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# Predictive nomogram for early detection of invasive fungal disease deterioration --- a 10-year retrospective cohort study

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## Abstract

**Background** Invasive fungal disease (IFD) is characterized by its capacity to rapidly escalate to life-threatening conditions, even when patients are hospitalized. However, the precise prognostic significance of baseline clinical characteristics related to the progression outcome of IFD remains elusive.

**Methods** A retrospective cohort study spanning a duration of 10 years was conducted at two prominent tertiary teaching hospitals in Southern China. Patients with proven IFD were queried and divided into serious and non-serious groups based on the disease deterioration. To establish robust predictive models, patients from the first hospital were randomly assigned to either a training set or an internal validation set, while patients from the second hospital constituted an external test set. To analyze the potential predictors of IFD deterioration and identify independent predictors, the study employed the least absolute shrinkage and selection operator (LASSO) method in conjunction with binary logistic regressions. Based on the outcomes of this analysis, a predictive nomogram was constructed. The performance of the developed model was thoroughly evaluated using the training set, internal validation set, and external test set.

**Results** A total of 480 cases from the first hospital and 256 cases from the second hospital were included in the study. Among the 480 patients, 81 cases (16.9%) experienced deterioration, and out of those, 45 (55.6%) cases resulted in mortality. Seven independent predictors were identified and utilized to construct a predictive nomogram. The nomogram exhibited excellent predictive performance in all three sets: the training set, internal validation set, and external test set. The area under the receiver operating characteristic curve (AUC) for the training set was 0.88, for the internal validation set was 0.91, and for the external test set was 0.90. The Hosmer–Lemeshow test and Brier score indicated a high goodness of fit for the model. Furthermore, the calibration curve demonstrated a strong agreement between the predicted outcomes from the nomogram and the actual observations. Additionally, the decision curve analysis exhibited that the nomogram provided significant clinical net benefits in predicting IFD deterioration.

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**Conclusions** The study successfully identified seven independent predictors and developed a predictive nomogram for early assessment of the likelihood of IFD deterioration.

**Keywords** Invasive fungal disease, Independent predictor, Nomogram, Prediction probability

## Background

The colonization of fungal spores on luminal surfaces in vivo has the potential to penetrate tissues and progress to invasive fungal disease (IFD), especially in individuals with compromised immune status [1, 2]. A significant proportion of these patients experienced fungal dissemination and disease progression to life-threatening conditions even after hospitalization [3]. The IFD-related mortality ranges from 30 to 60% for invasive pulmonary aspergillosis, 40% to 60% for invasive candidiasis, and 31.3% to 50% in patients post hematopoietic stem cell transplantation, imposing heavy psycho-physiological and economic burden on patients, their family members, and health institutions [1, 4–6].

Early detection and preemptive intervention of IFD deterioration are crucial for enhancing patients' prognosis [6, 7]. However, early prediction of risk for disease progression in IFD patient is challenging due to the diversity of clinical presentation and disease course [8]. Approximately 30% to 80% of patients with pulmonary cryptococcosis are asymptomatic [5]. In non-neutropenic patients, the clinical manifestation of IFD is less pronounced than in neutropenic individuals, often leading to delayed diagnosis and treatment [9]. This delay, along with factors such as inadequate or inappropriate treatment and the presence of multidrug-resistant fungal strains, contributes to disease deterioration and life-threatening complications [10, 11]. Moreover, these indicators are typically observed in later stages, making early prediction particularly challenging. Nonetheless, it was reported that the disease progress from fungal colonization to tissue breakthrough is not only related to the number of fungal spores exposed, but also related to the baseline variables of underlying conditions and immune status of patients [12, 13]. The findings make it possible to predict disease deterioration early based on baseline indicators.

Currently, nomogram has emerged as a highly promising instrument for predicting clinical outcomes in various disease contexts, including fungal infections [14–16]. This tool enables the incorporation of multiple risk factors into a single predictive model, offering a graphical depiction of the probability of an event. Consequently, clinicians can utilize nomograms to guide targeted therapies and tailor interventions to the patients most in need [17]. Presently, there is a noticeable absence of clinical prediction models specifically designed for early identification of IFD deterioration. Recognizing this gap, our study aims to contribute to the field by introducing a novel and practical predictive tool. We developed a prototype nomogram that utilizes a comprehensive set of baseline clinical characteristics collected from IFD patients upon admission to predict disease deterioration early and effectively, enabling clinicians to implement timely interventions and improve patient prognoses.

## Methods

### Study design and ethics

A 10-year retrospective cohort study was conducted in two tertiary teaching hospitals in Southern China. Ethical approval was obtained from the Medical Ethics Committee of Zhujiang Hospital, Southern Medical University, and the Medical Ethics Committee of the Affiliated Guangdong Second Provincial General Hospital, Jinan University. In view of the retrospective design and the use of de-identified data, the requirement for written informed consent to participate was waived by both committees. The study protocol complied with the principles outlined in the Declaration of Helsinki [18].

### Definitions

The criteria for clinical proven IFD consist with the EORTC/MSGERC guideline [19]. Host factors are defined as any of the followings: recent history of neutropenia (neutrophils $< 0.5 \times 10^9$/L for $> 10$ days); hematologic malignancy; the receipt of an allogeneic stem cell or solid organ transplant (SOT); prolonged use of corticosteroids ($\geq 0.3$ mg/kg for $\geq 3$ weeks in the past 60 days); treatment with T-cell immunosuppressant during the past 90 days; treatment with recognized B-cell immunosuppressant; inherited severe immunodeficiency [19]. Time from onset to diagnosis is defined as the period of first appearance of symptoms to IFD confirmation [20]. If a precise date of the onset of symptom could not be determined, the date of the patient's first clinic visit, or admission to hospital with suspected IFD are deemed as the date of illness onset. We defined IFD deterioration as the development of fungal dissemination and life-threatening conditions, with at least one or more organ dysfunction requiring supportive therapies, including sepsis, septic shock, respiratory failure requiring mechanical ventilation, candidemia, endocarditis, osteomyelitis, central nervous system infection, extension of fungal

sinusitis with endophthalmitis or encephalitis, or intra-abdominal infection, etc., as documented during the disease course [1, 4, 21–28].

#### Patient retrieval

Patients who hospitalized with suspected IFD from January 1, 2011 to June 30, 2021 were queried through the Electronic Medical Record System (eMRS) using the search string of 'fungal', 'mycosis', 'aspergillosis', 'mucormycosis', 'cryptococcosis', 'pneumocystis' or 'candidiasis'. Then, medical records were manually reviewed, if the following criteria were met, patients were eligible for enrollment: 1) aged ≥ 18 years; 2) with pathologically confirmed IFD at discharge; 3) complete clinical data; and 4) able to follow-up from admission to discharge or event of death through the eMRS. If any of the followings was met, patient was excluded: 1) history of IFD prior to admission, e.g., chronic cavitary pulmonary aspergillosis; 2) concomitant with fatal infection and organ dysfunction at admission; 3) dermatomycosis; 4) missing more than 20% data, including clinical or laboratory variables; 5) known pregnancy.

#### Data acquisition

Baseline clinical characteristics upon admission were systematically collected from patients admitted to the first hospital, covering a wide range of factors, including demographic information, time from onset to diagnosis, seasonal onset patterns, host-related factors, comorbidities, symptoms presented upon admission, laboratory test results, pathological evidence, site of infection, fungal species, co-infection with other definitive pathogens, and ultimate outcomes. For patients from the second hospital (external validation set), only the independent predictors identified through binary logistic regression analysis were collected, streamlining the data collection process. To ensure accuracy and reliability, data cross-checking and entry into an electronic case report form were performed by two pairs of researchers, minimizing the potential for errors or inconsistencies.

#### Nomogram configuration and evaluation

A systematic approach was followed to develop and evaluate the predictive nomogram for IFD deterioration. 1) Patient categorization: after enrollment, patients with IFD deterioration were assigned to the serious group, while the remaining cases to the non-serious group. 2) Dataset splitting: data of patients from the first hospital were randomly allocated to a training set and an internal validation set, with a ratio of 7:3. Patients from the second hospital constituted the external test set. To validate the model's generalization ability, we did not strictly maintain the same case-to-control ratio between the training and validation sets during the data splitting. Instead, random assignment was adopted to ensure data representativeness. Similarly, for the external test set, we did not match the class proportions to those in the training set, but instead utilized all available data. Prior to the splitting, a thorough comparison of baseline clinical characteristics between the training and validation sets was conducted to ensure there were no statistically significant differences. 3) Selection of predictors and nomogram construction: LASSO regression was performed on the baseline clinical characteristics in the training set to determine the optimal predictors for IFD deterioration, with aim to reduce unnecessary predictor variables and address collinearity issues. The regularization parameter (λ) for the regression model was determined through tenfold cross-validation. The optimal λ value that minimized the number of predictor variables, reduced regression error, and maximized predictive performance was selected [29]. Given that each variable in the regression model should correspond to at least 10 positive events [30], and to ensure the model's stability and avoid overfitting, we applied a stepwise regression (backward elimination) method for feature selection following the LASSO regression. Specifically, in each step, the clinical features with $P$-values ≥ 0.05 were removed until we identified the independent and statistically significant features. The selected features were then used to construct the predictive nomogram. 4) Model evaluation: the performance of the nomogram including prediction, calibration and clinical utility was evaluated using the training set, internal validation set, and external test set, respectively.

#### Statistical analysis

Statistical analysis was performed using R software (version 4.2.2, http://www.r-project.org), and SPSS 21.0 (SPSS, Inc., Chicago, IL, USA). Discrete variables were presented as median (25% percentile, 75% percentile) and compared using the Mann–Whitney U test. Categorical data were expressed as numbers (percentages) and analyzed with the Chi-square test. LASSO regression and binary logistic regression were performed to determine the optimal predictors and independent predictors for IFD deterioration. The variance inflation factor (VIF) was calculated to assess multicollinearity among the independent predictors selected through logistic regression in the training set, ensuring that the variables do not interfere with each other. Variables with more than 20% missing data (e.g., body mass index) were excluded from the analysis. After excluding these variables, the remaining dataset had only a small proportion of missing values, we used the random forest regression method for imputation [31]. Additionally, we randomly deleted 10% of the non-missing data from the training set, internal validation set,

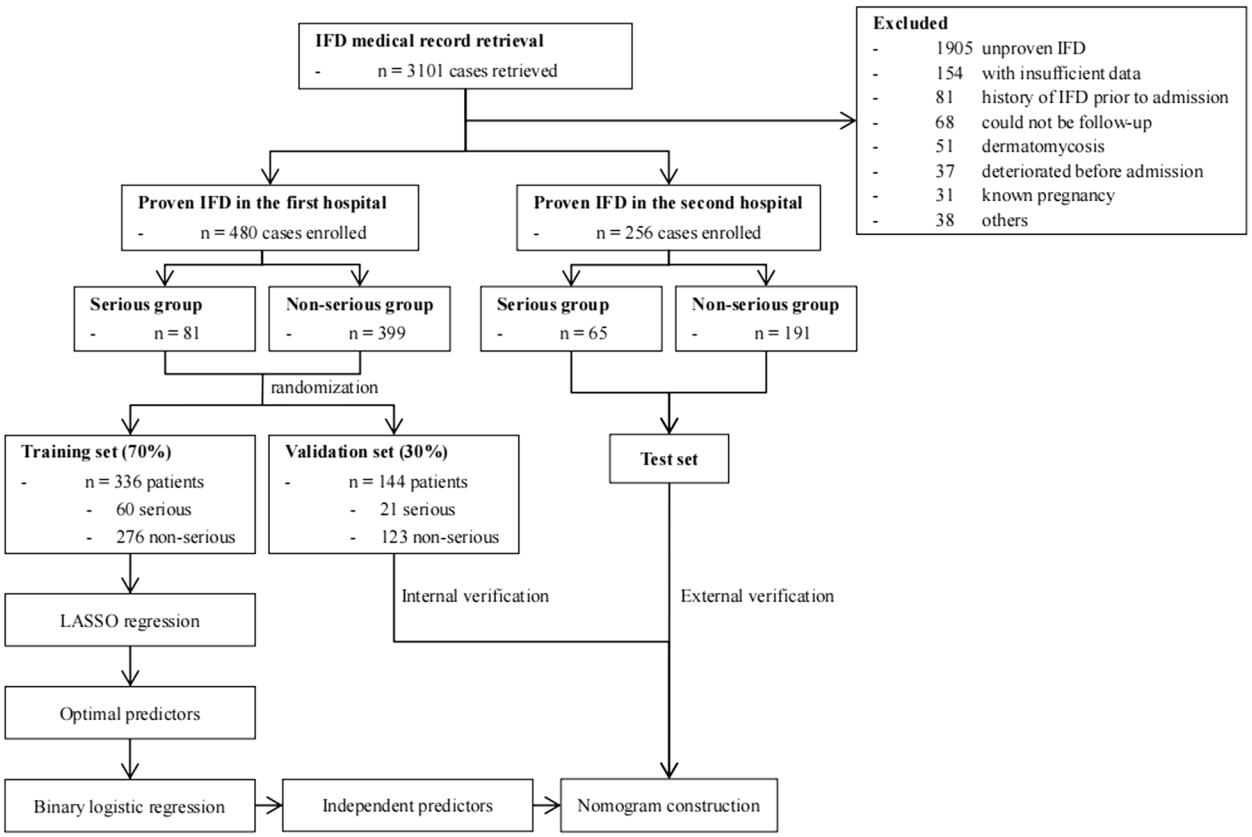


**Fig. 1** Patient enrolment and study flowchart. Notes: IFD, invasive fungal disease; LASSO, least absolute shrinkage and selection operator

and external test set, and calculated the mean squared error (MSE) between the imputed data and the original data for each dataset. The MSE values for the three datasets were 0.092, 0.11, and 0.096, respectively, indicating that the imputation method demonstrates good robustness. The discrimination metrics of the model included the area under the receiver operating characteristic curve (AUC), accuracy, sensitivity, and specificity. To assess the model's calibration, the Hosmer–Lemeshow test and Brier score were performed on the training set, internal validation set, and external test set. The calibration curve was employed to evaluate the consistency between predicted probabilities and actual observations. Decision curve analysis (DCA) was adopted to assess the clinical utility by estimating the net benefit at different probability thresholds [32]. All statistical tests were two-sided, and $P \leq 0.05$ was considered statistically significant.

## Results

### Patient enrollment and clinical characteristics

Figure 1 illustrates the patient retrieval and study flowchart. A total of 736 patients with proven IFD were included in this study, with 480 cases originating from the first hospital and 256 cases from the second hospital. Among the patients from the first hospital, 81 cases (16.9%) experienced disease deterioration and 45 patients (55.6%) died during their hospital stay. The demographics and baseline clinical characteristics of the patients from the first hospital are shown in Table 1.

### Optimal predictors

Among the patients in the first hospital, 336 cases were randomly assigned to the training set, while 144 patients were allocated to the internal validation set. There were no significant differences in baseline variables between the two sets, as shown in Table 2. The LASSO regression analysis identified 16 baseline variables as optimal predictors for IFD deterioration, including sex, SOT, chronic heart disease (CHD), one or more comorbidities, fever, respiratory symptoms, leukopenia, leukocytosis, lymphocytopenia, normal lymphocyte, non-anemia, moderate anemia, normal thrombocyte, thrombocytopenia, abdominal pain and bloody runny nose, as shown in Fig. 2.

### Nomogram configuration

Binary logistic regression analysis identified seven independent predictors for IFD deterioration, namely SOT,

**Table 1** Demographics and characteristics of patients with serious and non-serious IFD in the first hospital

| Variables | Serious ($n=81$) | Non-serious ($n=399$) |
|---|---|---|
| Age, years, n (%) | | |
| 18—44 | 18 (22.2) | 109 (27.3) |
| 45—59 | 28 (34.6) | 177 (44.4) |
| ≥ 60 | 35 (43.2) | 113 (28.3) |
| Sex, n (%) | | |
| Male | 54 (66.7) | 197 (49.4) |
| Female | 27 (33.3) | 202 (50.6) |
| Current smoker, n (%) | 13 (16) | 35 (8.8) |
| Onset to diagnosis, day, *Md* (IQR) | 20 (10—31) | 38 (18—181) |
| Season of onset, month, n (%) | | |
| 1–3 | 16 (19.8) | 104 (26.1) |
| 4–6 | 27 (33.3) | 119 (29.8) |
| 7–9 | 14 (17.3) | 85 (21.3) |
| 10–12 | 24 (29.6) | 91 (22.8) |
| Host factors, n (%) | | |
| Severe immunodeficiency | 26 (32.1) | 37 (9.3) |
| T/B-cell immunosuppressants | 17 (21) | 20 (5) |
| Prolonged use of corticosteroids | 13 (16) | 27 (6.8) |
| Hematological malignancy | 10 (12.3) | 17 (4.3) |
| Solid organ transplant | 6 (7.4) | 5 (1.3) |
| Neutropenia | 6 (7.4) | 6 (1.5) |
| Allogeneic stem cell transplantation | 2 (2.5) | 5 (1.3) |
| Comorbidities, n (%) | | |
| Malignancy | 23 (28.4) | 38 (9.5) |
| Chronic kidney disease | 23 (28.4) | 39 (9.8) |
| Diabetes mellitus | 16 (19.8) | 36 (9.0) |
| Liver disease | 12 (14.8) | 34 (8.5) |
| Chronic heart disease | 8 (9.9) | 6 (1.5) |
| Chronic lung disease | 6 (7.4) | 20 (5) |
| Tuberculosis | 6 (7.4) | 19 (4.8) |
| Severe respiratory viral infection | 3 (3.7) | 6 (1.5) |
| Others | 47 (58) | 95 (23.8) |
| Symptoms at admission, n (%) | | |
| Asymptomatic | 0 (0) | 24 (6) |
| Fever | 52 (64.2) | 59 (14.8) |
| Respiratory symptoms | 50 (61.7) | 147 (36.8) |
| Bloody runny nose | 2 (2.5) | 68 (17) |
| Abdominal pain | 12 (14.8) | 15 (3.8) |
| Others | 61 (75.3) | 222 (55.6) |
| Laboratory examinations, n (%) | | |
| White blood cell count, $\times 10^9$/L | | |
| < 0.5 | 1 (1.2) | 1 (0.3) |
| 0.5—3.9 | 7 (8.6) | 31 (7.8) |
| 4—10 | 34 (42) | 309 (77.4) |
| > 10 | 39 (48.1) | 58 (14.5) |
| Lymphocyte, $\times 10^9$/L | | |
| < 0.6 | 21 (25.9) | 21 (5.3) |
| 0.6—0.9 | 19 (23.5) | 35 (8.8) |
| 1—4 | 38 (46.9) | 337 (84.5) |

**Table 1** (continued)

| Variables | Serious ($n=81$) | Non-serious ($n=399$) |
|---|---|---|
| >4 | 3 (3.7) | 6 (1.5) |
| Hemoglobin, g/L | | |
| 30—59 | 6 (7.4) | 6 (1.5) |
| 60—89 | 30 (37) | 25 (6.3) |
| 90—120 | 23 (28.4) | 61 (15.3) |
| >120 | 22 (27.2) | 307 (76.9) |
| Platelet, g/L | | |
| <100 | 26 (32.1) | 14 (3.5) |
| 100—300 | 38 (46.9) | 302 (75.7) |
| >300 | 17 (21) | 83 (20.8) |
| Infection sites, n (%) | | |
| Oronasopharyngeal cavity | 3 (3.7) | 185 (46.4) |
| Lung/lower respiratory tract | 29 (35.8) | 157 (39.3) |
| Central nervous system | 9 (11.1) | 26 (6.5) |
| Blood | 27 (33.3) | 4 (1) |
| Abdomen | 12 (14.8) | 13 (3.3) |
| Others | 1 (1.2) | 14 (3.5) |
| Fungal spectrum, n (%) | | |
| *Aspergillus spp.* | 23 (28.4) | 198 (49.6) |
| *Cryptococcus spp.* | 8 (9.9) | 87 (21.8) |
| *Candida spp.* | 29 (35.8) | 12 (3) |
| *Mucor spp.* | 3 (3.7) | 27 (6.8) |
| *Pneumocystis spp.* | 7 (8.6) | 7 (1.8) |
| Unidentified | 8 (9.9) | 63 (15.8) |
| Others | 3 (3.7) | 5 (1.3) |
| Co-infection, n (%) | 64 (79) | 81 (20.3) |
| Outcomes | | |
| LOS, day, *Md* (IQR) | 16 (11—27) | 9 (6—15) |
| Hospital-mortality, n (%) | 45 (55.6) | 0 (0) |

Neutropenia denotes neutrophils $< 0.5 \times 10^9$/L for more than 10 days; prolonged use of corticosteroids indicates ≥ 0.3 mg/kg for ≥ 3 weeks in the past 60 days; use of immunosuppressants denotes administration during the past 90 days

*IFD* Invasive fungal disease, *Md* median, *IQR* interquartile range, *LOS* Length of stay

CHD, presence of one or more comorbidities, fever, leukocytosis, non-anemia, and thrombocytopenia, with no multicollinearity detected based on VIF assessment, as shown in Table 3. These independent predictors constitute the core components of the predictive nomogram. The presence or absence of each independent predictor is assigned a score, and the total score corresponds to a prediction probability of IFD deterioration, as shown in Fig. 3. Table 4 presents the percentage of the independent predictors observed in the external test set.

### Nomogram evaluation

The nomogram showed high predictive performance for IFD deterioration in both the training and internal validation sets, with AUCs of 0.88 (95%CI: 0.83–0.93) and 0.91 (95%CI: 0.86–0.97), respectively. The Youden-derived optimal cut-off values were 0.17 and 0.15, with accuracies of 85.1% and 76.4%, sensitivities of 0.80 and 0.95, and specificities of 0.86 and 0.73, respectively. When verified externally, the AUC was 0.90 (95%CI: 0.87–0.94). The Youden-derived optimal cut-off values was 0.40, with an accuracy of 85.9%, a sensitivity of 0.86 and a specificity of 0.86, as shown in Fig. 4 (a) and (b) and (c). The calibration curve showed a high consistency between predictive and actual observation, as shown in Fig. 4 (d) and (e) and (f). The Hosmer–Lemeshow test yielded *P*-values of 0.881, 0.731, and 0.716 for the training set, internal validation set and external test sets, indicating no significant differences between the predicted and observed values of the model.

**Table 2** Comparison of baseline variables of patients at admission in the training and validation sets

| Baseline variables | Training set (n = 336) | Validation set (n = 144) | *P* value |
|---|---|---|---|
| **Seriously ill**, n (%) | 60 (17.9) | 21 (14.6) | 0.380 |
| **Age**, years, n (%) | | | |
| 18—44 (youth) | 91 (27.1) | 36 (25) | 0.635 |
| 45—59 (middle-aged) | 146 (43.5) | 59 (41) | 0.615 |
| ≥ 60 (senior) | 99 (29.5) | 49 (34) | 0.321 |
| **Sex**, n (%) | | | |
| Male | 173 (51.5) | 78 (54.2) | 0.590 |
| Female | 163 (48.5) | 66 (45.8) | |
| **Current smoker**, n (%) | 33 (9.8) | 15 (10.4) | 0.842 |
| **Onset to diagnosis**, day, *Md* (IQR) | 34.5 (15—150.75) | 31.5 (15—124.5) | 0.992 |
| **Season of onset**, month, n (%) | | | |
| 1–3 | 88 (26.2%) | 32 (22.2%) | 0.358 |
| 4–6 | 99 (29.5%) | 47 (32.6%) | 0.488 |
| 7–9 | 70 (20.8%) | 29 (20.1%) | 0.863 |
| 10–12 | 79 (23.5%) | 36 (25%) | 0.726 |
| **Host factors**, n (%) | | | |
| Severe immunodeficiency | 43 (12.8%) | 20 (13.9%) | 0.746 |
| T/B-cell immunosuppressants | 25 (7.4%) | 12 (8.3%) | 0.737 |
| Prolonged use of corticosteroids | 23 (6.8%) | 17 (11.8%) | 0.064 |
| Hematological malignancy | 18 (5.4%) | 9 (6.3%) | 0.697 |
| Solid organ transplant | 6 (1.8%) | 5 (3.5%) | 0.258 |
| Neutropenia | 8 (2.4%) | 4 (2.8%) | 0.799 |
| Allogeneic stem cell transplantation | 3 (0.9%) | 4 (2.8%) | 0.114 |
| **Comorbidities**, n (%) | | | |
| Malignancy | 38 (11.3%) | 23 (16%) | 0.160 |
| Chronic kidney disease | 41 (12.2%) | 21 (14.6%) | 0.476 |
| Diabetes mellitus | 39 (11.6%) | 13 (9%) | 0.405 |
| Liver disease | 33 (9.8%) | 13 (9%) | 0.787 |
| Chronic heart disease | 8 (2.4%) | 6 (4.2%) | 0.287 |
| Chronic lung disease | 22 (6.5%) | 4 (2.8%) | 0.094 |
| Tuberculosis | 21 (6.3%) | 4 (2.8%) | 0.117 |
| Severe respiratory viral infection | 5 (1.5%) | 4 (2.8%) | 0.340 |
| One or more comorbidities | 219 (65.2%) | 102 (70.8%) | 0.228 |
| **Symptoms at admission**, n (%) | | | |
| Asymptomatic | 19 (5.7%) | 5 (3.5%) | 0.315 |
| Fever | 70 (20.8%) | 41 (28.5%) | 0.069 |
| Respiratory symptoms | 142 (42.3%) | 55 (38.2%) | 0.406 |
| Bloody runny nose | 47 (14%) | 23 (16%) | 0.572 |
| Abdominal pain | 18 (5.4%) | 9 (6.3%) | 0.697 |
| **Laboratory examinations**, n (%) | | | |
| White blood cell count, $\times 10^9$/L | | | |
| < 0.5 (severe) | 2 (0.6%) | 0 (0) | 0.354 |
| 0.5—3.9 (leukopenia) | 24 (7.1%) | 14 (9.7%) | 0.337 |
| 4—10 (normal) | 242 (72%) | 101 (70.1%) | 0.675 |
| > 10 (leukocytosis) | 68 (20.2%) | 29 (20.1%) | 0.980 |
| Lymphocyte, $\times 10^9$/L, n (%) | | | |
| < 0.6 (severe) | 26 (7.7%) | 16 (11.1%) | 0.231 |
| 0.6—0.9 (lymphocytopenia) | 44 (13.1%) | 10 (6.9%) | 0.051 |
| 1—4 (normal) | 260 (77.4%) | 115 (79.9%) | 0.547 |

**Table 2** (continued)

| Baseline variables | Training set (n = 336) | Validation set (n = 144) | *P* value |
|---|---|---|---|
| > 4 (lymphocytosis) | 6 (1.8%) | 3 (2.1%) | 0.826 |
| Hemoglobin, g/L, n (%) | | | |
| 30—59 (severe) | 6 (1.8%) | 6 (4.2%) | 0.126 |
| 60—89 (moderate) | 38 (11.3%) | 17 (11.8%) | 0.876 |
| 90—120 (mild) | 55 (16.4%) | 29 (20.1%) | 0.319 |
| > 120 (non-anemia) | 237 (70.5%) | 92 (63.9%) | 0.151 |
| Platelet, g/L, n (%) | | | |
| < 100 (thrombocytopenia) | 28 (8.3%) | 12 (8.3%) | 1.000 |
| 100—300 (normal) | 238 (70.8%) | 102 (70.8%) | 1.000 |
| > 300 (thrombocytosis) | 70 (20.8%) | 30 (20.8%) | 1.000 |

*Md* median, *IQR* interquartile range

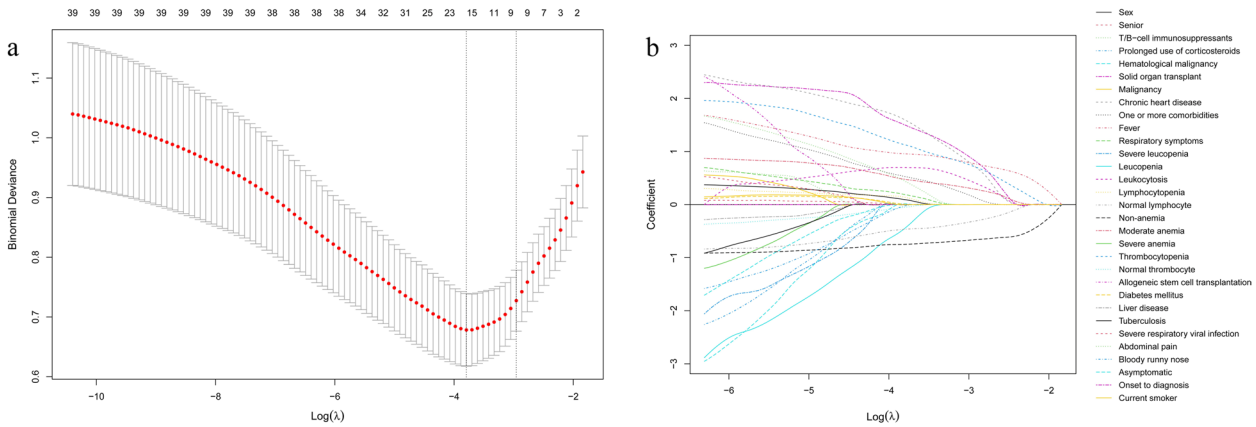


**Fig. 2** Selection of optimal predictors using the LASSO regression. Notes: **a** Determination of optimal regularization parameter λ of the LASSO model to select the optimal predictors for IFD deterioration. When log(λ) is -3.79, LASSO shows the best predictive performance with the minimum number of predictors and regression errors, where the coefficients of 27 out of 43 baseline variables are shrunk to zero. **b** The coefficient profile of LASSO. The trajectory of each IFD-related feature coefficient is observed in the LASSO coefficient profiles with the changing of the λ values. LASSO, least absolute shrinkage and selection operator; IFD, invasive fungal disease

**Table 3** Statistics of the independent predictors for IFD deterioration in training set

| Variables | VIF | Wald Z | Odds ratio (95%CI) | *P* value |
|---|---|---|---|---|
| SOT | 1.05 | 2.23 | 13.81 (1.37—138.85) | 0.026 |
| CHD | 1.05 | 2.41 | 11.43 (1.57—83.2) | 0.016 |
| Comorbidities | 1.08 | 2.44 | 3.48 (1.28—9.48) | 0.015 |
| Fever | 1.28 | 3.54 | 4.2 (1.9—9.32) | < 0.001 |
| Leukocytosis | 1.09 | 3.47 | 4 (1.83—8.76) | < 0.001 |
| Non-anemia | 1.36 | -2.94 | 0.3 (0.14—0.67) | 0.003 |
| Thrombocytopenia | 1.27 | 2.89 | 4.95 (1.67—14.63) | 0.004 |

*IFD* invasive fungal disease, *VIF* variance inflation factor, *SOT* solid organ transplant, *CHD* chronic heart disease, *Comorbidities* with one or more comorbidities

Additionally, the corresponding Brier scores were 0.087, 0.096, and 0.112, reflecting higher consistency between predicted probabilities and actual outcomes.

### Clinical utility

The results of the DCA showed that, in both the training set (threshold: 2%-97%) and the external test set (threshold: 1%-96%), the net benefit of using the nomogram to predict IFD deterioration was higher than that of the other strategies, including using independent predictors alone, treat all, or treat none. In the internal validation set, the net benefit of the nomogram was superior to these strategies at threshold of 1%-21% and 23%-94%. However, at a threshold of 22%, the net benefit of using fever to predict IFD deterioration was slightly higher than that of the nomogram, as shown in Fig. 5.

## Discussion

In this study, we developed a prototype nomogram for prediction of IFD deterioration based on baseline independent predictors, which demonstrated strong predictive performance. In view of the high death risk of

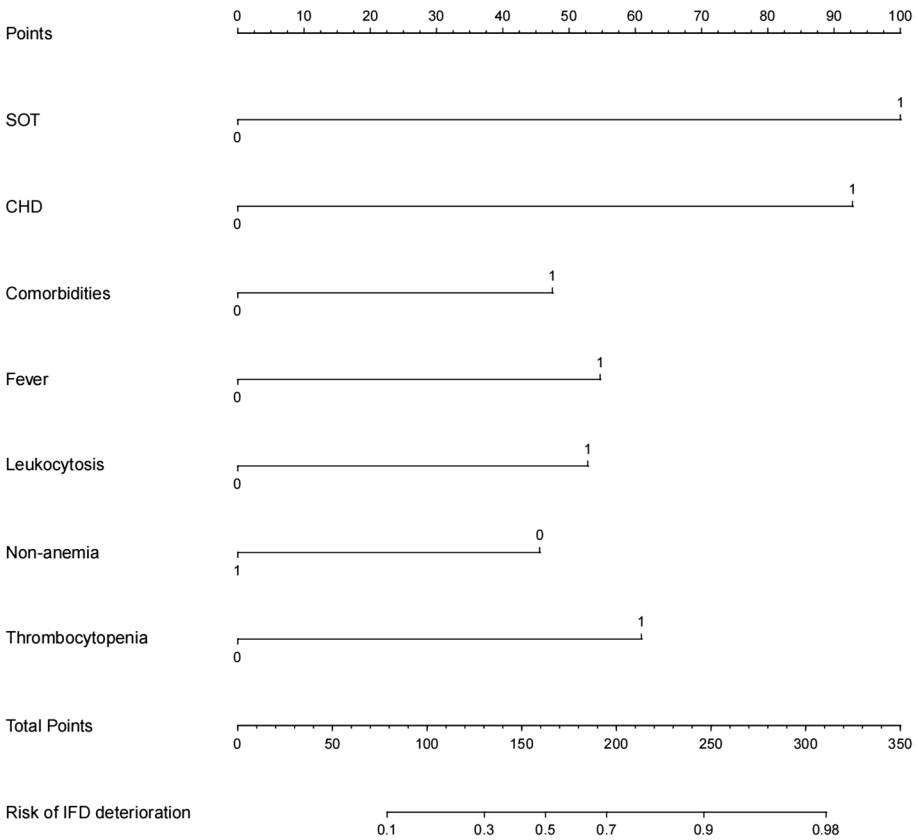


**Fig. 3** Predictive nomogram for early detection of IFD deterioration. Notes: Each independent predictor is represented as 0 for "no" and 1 for "yes", and the corresponding score is marked on the uppermost points axis. Total score for all predictors can be obtained by adding the scores of each predictor, and the bottom horizontal axis shows the corresponding risk of IFD deterioration. IFD, invasive fungal disease; SOT, solid organ transplant; CHD, chronic heart disease; Comorbidities, one or more comorbidities

**Table 4** Percentage of independent predictors of IFD deterioration in external test set

| Independent predictors, n (%) | Serious ($n=65$) | Non-serious ($n=191$) |
|---|---|---|
| SOT | 7 (10.8) | 8 (4.2) |
| CHD | 23 (35.4) | 15 (7.9) |
| Comorbidities | 65 (100) | 117 (61.3) |
| Fever | 49 (75.4) | 27 (14.1) |
| Leukocytosis | 39 (60) | 29 (15.2) |
| Non-anemia | 17 (26.2) | 135 (70.7) |
| Thrombocytopenia | 8 (12.3) | 8 (4.2) |

*IFD* invasive fungal disease, *SOT* solid organ transplant, *CHD* chronic heart disease, *Comorbidities* with one or more comorbidities

patients with deteriorated IFD, the nomogram could not only provide clinicians with an effective prediction tool for early identification of IFD deterioration, but also enable them to implement timely intervention and improve the prognosis of patients. The nomogram is of simplicity, non-invasiveness, and feasibility, and it can be widely used in outpatients, inpatients, healthcare facilities with limited resource, and even home care.

The nomogram achieved AUCs of 0.91 and 0.90 in the internal validation set and external test set, respectively, slightly higher than the AUC of 0.88 in the training set, which is uncommon. However, the calibration curves for the three datasets showed good consistency between the model's predicted outcomes and the actual risk of IFD deterioration, validating the model's accuracy. The Hosmer–Lemeshow test and Brier score also indicated no significant differences between the predicted and actual risks, further confirming the goodness of fit of the model. The DCA affirmed the clinical utility of the nomogram model. These results suggest that the model has strong robustness and a low risk of overfitting. Therefore, the slightly higher AUC values in the internal validation and external test sets may indicate the model's stronger generalization ability. It is worth noting that studies on nomogram models have

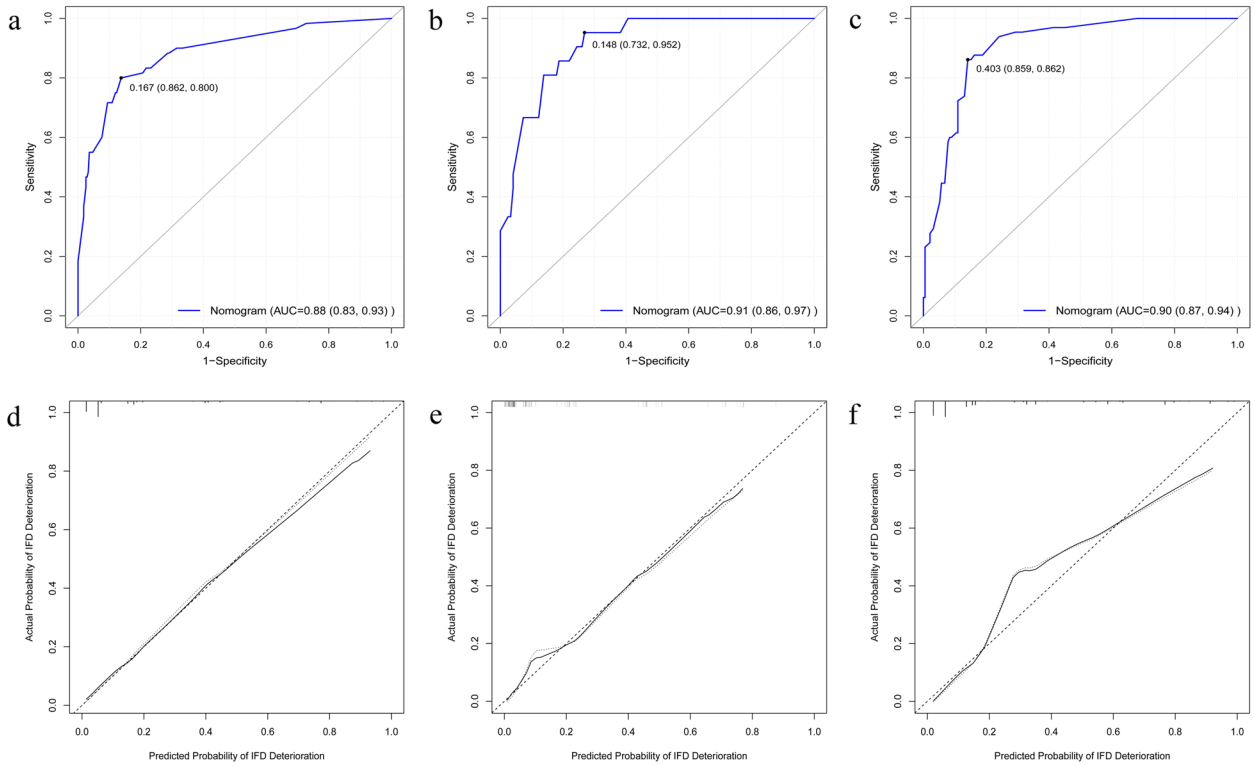


**Fig. 4** Receiver operating characteristic curves and calibration curves of the nomogram. Notes: Figure **a**, **b**, and **c** indicate the AUCs of the nomogram, with sensitivities and specificities, and d and e and f denote the calibration curves in the training set, internal validation set and external test set, respectively. The horizontal axis of figure **d**, **e**, and **f** show the predicted probability of IFD deterioration and the vertical axis show the actual probability. The predictive performance of the nomogram (black line) closer to the ideal prediction line (dotted line) represents a higher predictive accuracy. AUC, area under the receiver operating characteristic curve

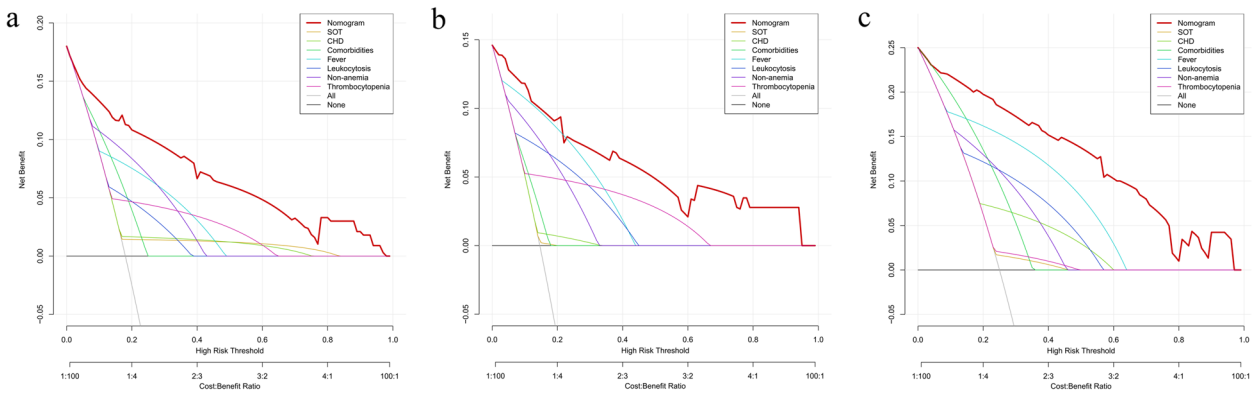


**Fig. 5** Decision curve analysis of the prediction nomogram. Notes: Decision curve analysis of the nomogram prediction in the training set (**a**), internal validation set (**b**), and external test set (**c**). The vertical axis represents the net benefit, while the horizontal axis denotes the threshold probability. The black horizontal line corresponds to the "treat none" strategy, assuming no patients receive intervention. The gray slanted line corresponds to the "treat all" strategy, assuming all patients are predicted to be positive and thus receive intervention. The farther the decision curve is above these two reference lines, the greater the net clinical benefit of the model. IFD, invasive fungal disease; SOT, solid organ transplant; CHD, chronic heart disease; Comorbidities, one or more comorbidities

also observed higher AUC values in the validation set compared to the training set, which typically reflects better model adaptation to external datasets [33–35].

Of the independent predictors identified in our study, SOT exhibits the greatest power in prediction of IFD deterioration, consistent with its role as a well-known host factor for IFD [19]. Fever and comorbidities are common in most IFD patients, but they may not usually be considered as risk factors for disease deterioration, and neglect may complicate diagnosis [6]. Cardiac disease has been proven to be an indicator of impending candidemia in ICU patients [36], and CHD could increase the risk of bacterial and fungal superinfection in critical COVID-19 patients [37]. It was reported that thrombocytopenia is clinically relevant and associated with patients' prognoses, whereas baseline platelet count ≥ 65,000 platelets/$mm^3$ is an independent predictor of a better prognosis in neutropenic-related invasive aspergillosis [38]. Our results showed a negative association between non-anemia and IFD deterioration, with a Wald Z value of -2.94, indicating that IFD patients with anemia might be more likely to develop serious illness. Anemia has been proven to be an independent risk factor for IFD in patients with multiple myeloma [39], and is associated with invasive non-albicans candidiasis [40]. Severe anemia is linked to a 3.1 times higher relative risk of death in patients with HIV infection and cryptococcal meningitis [41], and 3.5 times increase in the incidence of IFD in patients with type 2 diabetes, while correction of anemia may improve the prognosis of patients [42]. These findings may be mechanistically linked to the critical role of heme derived from hemoglobin degradation in immune defense. As an endogenous antimicrobial peptide, heme has broad-spectrum antimicrobial activity and can effectively inhibit the growth of various bacteria and fungi, thereby non-anemia may be a protective factor against the deterioration of IFD [43]. Additionally, our study suggests that leukocytosis is an important predictor of IFD deterioration, which contrasts with the conclusions in the literature that neutropenia is a major risk factor for IFD [44, 45]. Nonetheless, IFD has increasingly been recognized as an emerging disease in non-neutropenic patients [46]. Studies have shown that leukocytosis is a significant risk factor in patients with fatal candidemia caused by Candida albicans who do not have neutropenia [47]. Additionally, leukocytosis is one of the typical manifestations of acute infections [48], which enhances the immune response to help control the infection [49]. Therefore, leukocytosis may indicate that IFD patients are in an active infection state, rather than simply being associated with fungal contamination or colonization [50]. Our study showed a higher rate of concurrent infections in the IFD deterioration cohort (79% vs. 20.3%), which may be an important cause of leukocytosis. Relevant research also found that leukocytosis was prominent in IFD patients with influenza or COVID-19 [51, 52].

Currently, the nomograms and machine learning-based models developed for IFD mainly focus on the differential diagnosis, risk prediction of onset and death of IFD in patients with cancer, hematologic malignancies, COVID-19, lower respiratory tract infections, with AUCs ranged of 0.84–0.86 [14–16] and 0.77–0.95 [53–56], respectively. Although the nomograms exhibit similar performance to machine learning-based models, it shows advantages in interpretability and clinical usability. Nomograms graphically display the weights of variables and their impact on prediction, simplifying complex statistical model and enabling clinicians to make quick decisions. While the processes of machine learning models are opaque, making it difficult to directly interpret model decisions. The lack of transparency may lead to skepticism among clinicians, and the high demands for data, computational resources, and training time limit their application in resource-limited settings [57]. Overall, our model is superior to most existing ones, but there exist significant differences in the optimal predictors. In the aforementioned studies, the independent risk factors identified for predicting IFD-related mortality include bloodstream infection, ICU admission longer than 3 days, absence of prior surgery, presence of metastasis, and lack of effective source control. These differences may arise from several aspects. First, our model focuses on the early detection of IFD deterioration based on the variables of patients at admission, rather than the dynamic follow-up variables collected during hospitalization. Second, the differences in the use of diagnostic criteria may have a role on the results. Our study predominantly relied on pathological biopsy, while most other studies used non-invasive diagnostic methods, which may have an impact on the inclusion of patients. Third, the differences in underlying diseases and fungal species infected by patients may also account for the inconsistencies in predictive variables.

Limitations exist in our study. First, the participants in this study were solely from two hospitals in southern China, and patients who were undiagnosed with IFD, had concomitant fatal infections or organ dysfunction, or had missing data exceeding 20% were excluded. This may have reduced the diversity of the data, resulting in findings that are applicable only to specific regions and populations, thus affecting the generalizability of the results. Second, due to the inability to obtain chest CT images and fungal serology results upon admission, these variables were not included in the regression analysis. For other missing data, we used a random forest regression algorithm for imputation. These factors may collectively influence the reliability

of the data. Third, the imbalance in the proportion of serious and non-serious IFD patients may introduce bias into the model, resulting in inaccuracy. Fourth, the model did not include dynamic follow-up variables. As a result, the model may not fully capture changes during the disease course, which potentially leads to bias in predicting disease deterioration. In future studies, multi-center studies including patients with IFD from different regions with complete data are required to enhance the predictive performance and generalization of the model.

## Conclusions

This study identified seven independent predictors and developed a predictive nomogram to assess the likelihood of deterioration in IFD at the early stage of the disease. The nomogram demonstrated excellent predictive performance across multiple datasets, with strong discriminatory power and good model fit. Further research and validation are needed to solidify the findings and expand the generalization ability and applicability of the nomogram in varied medical scenarios.

#### Abbreviations

| | |
|---|---|
| AUC | Area under the receiver operating characteristic curve |
| CHD | Chronic heart disease |
| CT | Compute tomography |
| DCA | Decision curve analysis |
| eMRS | Electronic Medical Record System |
| IFD | Invasive fungal disease |
| LASSO | Least absolute shrinkage and selection operator |
| SOT | Solid organ transplant |
| MSE | Mean squared error |
| VIF | Variance inflation factor |

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#### Authors' contributions

WW, YL and HW contributed equally to the conception and design of the research and drafted the manuscript; WW, YL, JT and MW contributed to the literature review, and data acquisition, interpretation, and analysis; MC and YD provided consultation regarding the retrieved literature, study protocol revision and statistical analysis; CC, QL and WC were the principal investigators, who supervised the project and made important amendments to the manuscript. All the authors have critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and have read and approved the final manuscript.

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#### Data availability

The data supporting the findings of this study are available upon request from the corresponding authors.

## Declarations

#### Ethics approval and consent to participate

This retrospective study was approved by the Medical Ethics Committee of Zhujiang Hospital, Southern Medical University, and the Medical Ethics Committee of the Affiliated Guangdong Second Provincial General Hospital, Jinan University. Given the retrospective nature of the study and the use of de-identified data, the requirement for written informed consent to participate was waived by both the Medical Ethics Committee of Zhujiang Hospital, Southern Medical University, and the Medical Ethics Committee of the Affiliated Guangdong Second Provincial General Hospital, Jinan University. This waiver aligns with national regulations and ethical guidelines for retrospective studies involving de-identified data.

#### Consent for publication

Not applicable.

#### Competing interests

The authors declare no competing interests.

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#### References

1. Chinese Association Hematologists; Chinese Invasive Fungal Infection Working Group. The Chinese guidelines for the diagnosis and treatment of invasive fungal disease in patients with hematological disorders and cancers (the 6th revision). Zhonghua Nei Ke Za Zhi. 2020, 59(10): 754-763. (in Chinese).
2. Webb BJ, Ferraro JP, Rea S, Kaufusi S, Goodman BE, Spalding J. Epidemiology and clinical features of invasive fungal infection in a US health care network. Open Forum Infect Dis. 2018;5(8):ofy187.
3. Azim A, Ahmed A. Diagnosis and management of invasive fungal diseases in non-neutropenic ICU patients, with focus on candidiasis and aspergillosis: a comprehensive review. Front Cell Infect Microbiol. 2024;14:1256158.
4. Chinese Adult Candidiasis Diagnosis and Management Expert Consensus Group. Chinese consensus on the diagnosis and management of adult candidiasis. Zhonghua Nei Ke Za Zhi. 2020;59(1):5–17 (in Chinese).
5. Jenks JD, Mehta SR, Taplitz R, Aslam S, Reed SL, Hoenigl M. Point-of-care diagnosis of invasive aspergillosis in non-neutropenic patients: aspergillus galactomannan lateral flow assay versus aspergillus-specific lateral flow device test in bronchoalveolar lavage. Mycoses. 2019;62(3):230–6.
6. Cornely OA, Lass-Flörl C, Lagrou K, Arsic-Arsenijevic V, Hoenigl M. Improving outcome of fungal diseases - Guiding experts and patients towards excellence. Mycoses. 2017;60(7):420–5.
7. Inoue K, Muramatsu K, Nishimura T, Fujino Y, Matsuda S, Fushimi K, et al. Association between early diagnosis of and inpatient mortality from invasive pulmonary aspergillosis among patients without

immunocompromised host factors: a nationwide observational study. Int J Infect Dis. 2022;122:279–84.
8. Schmiedel Y, Zimmerli S. Common invasive fungal diseases: an overview of invasive candidiasis, aspergillosis, cryptococcosis, and pneumocystis pneumonia. Swiss Med Wkly. 2016;146:w14281.
9. Kreitmann L, Blot S, Nseir S. Invasive fungal infections in non-neutropenic patients. Intensive Care Med. 2024;50(12):2166–70.
10. Rayens E, Norris KA, Cordero JF. Mortality trends in risk conditions and invasive mycotic disease in the United States, 1999–2018. Clin Infect Dis. 2022;74(2):309–18.
11. Firacative C. Invasive fungal disease in humans: are we aware of the real impact? Mem Inst Oswaldo Cruz. 2020;115: e200430.
12. Bergeron A, Porcher R, Sulahian A, de Bazelaire C, Chagnon K, Raffoux E, et al. The strategy for the diagnosis of invasive pulmonary aspergillosis should depend on both the underlying condition and the leukocyte count of patients with hematologic malignancies. Blood. 2012;119(8):1831–7.
13. Nicolle MC, Benet T, Vanhems P. Aspergillosis: nosocomial or community-acquired? Med Mycol. 2011;49(Suppl 1):S24–9.
14. Yan C, Hao P, Wu G, Lin J, Xu J, Zhang T, et al. Machine learning-based combined nomogram for predicting the risk of pulmonary invasive fungal infection in severely immunocompromised patients. Ann Transl Med. 2022;10(9):514.
15. Li D, Li T, Bai C, Zhang Q, Li Z, Li X. A predictive nomogram for mortality of cancer patients with invasive candidiasis: a 10-year study in a cancer center of North China. BMC Infect Dis. 2021;21(1):76.
16. Kayaaslan B, Eser F, Asilturk D, Oktay Z, Hasanoglu I, Kalem AK, et al. Development and validation of COVID-19 associated candidemia score (CAC-Score) in ICU patients. Mycoses. 2023;66(2):128–37.
17. Balachandran VP, Gonen M, Smith JJ, DeMatteo RP. Nomograms in oncology: more than meets the eye. Lancet Oncol. 2015;16(4):e173–80.
18. Declaration of Helsinki: World Medical Association. World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013, 310(20): 2191–2194.
19. Donnelly JP, Chen SC, Kauffman CA, Steinbach WJ, Baddley JW, Verweij PE, et al. Revision and update of the consensus definitions of invasive fungal disease from the european organization for research and treatment of cancer and the mycoses study group education and research consortium. Clin Infect Dis. 2020;71(6):1367–76.
20. Brenier-Pinchart MP, Lebeau B, Borel JL, Quesada JL, Mallaret MR, Garban F, et al. Community-acquired invasive aspergillosis and outdoor filamentous fungal spore load: a relationship? Clin Microbiol Infect. 2011;17(9):1387–90.
21. Singer M, Deutschman CS, Seymour CW, Shankar-Hari M, Annane D, Bauer M, et al. The third international consensus definitions for sepsis and septic shock (Sepsis-3). JAMA. 2016;315(8):801–10.
22. Metlay JP, Waterer GW. Update in adult community-acquired pneumonia: key points from the new American thoracic society/infectious diseases society of America 2019 guideline. Curr Opin Pulm Med. 2020;26(3):203–7.
23. Ullmann AJ, Aguado JM, Arikan-Akdagli S, Denning DW, Groll AH, Lagrou K, et al. Diagnosis and management of Aspergillus diseases: executive summary of the 2017 ESCMID-ECMM-ERS guideline. Clin Microbiol Infect. 2018;24(Suppl 1):e1–38.
24. Cornely OA, Alastruey-Izquierdo A, Arenz D, Chen SCA, Dannaoui E, Hochhegger B, et al. Global guideline for the diagnosis and management of mucormycosis: an initiative of the European confederation of medical mycology in cooperation with the mycoses study group education and research consortium. Lancet Infect Dis. 2019;19(12):e405–21.
25. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. Clin Infect Dis. 2016;62(4):e1–50.
26. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. Clin Microbiol Infect. 2012;18(Suppl 7):9–18.
27. Bateman M, Oladele R, Kolls JK. Diagnosing Pneumocystis jirovecii pneumonia: A review of current methods and novel approaches. Med Mycol. 2020;58(8):1015–28.
28. Thompson GR 3rd, Young JH. Aspergillus Infections. N Engl J Med. 2021;385(16):1496–509.
29. Tibshirani R, Bien J, Friedman J, Hastie T, Simon N, Taylor J, et al. Strong rules for discarding predictors in lasso-type problems. J R Stat Soc Series B Stat Methodol. 2012;74(2):245–66.
30. Iasonos A, Schrag D, Raj GV, Panageas KS. How to build and interpret a nomogram for cancer prognosis. J Clin Oncol. 2008;26(8):1364–70.
31. Stekhoven DJ, Bühlmann P. MissForest–non-parametric missing value imputation for mixed-type data. Bioinformatics. 2012;28(1):112–8.
32. Liu L, He C, Yang J, Chen W, Xie Y, Chen X. Development and validation of a nomogram for predicting nutritional risk based on frailty scores in older stroke patients. Aging Clin Exp Res. 2024;36(1):112.
33. Wei J, Liang R, Liu S, et al. Nomogram predictive model for in-hospital mortality risk in elderly ICU patients with urosepsis. BMC Infect Dis. 2024;24(1):442.
34. Zhu HH, Wang YC, He LC, et al. Novel inflammatory and insulin resistance indices provide a clue in cerebral amyloid angiopathy. Sci Rep. 2024;14(1):11474.
35. Shi Q, Zhao Z, Lin J, Zhang Y, Dai J. A prediction model for the efficacy of continuous positive airway pressure on bronchiolitis. Front Pediatr. 2022;10:1033992.
36. Poissy J, Damonti L, Bignon A, Khanna N, Von Kietzell M, Boggian K, et al. Risk factors for candidemia: a prospective matched case-control study. Crit Care. 2020;24:109.
37. Seitz T, Holbik J, Grieb A, Karolyi M, Hind J, Gibas G, et al. The role of bacterial and fungal superinfection in critical COVID-19. Viruses. 2022;14(12):2785.
38. Nouér SA, Nucci M, Kumar NS, Grazziutti M, Restrepo A, Anaissie E. Baseline platelet count and creatinine clearance rate predict the outcome of neutropenia-related invasive aspergillosis. Clin Infect Dis. 2012;54(12):e173–83.
39. Tsai CK, Liu YC, Kuan AS, Lee KL, Yeh CM, Lee YT, et al. Risk and impact of invasive fungal infections in patients with multiple myeloma. Ann Hematol. 2020;99(8):1813–22.
40. Yang ZH, Song YG, Li RY. A ten-year retrospective study of invasive candidiasis in a tertiary hospital in Beijing. Biomed Environ Sci. 2021;34(10):773–88.
41. Teekaput C, Yasri S, Chaiwarith R. Cryptococcal meningitis: differences between patients with and without HIV-Infection. Pathogens. 2023;12(3):427.
42. Lao M, Li C, Li J, Chen D, Ding M, Gong Y. Opportunistic invasive fungal disease in patients with type 2 diabetes mellitus from Southern China: clinical features and associated factors. J Diabetes Investig. 2020;11(3):731–44.
43. Sheshadri P, Abraham J. Antimicrobial properties of hemoglobin. Immunopharmacol Immunotoxicol. 2012;34(6):896–900.
44. Maertens J, Lodewyck T, Donnelly JP, Chantepie S, Robin C, Blijlevens N, et al. Infectious Diseases Group and the Acute Leukemia Group of the European Organization for Research and Treatment of Cancer. Empiric vs preemptive antifungal strategy in high-risk neutropenic patients on fluconazole prophylaxis: a randomized trial of the European organization for research and treatment of cancer. Clin Infect Dis. 2023;76(4):674–82.
45. Koehler P, Salmanton-García J, Gräfe SK, Koehler FC, Mellinghoff SC, Seidel D, et al. Baseline predictors influencing the prognosis of invasive aspergillosis in adults. Mycoses. 2019;62(8):651–8.
46. Bassetti M, Peghin M, Vena A. Challenges and solution of invasive aspergillosis in non-neutropenic patients: a review. Infect Dis Ther. 2018;7(1):17–27.
47. Cheng MF, Yang YL, Yao TJ, et al. Risk factors for fatal candidemia caused by Candida albicans and non-albicans Candida species. BMC Infect Dis. 2005;5:22.
48. Riley LK, Rupert J. Evaluation of patients with leukocytosis. Am Fam Physician. 2015;92(11):1004–11.
49. Panopoulos AD, Watowich SS. Granulocyte colony-stimulating factor: molecular mechanisms of action during steady state and "emergency" hematopoiesis. Cytokine. 2008;42(3):277–88.
50. Ko SC, Chen KY, Hsueh PR, Luh KT, Yang PC. Fungal empyema thoracis: an emerging clinical entity. Chest. 2000;117(6):1672–8.
51. Huang L, Zhang N, Huang X, Xiong S, Feng Y, Zhang Y, et al. Invasive pulmonary aspergillosis in patients with influenza infection:

a retrospective study and review of the literature. Clin Respir J. 2019;13(4):202–11.
52. Patel SN, Shah S, Panchal J, Desai C, Upadhya IB, Patel M. Spotlight on the mucormycosis outbreak: a deadly fungal infection that followed the COVID-19 pandemic. Cureus. 2023;15(2):e35095.
53. Cao Y, Li Y, Wang M, et al. Interpretable machine learning for predicting risk of invasive fungal infection in critically ill patients in the intensive care unit: a retrospective cohort study based on MIMIC-IV database. Shock. 2024;61(6):817–27.
54. Liu T, Zhang ZH, Zhou QH, et al. MI-DenseCFNet: deep learning-based multimodal diagnosis models for Aureus and Aspergillus pneumonia. Eur Radiol. 2024;34(8):5066–76.
55. Li Y, Chen D, Liu S, et al. Supervised training models with or without manual lesion delineation outperform clinicians in distinguishing pulmonary cryptococcosis from lung adenocarcinoma on chest CT. Mycoses. 2024;67(1):e13692.
56. Wang W, Li M, Fan P, et al. Prototype early diagnostic model for invasive pulmonary aspergillosis based on deep learning and big data training. Mycoses. 2023;66(2):118–27.
57. Zhou T, Yang M, Wang M, et al. Prediction of axillary lymph node pathological complete response to neoadjuvant therapy using nomogram and machine learning methods. Front Oncol. 2022;12:1046039.

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