 100	3.72 (1.90–7.29, p < .001)	2.58 (1.21–5.47, p = .014)
Albumin(g/L)	< 30	3.01 (1.61–5.62, p < .001)	2.44 (1.22–4.90, p = .012)
Serum sodium(mmol/L)	< 130	2.67 (1.41–5.07, p = .003)	
Mechanical ventilation	Yes	3.70 (1.65–8.28, p = .002)	2.64 (1.03–6.73, p = .042)

Abbreviations: OR odds ratio, ECOG-PS Eastern Cooperative Oncology Group Performance Status, ICU intensive care u unit, CCI Charlson Co-morbidity Index score

3.5 Nomogram establishment and evaluation

Based on the results of multivariate logistic analysis, the final factors included were: ECOG-PS, lung metastases, platelet count, serum albumin level, and mechanical ventilation. Thus, we established a nomogram to predict the risk of nosocomial death from nosocomial infections in patients with oncology (Fig. 2). Multiple methods were performed to assess the discrimination and calibration abilities of the nomogram, including ROC and calibration curves. The area under the ROC curve (AUC) of the nomogram was 0.759 (95%CI: 0.682–0.835) (Fig. 3), suggesting an excellent discrimination ability in predicting the in-hospital death risk of these patients. Besides, the calibration curve showed that there was a high consistency between the predicted and actual in-hospital death risk of the nomogram (Fig. 4), indicating a reliable calibration ability of the nomogram. Due to the ROC curve and calibration curves depending on the nomogram's sensitivity and specificity, so they could not identify “false negative” and “false positive” events. Therefore, DCA was conducted to evaluate the net clinical benefit of the nomogram when it was adopted to guide clinical decision-making. The results demonstrated that the nomogram would bring more net clinical benefit to these patients at the whole range of risk threshold compared to other single factors in the nomogram (Fig. 5). Taken together, the constructed nomogram is a reliable risk classifier to predict the in-hospital death risk of nosocomial infections caused by fungi in patients with solid tumors.

4. Discussion

Patients with malignant tumors are more likely to develop infections for various reasons[5, 6]. Therefore, we conducted this study to fully understand the clinical features of nosocomial fungal infections in patients with solid tumors and established a nomogram to predict in-hospital mortality in these patients to accurately estimate the risk of nosocomial infections death in each patient.

In the current study, 1.3% of patients with solid tumor had nosocomial fungal infections over the eight years study period, which was low compared with the results of studies before[22]. This discrepancy could be explained by the fact that the prevalence of hospital acquired infections in cancer patients varies widely from region to region. Compared with other types of tumors, patients with respiratory tumors accounted for the highest proportion of the total population (34%), followed by gastrointestinal tumors (24%) and hepatobiliary and pancreatic system tumors (24%). This may be related to the incidence of these neoplasms[23]. Meanwhile, lung cancer patients infiltrate and continuously secrete immunosuppressive factors by respiratory tumor cells, and the body's natural barrier function is inhibited, resulting in increased alveoli and bronchial secretions and mass obstruction of bronchi making lung cancer patients more susceptible to co-infection than non-lung cancer patients[24, 25].

In this study, we observed that C.Albicans is the essential microbe causing fungal infections in patients with solid tumors, accounting for 68%, followed by other Candida genera (19%). This result is consistent with the results of previous studies[11, 26]. Unfortunately, the study was retrospective, and whether patients had a swab to screen for colonizing microbiota is unknown. C.Albicans is the most common fungal

infection and strain that causes invasive fungal disease. However, in recent years, studies have found that the proportion of non-C. Albicans detected in Candida and Aspergillus are increasing, and the case fatality rate is higher[27].

In this retrospective study, 76 patients (36%) received antibacterial therapy within 30 days before the diagnosis of fungal infection, the most crucial treatment received in the previous 30 days for the general population. This is consistent with our standard view: antibiotics may lead to dysbacteriosis and fungal proliferation. So patients who have previously received antibiotics need to be alert to fungal infections. Nosocomial deaths occurred in 26 of the 76 patients, accounting for 46% of the total deaths. In addition to fungal pathogenicity and invasiveness, this may also be associated with suppressed immune function in cancer patients [1, 2]. One hundred thirty-five patients received invasive procedures within 30 days of the diagnosis of fungal infection, accounting for 62% of the total population. Invasive operations such as indwelling catheterization and PICC damage the mucous membrane of the body cavity and the inner wall of blood vessels, destroying the physiological immune barrier of the human body so that fungal displacement and colonization result in infection. A prospective study published in 2018 showed a 9.1% incidence of concurrent infection of central venous catheters[3]. Therefore, patients with solid tumors should be particularly concerned about potential fungal infections when receiving antibiotic therapy or invasive procedures to avoid fungal-related deaths.

Above all, we investigated the predictors of nosocomial mortality risk of nosocomial infections in people with cancer. We found ECOG-PS 3–4, lung metastases, mechanical ventilation, thrombocytopenic, and hypoalbuminemia to be independent risk factors for in-hospital mortality. This conclusion is similar to a previous study of nosocomial mortality from bacterial infections[28]. Patients with cancer with poor ECOG-PS and distant metastases are known to be associated with adverse survival outcomes, as in our study. It recommends that we pay more attention to patients with higher ECOG-PS and those with pulmonary metastases for more refined management. Patients who received mechanical ventilation during hospitalization had a poorer prognosis, consistent with previous studies of bacterial infections[18, 21, 29, 30]. That is due to concomitant circulatory and/or respiratory dysfunction in these patients, resulting in poor clinical outcomes. We also found that patients with hypoalbuminemia and low platelets were significantly associated with higher in-hospital mortality. For one thing, because lower albumin level is often associated with immunosuppression, decreased muscle mass, malnutrition, and weight loss in patients with malignancy, these patients have a poor prognosis and an increase in cancer-related deaths[31–33]. For another, low albumin levels lead to low PNI, which one study confirmed as an independent risk factor for NSCLC[34]. At the same time, related studies have shown that thrombocytopenia is associated with a poor prognosis for many diseases[35, 36]. Our findings further confirm this view.

In this study, we developed a nomogram to predict the risk of nosocomial death from nosocomial fungal infections in cancer patients and evaluated its predictive power and clinical utility. This nomogram has good performance in predicting the risk of in-hospital death in these people. To our knowledge, this is the

first study to systematically evaluate the clinical features of nosocomial fungal infections in cancer patients in northwest China and develop and validate a nomogram that can accurately predict the risk of nosocomial death from nosocomial infections in these patients. Still, there are some inevitable limits to our study. First, due to the design of the single-center retrospective analysis, it is challenging to collect variables such as specific chemotherapy and radiation doses, specific prior antibiotic treatment information, and more detailed laboratory results. Thus, there may be potential biases in the analysis of the relationships. Second, although we established a nomogram that effectively predicted the risk of in-hospital death from nosocomial infections in patients with solid tumors, internal cohort validation was not possible due to sample size, and there was a lack of independent external validation cohorts. Therefore, there is an urgent need for multi-center retrospective and well-designed prospective studies to verify the performance of nomograms.

5. Conclusion

In summary, in our study, Fungi-related nosocomial infections in cancer patients resulted in higher in-hospital mortality. The most common pathogen is C.Albicans, and the leading infection site is the respiratory system. ECOG-PS 3–4, pulmonary metastasis, thrombocytopenia, hypoalbuminemia, and mechanical ventilation were independent prognostic factors for in-hospital death in these patients. In addition, we constructed a new nomogram that accurately predicts the risk of in-hospital death from nosocomial fungal infections in cancer patients. Precise management of patients with lung metastases, high ECOG-PS, mechanical ventilation, and dynamic monitoring of serum albumin levels and platelets may improve the prognosis of these individuals.

Abbreviations

FN: Febrile neutropenia; OR: Odds ratio; CI: Confidence interval; ECOG-PS: Eastern Cooperative Oncology Group Performance Status; CCI: Charlson comorbidity index; G-CSF: Granulocyte colony-stimulating factor; ICU: Intensive care unit; PICC: Peripherally inserted central catheter.

Declarations

Author contributions

TT and YY conceived the study. RXW, AMJ, JHL and RZ were involved in data collecting, statistical analysis, and manuscript drafting. CCS and QQD conducted the data collection and analysis and provided the critical revision. SHL, FMZ, and YYM were involved in data collecting. XF participated in the study design and helped with the data collection. XL and ZPR participated in the study design and manuscript revision. All authors read and approved the final manuscript.

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Not applicable.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

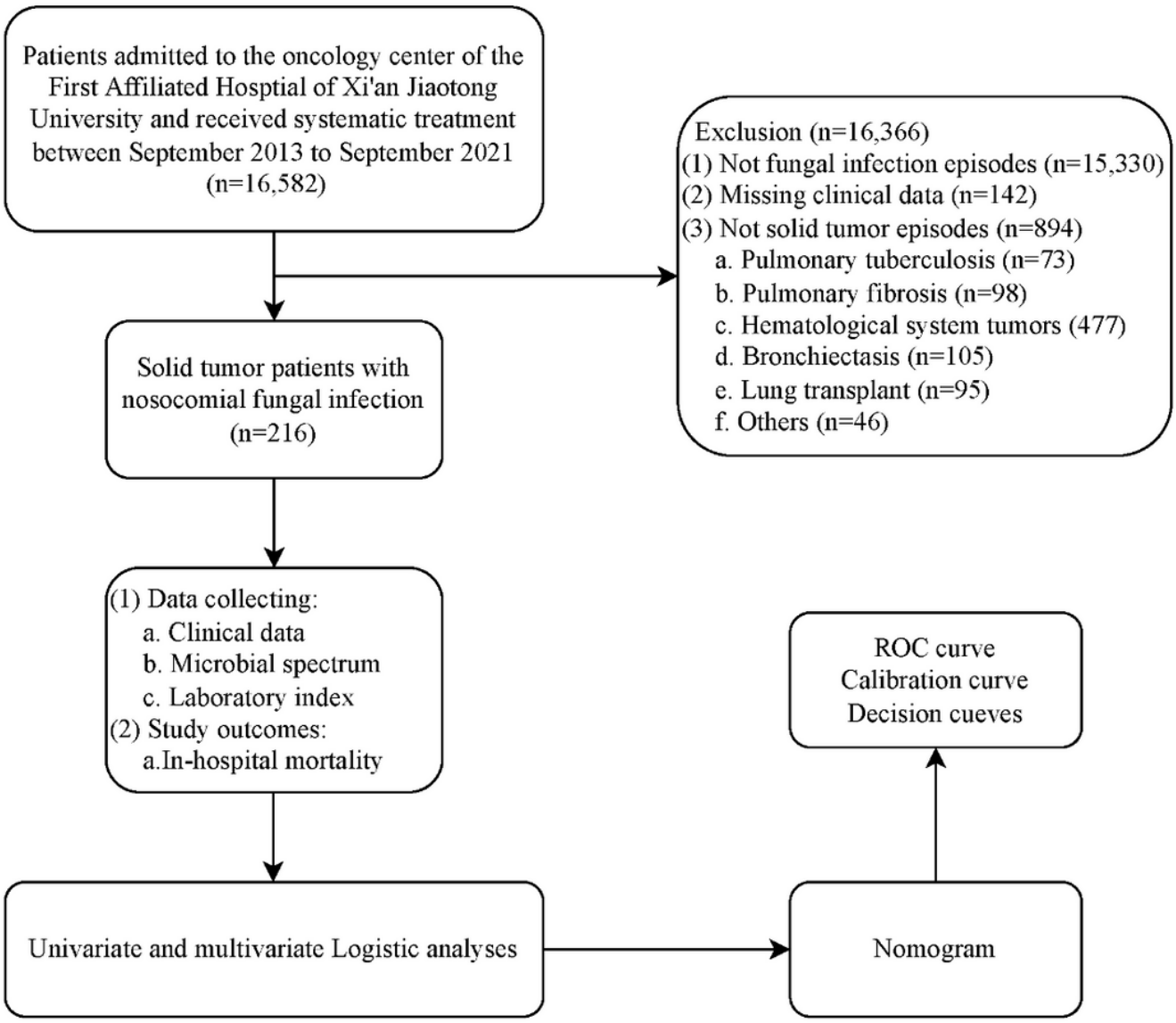

Figure 1

Flow chart of the study.

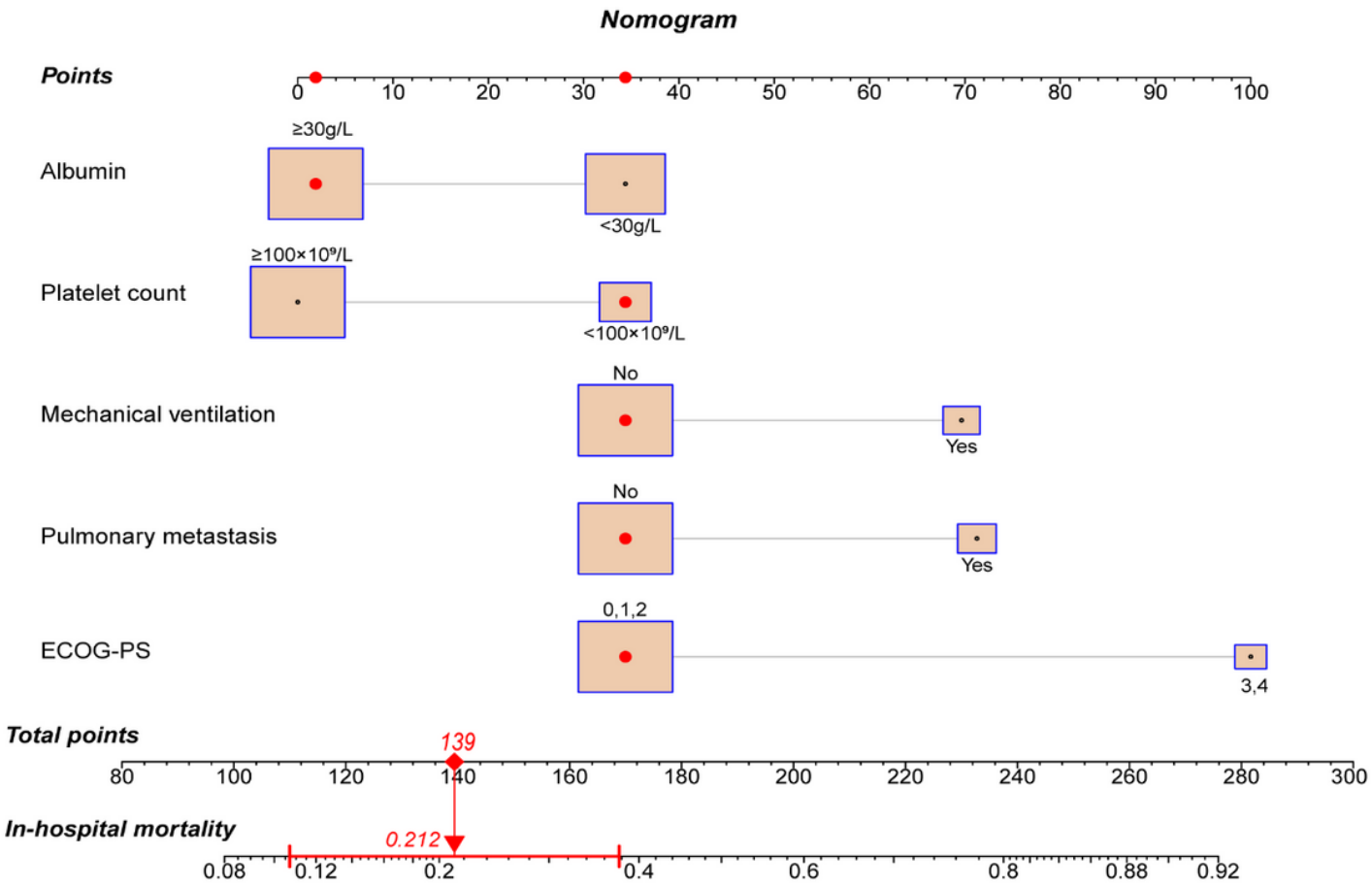

Figure 2

A nomogram to predict the risk of in-hospital death from fungal infections in cancer patients. This patient's albumin level was 35g/L, platelet count was 88×10^9/L, without mechanical ventilation, no pulmonary metastasis and ECOG-PS 1. According to the nomogram, we can calculate that the total point for this patient is 139 and its corresponding in-hospital death risk is 21.2%.

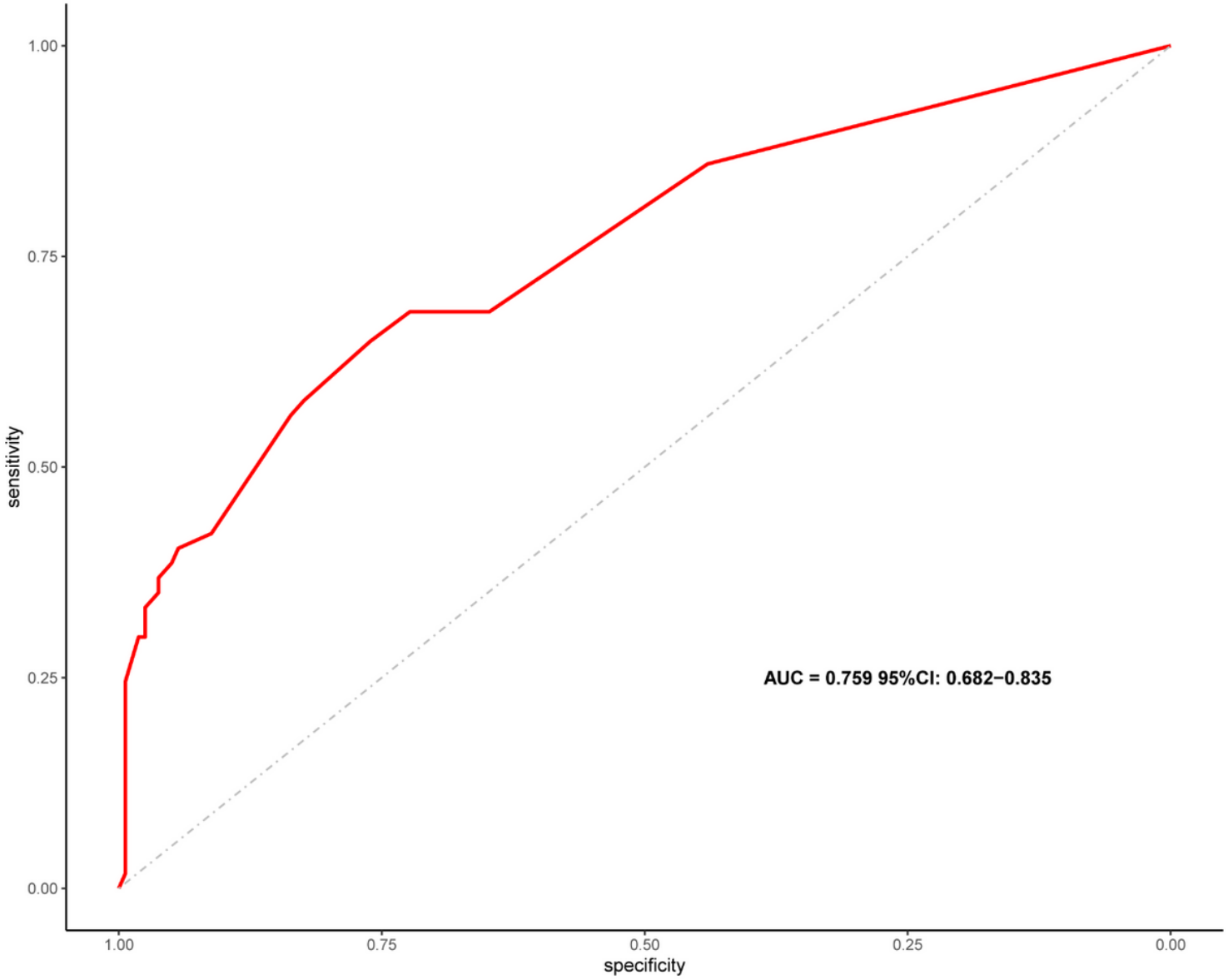

Figure 3

The ROC curve to evaluate the discrimination ability of the nomogram. AUC = 0.759 (95%CI: 0.682-0.835). ROC, receiver operating characteristic curve.

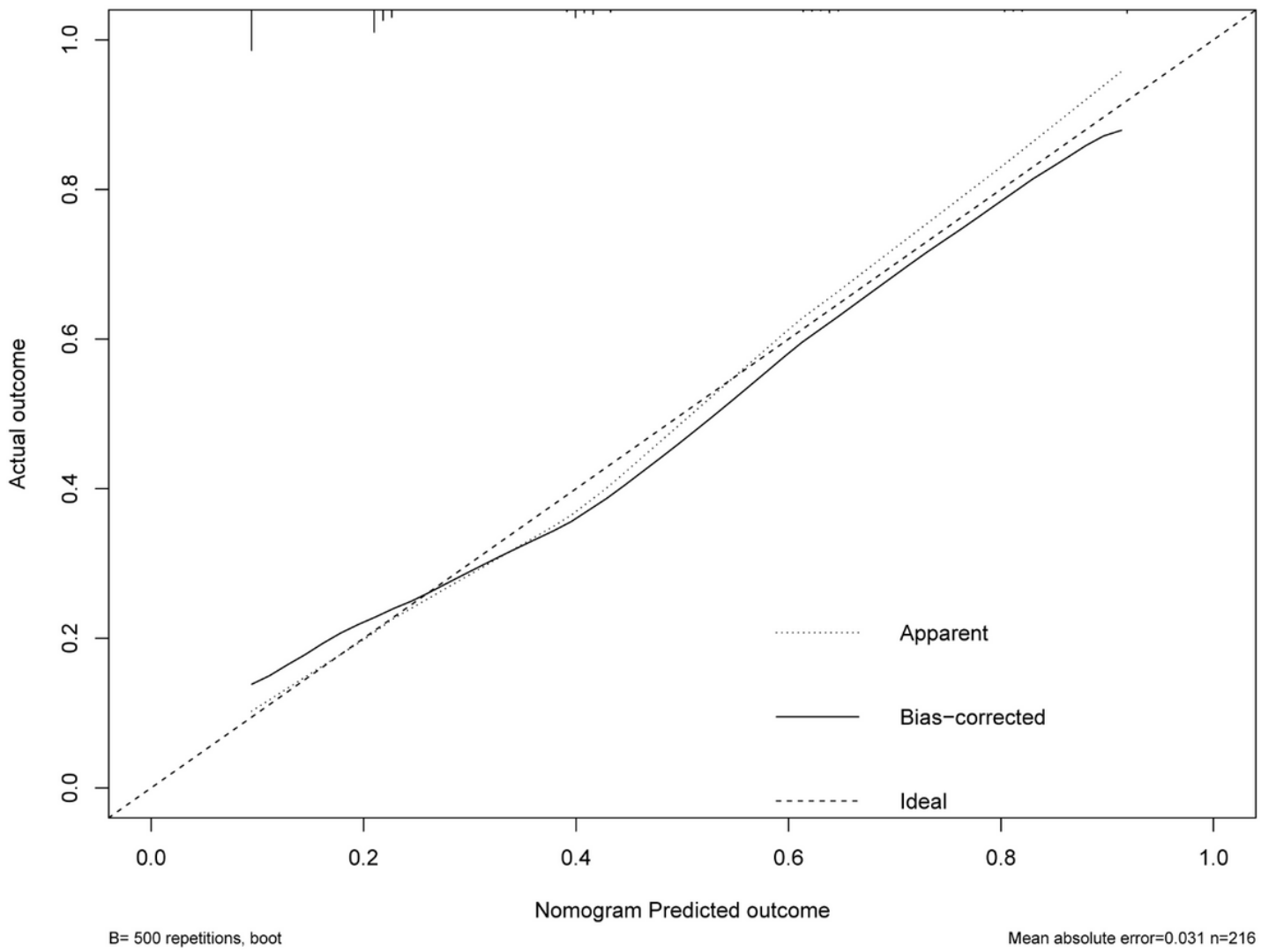

Figure 4

The calibration curve of the nomogram for predicting in-hospital death risk of nosocomial infections caused by fungi in cancer patients.

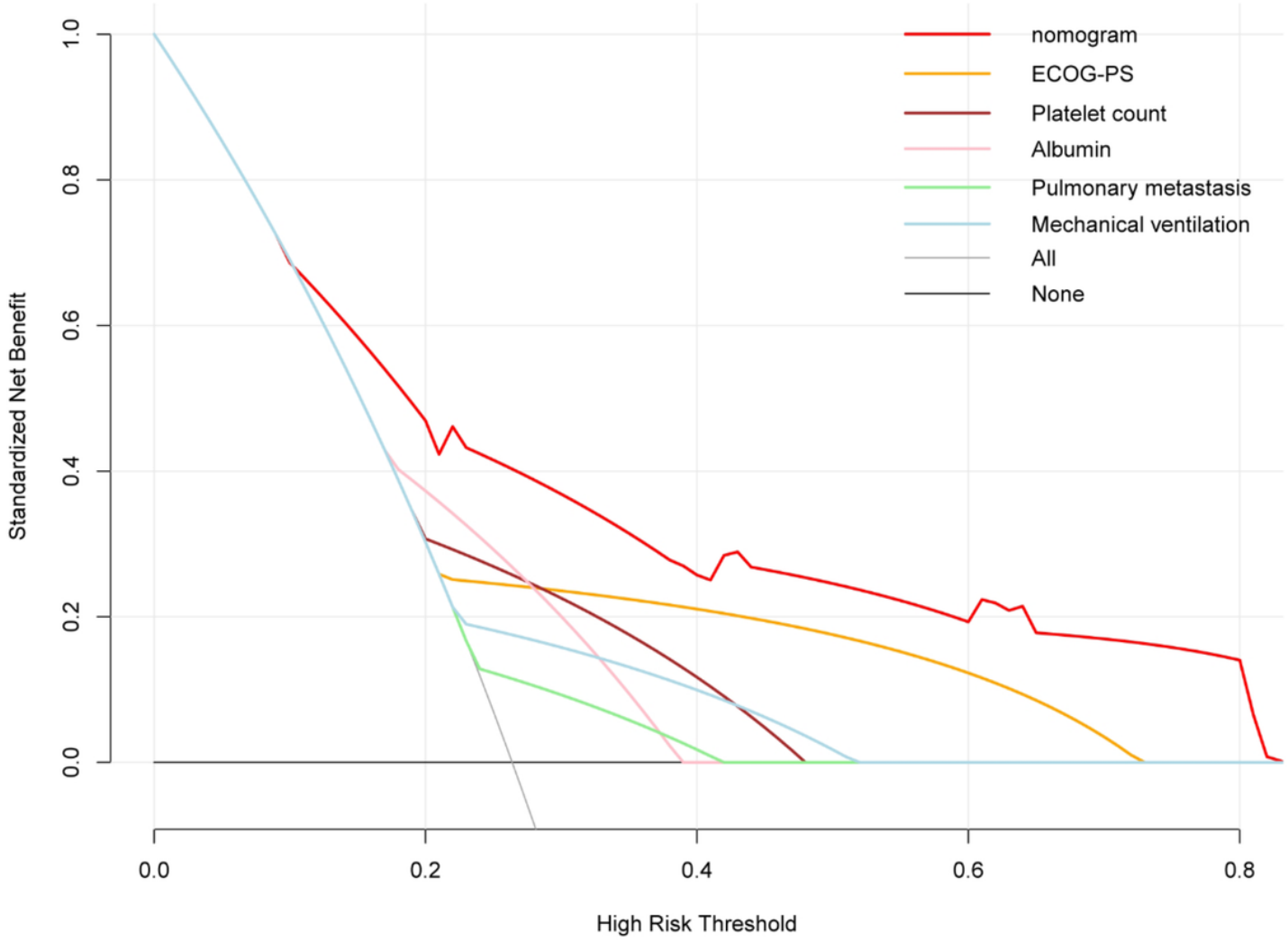

Figure 5

Decision curve analysis of the nomogram for predicting in-hospital death risk of nosocomial infections caused by fungi in cancer patients.