Prognostic Nomogram for Death from *Pneumocystis* Pneumonia in Non-HIV- and HIV-Infected Patients

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Research Article

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Abstract

Background: Pneumocystis pneumonia is a major cause of death in immunocompromised patients. Many risk factors for poor prognosis have been reported, but few studies have created predictive models with these variables to calculate the death rate accurately. This study created nomogram models for the precise prediction of mortality risk in non-human immunodeficiency virus (NHIV)- and human immunodeficiency virus (HIV)-infected patients with *Pneumocystis jirovecii* pneumonia (PJP).

Methods: A retrospective study was performed over a 10-year period to evaluate the clinical characteristics and outcomes of NHIV-PJP at Beijing Chaoyang Hospital and HIV-PJP at Beijing Ditan Hospital in China from 2010 to 2019. Univariate and multivariate logistic regression analyses were used to screen out mortality risk factors to create the nomograms. Nomogram models were evaluated by using a bootstrapped concordance index, calibration plots and receiver operating characteristic (ROC) curves.

Results: A total of 167 NHIV-PJP patients and 193 HIV-PJP patients were included in the study. Pneumothorax, febrile days after admission, CD4+ T cells ≤100/μl and sulfa combined with caspofungin (CAS) treatment were identified as independent risk factors for death that could be combined to accurately predict mortality risk in NHIV-PJP patients. We created a nomogram for mortality by using these variables. The area under the curve was 0.865 (95% confidence interval 0.799-0.931). The nomogram had a C-index of 0.865 and was well calibrated. The independent risk factors for death in HIV-PJP patients included in the nomogram were pneumothorax, platelet (PLT) $\leq 80\times10^9$/L, haemoglobin (HGB) ≤90 g/L, albumin (ALB), cytomegalovirus (CMV) coinfection and sulfa combined with CAS treatment. The nomogram showed good discrimination, with a C-index of 0.904 and excellent calibration. The area under the curve was 0.910 (95% confidence interval 0.850-0.970).

Conclusions: Our nomograms were useful tools for the precise prediction of mortality in NHIV-PJP and HIV-PJP patients.

Background

Pneumocystis jirovecii pneumonia (PJP), also known as interstitial plasma cell pneumonia, is a fungal infection of the respiratory system caused by *Pneumocystis jirovecii* (PJ). As one of the most common opportunistic infections in acquired immunodeficiency syndrome (AIDS) patients, it is a major cause of morbidity and mortality in them [1]. In recent years, with the widespread application of glucocorticoids and cytotoxic drugs, the fast development of tumour chemoradiotherapy, and the frequency of connective tissue diseases and various organ transplantation, the incidence of PJP in non-AIDS immunosuppressed patients has significantly increased [2]. PJP typically presents with acute and rapid progressive respiratory insufficiency. It has higher mortality in non-HIV patients than in HIV patients (30–60% versus 10–20%) [3, 4]. Many risk factors for poor prognosis have been reported [5], but it is difficult to predict the individual death rate accurately. More efficient prediction tools for estimating the prognosis of PJP patients are needed.

Nomograms are graphical models that enable users to calculate the overall probability of a specific clinical outcome for an individual patient [6, 7]. There are many nomograms used as prediction tools in various diseases, such as cancer [8]. The nomogram facilitates the clinical implementation and probability calculation of risk factors or other predictor variables. The objective of this study was to combine clinical manifestations, treatment variables, and laboratory variables that were associated with death into two prediction nomograms: We developed and validated nomograms that predicted death risk in NHIV and HIV patients.

Patients And Methods

Study Patients

We conducted a retrospective study to collect clinical data from Beijing Chaoyang Hospital and Beijing Ditan Hospital, Capital Medical University, and the study protocol was approved by the research ethics committee of the hospital. Because of the retrospective nature of the observational study, which lacked interventional aspects, informed written consent was waived by the ethics committee.

We retrospectively collected the data of these patients who were confirmed to have PJP and were hospitalized for the first time between 1 January 2010 and 31 December 2019 at either of the two hospitals of Capital Medical University, Beijing Chaoyang Hospital and Beijing Ditan Hospital, both tertiary care university hospitals in Beijing, China. By screening the eligible adult patients (age ≥ 18 years) from a computerized medical chart search system by ICD-10 (International Classification of Diseases, 10th revision) code, their medical records were reviewed, and data were extracted and registered in the research forms. All of these important data were entered into Excel for preservation. We defined confirmed PJP via three criteria: (1) clinical symptoms, such as fever, dry cough (occasionally expectorant) and progressive dyspnoea; (2) abnormal imaging findings: CT showed a broad range of features, from ground-glass opacity to nodules, cysts, patchy shadows and diffuse interstitial infiltrates; (3) a positive result for *Pneumocystis jirovecii* by Gomori-Grocott or toluidine blue stain or positive immunofluorescence test results in an induced sputum [9], low-tracheal-aspiration or bronchoalveolar lavage fluid (BALF) specimen. We did not include patients who only had positive PCR results.

Definite PJP cases with a first episode were included. Exclusion criteria: current pregnancy, allergy to sulfa drugs, and less than one week of hospitalization. The diagnosis of HIV/AIDS according to the Centers for Disease Control and Prevention (CDC) classification was based on Western blot conducted by the CDC to detect HIV-1 antibody positivity [10].

Data collection

The electronic medical charts for each enrolled patient were reviewed to obtain the following information: demographical data, underlying diseases, use of immunosuppressive drugs, clinical manifestations, radiology characteristics, laboratory tests, treatment and hospital mortality. Laboratory data used for analysis were those recorded within 48 hours or the worst values after admission. Febrile days meant the

unbroken duration of a daily temperature > 37.5°C after admission until discharge or death. Microbiological findings included CMV, Epstein-Barr virus (EBV) and coinfected bacteria.

Statistical Analysis

SPSS 20.0 (SPSS Institute, Chicago IL, USA) statistical software was used to perform statistical analysis. Nomogram models were created with R software (version 4.0.3; http://www.Rproject.org) using the “rms” package. Measurement data with a normal distribution are expressed as mean ± SD, while measurement data with a nonnormal distribution are expressed as median (interquartile range). Count variables are expressed as a percentage (%). The independent sample T-test was used for the continuous numerical variables obeying a normal distribution. Continuous variables that did not follow a normal distribution or graded variables were tested using the Mann-Whitney U test, and categorical variables were compared by using the Pearson chi-square test. $P < 0.05$ was statistically significant. The variables with statistical significance were selected for the binary logistic regression analysis of prognosis, and the variables with $P < 0.05$ in the univariate regression analysis were incorporated into the multivariate regression analysis model. To identify independent predictive factors of in-hospital mortality in a multivariate logistic regression analysis model, nomograms for hospital mortality risk were created based on the multivariate logistic regression model. The performance of the nomogram was evaluated through the concordance index and calibration plots with bootstrap samples.

Results

A total of 622 adult patients with a first episode of PJP were screened in the computer system from 2010 to 2019. Among these, 202 patients had probable PJP without microbiological results. Sixty patients were excluded: 26 for a sulfa drug allergy and 34 for hospitalization less than 1 week. Finally, 360 patients were included in the study: 167 patients in the NHIV-PJP group and 193 patients in the HIV-PJP group.

Patient Characteristics

We compared demographics, clinical characteristics, and auxiliary examinations of the two groups (Table 1) and recorded the underlying diseases in the NHIV-PJP group (Table 2). HIV-PJP patients were predominantly men (97.4% vs. 61.7%, P<0.001), were less often smokers (22.80% vs. 35.3%, P=0.009), and were younger (38.12±10.53 vs. 53.69±16.32 years, P<0.001) than NHIV-PJP patients. There was no difference in blood type between the NHIV-PJP and HIV-PJP groups except for the O type. One NHIV-PJP patient was Rh-negative (rhesus factor). Underlying diseases/conditions in the NHIV-PJP group included solid organ transplantation (n=49, kidney 43, liver 5, cornea 1), connective tissue diseases (n=46, systemic vasculitis 11, rheumatoid arthritis 8, glomerulonephritis 3, Wegener's granulomatosis 1, systemic lupus erythematosus 8, Sjögren syndrome 1, pemphigus 1, Bechet's disease 1, IgA nephropathy 2, dermatomyositis or polymyositis 4, adult onset still’s disease 3, pemphigus 1, giant cell arteritis 1 and nonspecific optic neuritis 1), haematological malignancies (n=8, non-Hodgkin lymphoma 4, myelodysplastic syndrome 1, multiple myeloma 1, chronic lymphocytic leukaemia 1 and autologous haematopoietic stem cell transplantation 1), solid tumours (n=14, lung cancer 6, oesophageal cancer 2,

malignant thymoma 2, breast cancer 2, cervical sarcoma 1, hepatic carcinoma 1), nephrotic syndrome (n=14), chronic lung diseases (n=53, interstitial lung disease 32, chronic obstructive pulmonary disease 8, chronic bronchiectasis 8, chronic bronchitis 4 and pneumoconiosis 1), and other chronic diseases (n =89, cardiovascular disease 49, diabetes mellitus 13, diabetes and cardiovascular disease 27). In the HIV-PJP group, past diseases included cardiovascular disease (10), diabetes mellitus (2), asthma (2), chronic hepatitis B (1) and schizophrenia (1).

Both NHIV-PJP and HIV-PJP patients had symptoms of fever (the most common) (89.8% vs. 86.0%, P=0.271), chest pain (3.60% vs. 3.10%, P=0.799), and the triad fever, cough, and dyspnoea (59.3% vs. 51.3%, P=0.129). These manifestations were not different between the two groups. However, there were an obviously shorter duration of fever before admission [7 (3-10) vs. 10 (4-15) days, P=0.004], higher temperature [39.0 (38.3-39.5) vs. 38.5 (37.6-39.0) °C, P<0.001], more cases of lung rales (54.5% vs. 15.0%, P<0.001), and a lower incidence of weight loss (18.6% vs. 69.4%, P<0.001) in the NHIV-PJP group.

A total of 154 (92.2%) of the NHIV-PJP patients were receiving immunosuppressants for their underlying diseases. Glucocorticoids alone were administered in 147 patients (88.0%), chemotherapeutic agents alone were administered in 19 patients (11.4%), and glucocorticoids combined with immunosuppressive or chemotherapeutic agents were administered in 115 patients (68.9%). The median time from beginning immunosuppressive medication to the PJP diagnosis was 186 days (range: 99-372 days). Laboratory data, including routine blood tests, β-D-glucan, CD4+ T cells, CD8+ T cells, the CD4/CD8 ratio, procalcitonin (PCT), C-reactive protein (CRP), lactic dehydrogenase, ALB and oxygenation index, were available from 360 patients. The PLT count, HGB level, CD8+ cell count, CRP level, ALB level and oxygenation index were significantly lower in the NHIV-PJP group than the HIV-PJP group. In contrast, CD4+ T cells, the CD4/CD8 ratio, PCT and lactic dehydrogenase were significantly higher in the NHIV-PJP group. Using a multivariate logistic regression model, febrile days after admission, CD4+ T cells ≤100/μl, pneumothorax, and sulfa combined with CAS treatment were identified as significantly associated with mortality in the NHIV-PJP group. Six parameters were identified as significantly associated with mortality in the HIV-PJP group: PLT≤80 ($x10^9$/L), HGB≤90 g/L, ALB, CMV coinfection, pneumothorax and sulfa combined with CAS treatment.

Coinfections in the respiratory tract were detected in both NHIV-PJP and HIV-PJP patients [87 (52.0%) vs. 136 (70.4%), p<0.001], with 54 patients infected by 2 or more pathogens simultaneously. A positive serum assay for CMV was identified in 241 patients altogether in the NHIV-PJP and HIV-PJP groups [112 (67.1%) vs. 129 (66.5%)], EBV in 101 patients [97 (58.1%) vs. 4 (2.1%)], and H1N1 virus in 3 patients [2 (1.2%) vs. 1 (0.5%)]. Other pathogens found in respiratory samples were *Mycobacterium tuberculosis* [n=5, 1(0.5%) vs. 4(2.1%)], Pseudomonas aeruginosa [n=19, 13(7.8%) vs. 6(3.1%)], *Klebsiella pneumoniae* [n=4, 4(2.4%) vs. 0 (0.0%)], *Escherichia coli* [n =9, 5(3.0%) vs. 4(2.1%)], fungi [n=80,60 (35.9%)vs. 20 (10.3%)], *Acinetobacter baumannii* [n=7, 5(3.0%) vs. 2(1.0%)], and atypical pathogens [n=4, 2(2.1%) vs. 2(1.0%)]. Coinfections in blood: Cytomegalovirus virusemia [n = 6, 0 (0.0%) vs. 6 (3.1%)], Gram-positive coccus septicemia [n = 14, 9 (5.4%) vs. 5 (2.6%)], Gram-negative bacillus septicemia [n = 9, 7 (4.2%) vs. 2 (1.0%)].

Treatment and outcome

A total of 354 patients received TMP-SMX (720 mg of trimethoprim, 3600 mg of sulfamethoxazole daily), and 125 patients received TMP-SMX (720 mg of trimethoprim, 3600 mg of sulfamethoxazole daily) combined with caspofungin (50 mg daily). Adverse effects of TMP-SMX included liver dysfunction (n=10), gastrointestinal reaction (n=3), minor myelosuppression (n=10), rash (n=22), and minor renal dysfunction (n=11). Adverse effects of TMP-SMX were more common in NHIV-PJP patients [22 (13.2%) vs. 21 (10.8%), p=0.504], but this difference did not reach statistical significance. Fifteen patients stopped taking TMP-SMX due to drug intolerance. A total of 351 patients received suitable antibiotic treatment based on antimicrobial susceptibility tests of respiratory samples or empiric antibiotic therapy. A total of 275 patients received systemic corticosteroids as adjunctive therapy.

NHIV-PJP caused more severe oxygenation impairment (oxygenation index, 287.57±119.28 vs. 310.78±100.68 mmHg, p=0.046), more transfers to the ICU [93 (55.69%) vs. 53 (27.46%), p<0.001], and more need for extracorporeal membrane oxygenation therapy [12 (7.2%) vs. 2 (1.0%), p = 0.040]. The mortality rate was higher in the NHIV-PJP group than in the HIV-PJP group [49 (29.3%) vs. 35 (18.1%), p=0.012], and this difference reached statistical significance.

Nomogram for mortality prediction

We investigated the association between clinical factors and all-cause mortality by univariate analysis in both groups. Febrile days after admission, PLT≤80(x10^9/L), HGB≤90 g/L, CD4+ T cells ≤100/μl, PCT, LDH≥500 U/L, ALB, CMV co-infection, EBV co-infection, pneumothorax, sulfa combined with CAS, ICU days, and ECMO were significantly associated with mortality in the NHIV-PJP group (Table 3). We then performed multivariate logistic regression analysis with these associated factors. We identified febrile days after admission, CD4+ cells ≤100/μl, pneumothorax and sulfa combined with CAS as independent risk factors. We found that a combination of these factors most precisely predicted mortality (Table 4). We then created a nomogram for mortality including all of these factors (Fig. 1). The area under the curve (AUC) was 0.865 (95% confidence interval 0.799-0.931, Fig. 2). The nomogram had a bootstrapped concordance index of 0.865 and was well calibrated (Fig. 3). In the same way, we created a nomogram for mortality in the HIV-PJP group (Fig. 4). The area under the curve (AUC) was 0.910 (95% confidence interval 0.850-0.970, Fig. 5). The nomogram had a bootstrapped concordance index of 0.904 and was well calibrated (Fig. 6).

Discussion

To our knowledge, this is the first study to create predictive nomogram models to calculate mortality risk precisely in PJP patients. This retrospective study describes the clinical characteristics and outcomes of NHIV-PJP cases and HIV-PJP cases. The results show that the PJP populations suffering from HIV and non-HIV immunosuppression are different depending on their baseline data. These HIV-negative patients were older than those in studies of HIV-positive patients, as found in a previous report[11]. Coinfections,

most notably with viruses, especially CMV coinfection, were considerably more prevalent among NHIV-PJP patients than HIV-PJP patients in our study, which was consistent with published findings [12]. PJP usually presents with atypical symptoms, such as fever, dry cough, and dyspnoea, occurring in up to 86%, 76%, and 81% of cases, respectively [13]. In our study, the fever rates in the HIV-PJP and NHIV-PJP groups were 86% and 89.8%, respectively. In the multivariate regression analysis, febrile days after admission was independently associated with death in NHIV-PJP patients. The results suggested that continuous fever as a predictive factor could enable clinicians to recognize the mortality risk of PJP earlier and avoid further deterioration of the patient's condition.

The main risk factors for immunosuppression in our study were drug-related immunosuppression and transplantation, which are obviously related to deficiencies in cellular immunity. Our study shows that almost 1/3 of PJP patients were renal transplant recipients, and 141 (84.4%) patients of the NHIV group had a low level of CD4 + T cells. This largely correlates to those patients who became organ transplant recipients, who remain at risk for PJP for many years after transplantation [2], but fewer recipients accepted TMP-SMX for PJP prophylaxis. On the other hand, these recipients took hormones and cytotoxic drugs simultaneously, which aggravated their immunodeficiency. Glucocorticoid treatment is a well-known risk factor for PJP in non-HIV patients and accounts for 55–97% of published cases [14, 15], including 88.0% in our study. The mechanism could be a decrease in peripheral CD4 + T cells caused by the glucocorticoid therapy [14]. Immunosuppressive agents such as thiopurine could reduce the absolute numbers of lymphocytes by inhibiting cell proliferation. Tacrolimus and cyclosporine can inhibit lymphocyte activation, and cytokines can inhibit lymphocyte function.

The main radiologic features of PJP identified through CT scanning are extensive ground-glass opacity (GGO) and reticulation [16, 17]. In our study, the rate of GGOs was higher in the non-HIV-PJP group (59.9%) and in the HIV-PJP group (88.1%) than other radiographic features. Pneumothorax is an unresolved problem in PJP because PJ has enough time to grow in the subpleural spaces and is thus difficult to eradicate by treatment [18]. In adults, the incidence of pneumothorax ranges from 4–36% [19]. When barotrauma occurs, it usually indicates a poor prognosis and a high mortality rate of 50%-100% [20–22]. The pneumothorax rates were 10.2% and 4.7% in our two groups, respectively. Nearly all patients with a poor prognosis developed pneumothorax. In particular, the NHIV-PJP group had a higher rate, and the difference was statistically significant. In the multivariate regression model, pneumothorax was an independent risk factor for mortality in both groups.

The auxiliary examination showed that the lymphocyte count, CD4 + T cells, serum ALB, and oxygenation index were below normal and that (1,3)-β-D-glucan and lactate dehydrogenase (LDH) levels were elevated in PJP patients. WBC count was normal in these patients. These findings are consistent with other studies [23]. Previous studies demonstrated that hypoalbuminaemia had a positive correlation with increased lung injury and could be a significant indicator of death in critically ill patients [24, 25]. In our study, the mean ALB level was higher in the HIV-PJP group than the NHIV-PJP group, but both were below normal. We showed that serum albumin was a significant independent factor of poor prognosis in only the HIV-PJP group and not in the NHIV-PJP group. This finding was similar to that of Kim et al., who showed that

hypoalbuminaemia was not considered an independent predictor of mortality [26]. These results suggest that ALB level might be a predictive factor for the prognosis of PJP patients. Overall, these results reflect that treatment strategies for HIV-PJP patients should be chosen with the awareness that the serum albumin level can be a warning of the risk of death. A low oxygenation index has also been associated with poor outcomes in PJP patients with immunosuppressive disease [27]. In our study, the oxygenation index in the NHIV-PJP and HIV-PJP groups was 287.57 ± 119.28 vs. 310.78 ± 100.68, respectively. A lower oxygenation index, which was also representative of ventilation-perfusion abnormalities, was related to death in both groups.

A decrease in haemoglobin indicates anaemia, and haemoglobin below 90 g/L is moderate to severe anaemia. Anaemia can also be defined as a lowered ability of the blood to carry oxygen. Therefore, we thought that anaemia might cause a worse prognosis in PJP patients. We found that HGB ≤ 90 g/L was an important risk factor for mortality in the two groups and an independent predictor of death in HIV-PJP patients. These results were consistent with a previous study[28], which indicated that timely discovery and correction of anaemia were necessary in patients with PJP.

Despite being associated with intolerance and adverse events, TMP-SMZ is still the first-line therapeutic regimen for PJP [9, 29, 30]. In our study, 55.1% of NHIV-PJP patients and 88.6% of HIV-PJP patients were initially treated with TMP-SMZ within 24 hours, but early anti-PCP treatment did not improve clinical prognosis[31]. Caspofungin was recognized as a second-line regimen. Its drug class, the echinocandins, were reported to inhibit the enzyme 1,3-β glucan synthase and improve overall mortality in patients with AIDS-PJP [32]. Other studies reported failure of echinocandin salvage therapy to improve survival among non-AIDS patients [33, 34]. Likewise, we found that sulfa combined with CAS treatment was an independent risk factor for death in multivariate analysis in both groups. This outcome reminds us to be careful about combining these two drugs for PJP treatment.

The overall mortality rate in NHIV-PJP patients is 31%, but it rises to almost 100% when PJP is not properly and quickly treated [35, 36]. In several studies, PJP was more often fatal in non-HIV-infected patients than in HIV-positive patients[11, 20]. We also observed that the mortality rate of 29.3% in the non-HIV group was higher than the 18.1% in the HIV group; previous rates on the order of 30–60% non-HIV patients and 10–20% in HIV patients have been reported. However, several studies have also reported mortality rates in the range of 7 to 14% [37, 38]. To calculate the precise mortality risk of PJP patients, we constructed a nomogram model incorporating clinical parameters and auxiliary examinations.

This study has some limitations. First, it is a retrospective study of two centres with a small population. Retrospective studies may be biased in terms of the data collected, such as physical examination data and the normal ranges in lab tests. A larger, prospective study is necessary. Second, the underlying diseases/conditions were mostly kidney transplants in the NHIV group, which is not very representative. Third, it only includes PJP patients who were hospitalized for more than 7 days. Some patients were not enrolled in this study because they left within 7 days after admission for any reason.

Conclusions

Our nomogram models provide a useful, convenient and applicable tool to evaluate the individualized prognosis of mortality in NHIV-PJP and HIV-PJP patients.

Abbreviations

PJP:pneumocystis jirovecii pneumonia, HIV:human immunodeficiency virus, BMI:body mass index, Rh:Rhesus, WBC:white blood cells, HGB:hemoglobin, PCT:procalcitonin, CRP:C-reactive protein, LDH:lactate dehydrogenase, ALB:albumin, OI:oxygenation index, EBV:Epstein-Barr virus, CMV:cytomegalovirus, CAS:caspofungine, GGO:ground-glass opacity, TMP-SMZ:trimethoprim-sulfamethoxazole, ICU:intensive care unit, HFNC:high-flow nasal cannula, NIMV:non-invasive mechanical ventilation, IMV:invasive mechanical ventilation, ECMO:extracorporeal membrane oxygenation

Declarations

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Authors' contributions

Z-HT and A-Li conceived and designed the experiments. Q-YF and J-JH contributed to the data collection and analysis. J-JH edited the manuscript. Q-YF contributed to the review and writing of the manuscript. Q-YF and J-JH contributed equally to this manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials

The data used and analysed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The Medical Ethics Committee of Beijing Chaoyang Hospital approved this study and waived the informed written consent given its observational nature.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1 Demographic characteristics of NHIV-PJP and HIV-PJP patients

Characteristic	NHIV-PJP (n=167)	HIV-PJP (n=193)	*P*-Value
Male sex	103 (61.70)	188 (97.4)	**<0.001**
Age, y	53.69±16.32	38.12±10.53	**<0.001**
BMI, kg/m^2	24.29±3.25	20.29±2.86	**<0.001**
Blood type, Rh+			
A	51 (30.50)	69 (35.8)	0.295
B	50 (29.9)	67 (34.7)	0.335
O	50 (29.9)	36 (18.7)	**0.012**
AB	16 (9.6)	21 (10.9)	0.685
Smoking history	59 (35.3)	44 (22.80)	**0.009**
Clinical manifestations			
Fever	150 (89.8)	166 (86.0)	0.271
Chest pain	6 (3.6)	6 (3.1)	0.799
Fever, cough, dyspnoea	99 (59.3)	99 (51.3)	0.129
Febrile days before admission, d	7 (3-10)	10 (4-15)	**0.004**
Highest temperature, °C	39 (38.3-39.5)	38.5 (37.6-39.0)	**<0.001**
Febrile days after admission, d	27 (16.2)	14 (7.3)	**0.008**
Loss of weight	31 (18.6)	134 (69.4)	**<0.001**
lung rale	91 (54.5)	29 (15)	**<0.001**
Laboratory examination			
WBC count (x10^9/L)	8.43±3.88	6.64±3.31	**<0.001**
Lymphocyte count (x10^9/L)	0.81±0.55	0.78±0.48	**0.475**
Platelet (x10^9/L)	179.31±79.68	251.71±89.03	**<0.001**
HGB, g/L	112.73±26.22	123.34±21.94	**<0.001**
(1,3)-β-D-glucan, pg/mL	77.06 (10.00-262.70)	88 (27.5-210.5)	0.998
CD4+ T cell, cells/ml	140.00 (69-258)	88 (27.5-210.5)	**<0.001**
CD8+ T cell, cells/ml	132.00 (73-270)	397.00 (241-622)	**<0.001**
CD4/CD8	1.10 (0.59-1.98)	0.05 (0.02-0.10)	**<0.001**
PCT, ng/ml	0.24 (0.06-1.52)	0.09 (0.05-0.25)	**<0.001**

CRP, mg/dl	7.66 (2.64-13.7)	39.2 (15-78.2)	**<0.001**
LDH, u/L	435 (323-599)	402 (289-489)	**0.002**
ALB, g/L	28.9 (24.2-33.1)	32.2 (28.25-35.40)	**<0.001**
OI	287.57±119.28	310.78±100.68	**0.046**
EBV co-infection	97 (58.1)	4 (2.1)	**<0.001**
CMV co-infection	112 (67.1)	129 (66.8)	0.964
Chest imaging			
GGO	100 (59.9)	170 (88.1)	**<0.001**
Interstitial infiltrates	63 (37.7)	12 (6.2)	**<0.001**
Cyst	2 (1.2)	1 (0.5)	0.599
Nodules	2 (1.2)	10 (5.2)	**0.041**
Pneumothorax	17 (10.2)	9 (4.7)	**0.044**
Treatment and result			
TMP-SMZ within 24 h	92 (55.1)	171 (88.6)	**<0.001**
Sulfa combine CAS	102 (61.1)	23 (11.9)	**<0.001**
TMP-SMZ adverse events	22 (13.2)	21 (10.9)	0.504
ICU, d	6 (0-16)	0 (0-3.5)	**<0.001**
HFNC	7 (4.2)	4 (2.1)	0.244
NIMV	39 (23.4)	2 (1)	**<0.001**
IMV	47 (28.1)	49 (25.4)	0.556
ECMO	12 (7.2)	2 (1)	**0.003**
Mortality rate	49 (29.3)	35 (18.1)	**0.012**

Data are presented as mean ±standard deviation, median (interquartile range) or No. (%). *BMI* body mass index, *Rh* Rhesus, *WBC* white blood cell, *HGB* haemoglobin, *PCT* procalcitonin, *CRP* C-reactive protein, *LDH* lactate dehydrogenase, *ALB* albumin, *OI* oxygenation index, *EBV* Epstein-Barr virus, *CMV* cytomegalovirus, *CAS* caspofungin, *GGO* ground-glass opacity, *TMP-SMZ* trimethoprim-sulfamethoxazole, *ICU* intensive care unit, *HFNC* high-flow nasal cannula, *NIMV* noninvasive mechanical ventilation, *IMV* invasive mechanical ventilation, *ECMO* extracorporeal membrane oxygenation

Table 2 Underlying diseases at diagnosis of NHIV-PJP

Underlying disease	Number of patients	
Haematological malignancy	8	(4.79)
Solid tumours	14	(8.38)
SOT	49	(29.34)
Cornea	1	
Renal	43	
Liver	5	
Connective tissue diseases	46	(27.55)
ILD	32	(19.16)
Nephrotic syndrome	14	(8.38)
Others	4	(2.40)
Treatment before PJP		
CS+IS	115	(68.90)
CS	147	(88.00)

Data are presented as No. (%). *SOT* solid organ transplantation, *ILD* interstitial lung disease, *CS* corticosteroid, *IS* immunosuppressor

Table 3 Prognostic factors in a univariate regression analysis in patients with PJP

	NHIV-PJP		HIV-PJP	
	Crude OR (95% CI)	*P*-Value	Crude OR (95% CI)	*P*-Value
Age	1.008(0.987-1.029)	0.441	1.025(0.990-1.060)	0.164
Male sex	0.678(0.344-1.335)	0.261	0.319(0.051-1.987)	0.221
Smoke	1.397(0.703-2.776)	0.340	0.818(0.330-2.024)	0.663
BMI	1.055(0.951-1.171)	0.309	0.904(0.791-1.033)	0.139
O type	1.265(0.601-2.662)	0.536	1.440(0.516-4.022)	0.487
Febrile days before admission	0.984(0.949-1.019)	0.359	1.012(0.986-1.038)	0.371
Highest temperature	1.105(0.773-1.580)	0.583	1.001(0.693-1.447)	0.994
Febrile days after admission	36.8(10.275-131.799)	**<0.001**	1.253(0.330-4.749)	0.740
Loss of weight	1.690(0.748-3.819)	0.207	0.692(0.321-1.493)	0.348
Lung rale	1.475(0.748-2.908)	0.261	3.565(1.499-8.476)	**0.004**
WBC	1.032(0.949-1.123)	0.460	1.016(0.911-1.132)	0.781
PLT≤80(x10^9/L)	3.916(1.708-8.979)	**0.001**	4.844(0.935-25.094)	0.060
HGB	0.987(0.974-1.000)	**0.049**	0.981(0.964-0.999)	**0.041**
HGB≤90 g/L	2.038(0.944-4.398)	0.070	4.463(1.398-14.245)	**0.012**
CD4+ T cells ≤100/ul	5.536(2.697-11.363)	**<0.001**	2.544(0.318-20.382)	0.379
CD4/CD8	0.955(0.747-1.222)	0.715	0.00(0.00-1.148)	0.054
PCT	1.091(1.025-1.161)	**0.006**	1.013(0.769-1.333)	0.929
CRP	1.014(0.989-1.040)	0.279	1.004(0.999-1.008)	0.087
LDH≥500U/L	5.543(2.693-11.410)	**<0.001**	2.731(1.250-5.970)	**0.012**
ALB	0.894(0.843-0.947)	**<0.001**	0.847(0.781-0.919)	**<0.001**
OI≤200	2.055(0.994-4.246)	0.052	4.068(1.685-9.818)	**0.002**
CMV co-infection	2.840(1.260-6.397)	**0.012**	4.674(2.162-10.106)	**<0.001**
EBV co-infection	2.588(1.247-5.368)	**0.011**	4.727(0.643-34.777)	0.127
Pneumothorax	7.330(2.422-22.182)	**<0.001**	19.50(3.851-98.746)	**<0.001**
Sulfa combine CAS	4.789(2.069-11.084)	**<0.001**	8.745(3.422-22.348)	**<0.001**
ICU days	1.029(1.004-1.054)	**0.021**	1.122(1.073-1.173)	**<0.001**
ECMO	3.767(1.133-12.519)	**0.030**	0.00(0.00)	

See Table 1 legend for definitions of abbreviations.

Table 4 Multivariate regression analysis for independent factors associated with death after admission

	NHIV-PJP patients		**HIV-PJP patients**	
	Adjusted OR (95% CI)	*P*-Value	Adjusted OR (95% CI)	*P*-Value
Age	1.02(0.98-1.06)	0.20	1.01(0.95-1.07)	0.620
Male sex	0.49(0.14-1.64)	0.25	0.09(0.00-12.65)	0.340
Febrile days after admission	33.68(4.75-238.63)	**<0.001**	0.83(0.08-8.03)	0.870
PLT≤80(x109/L)	1.79(0.40-8.00)	0.44	58.92(3.05-1137.99)	**0.007**
HGB≤90 g/L	2.46(0.29-20.61)	0.40	29.54(2.21-394.29)	**0.010**
CD4+≤100/μl	3.22(1.00-10.29)	**0.04**	20.01(0.09-47078.75)	0.440
ALB	0.97(0.82-1.08)	0.62	0.85(0.74-0.98)	**0.020**
CMV co-infection	0.95(0.23-3.86)	0.94	7.04(1.69-29.17)	**0.007**
Pneumothorax	20.20(2.39-170.74)	**0.006**	181.60(3.83-8600.46)	**0.008**
Sulfa combine CAS	8.11(2.07-31.77)	**0.003**	26.19(5.14-133.46)	**<0.001**

See Table 1 legend for definitions of abbreviations.

Figures

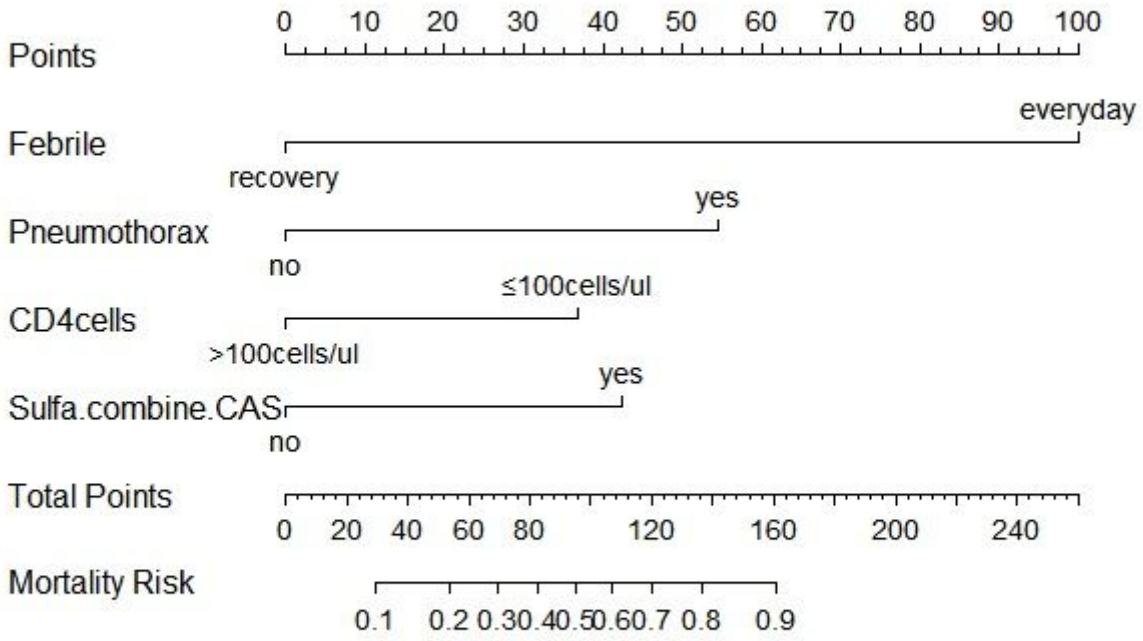

Figure 1

Nomogram for mortality in NHIV-PJP group. To estimate the probability of mortality, find the predictor point value on the uppermost point scale that corresponds to each patient variable and add all of them up. Next, mark the sum on the total point axis and draw a straight line perpendicular to the probability axis. Febrile recovery means that body temperature returns to normal after hospitalization.

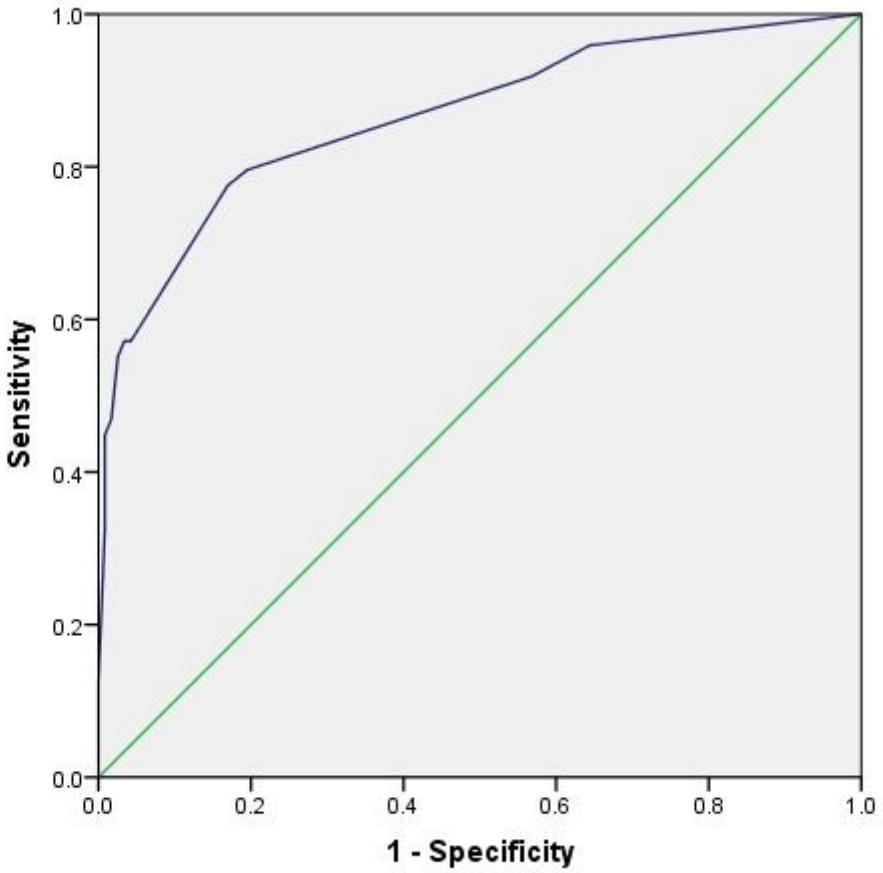

Figure 2

Receiver operating characteristic curve for the prediction model of the NHIV-PJP group. The area under the curve was 0.865 (95% confidence interval 0.799-0.931)

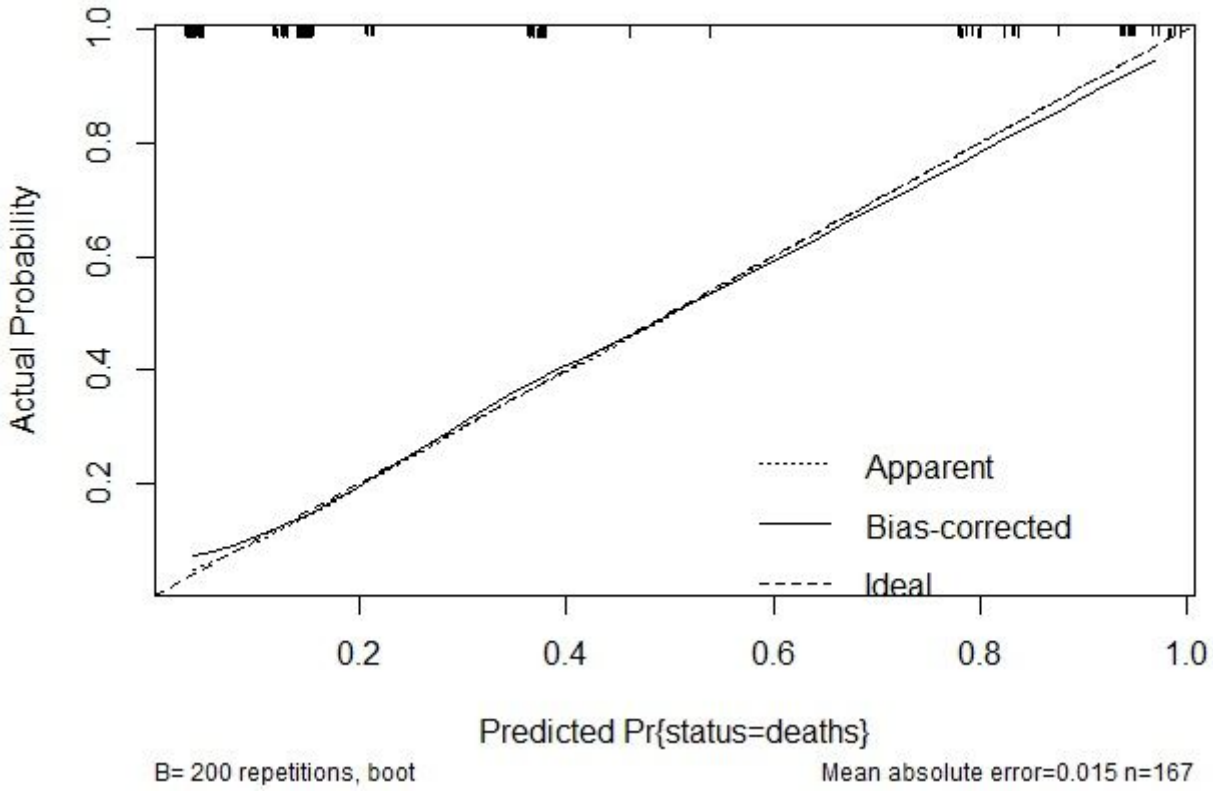

Figure 3

Calibration of the nomogram for mortality of the NHIV-PJP group. The x-axis shows the predicted probability of mortality, and the y-axis shows the observed probability of mortality.

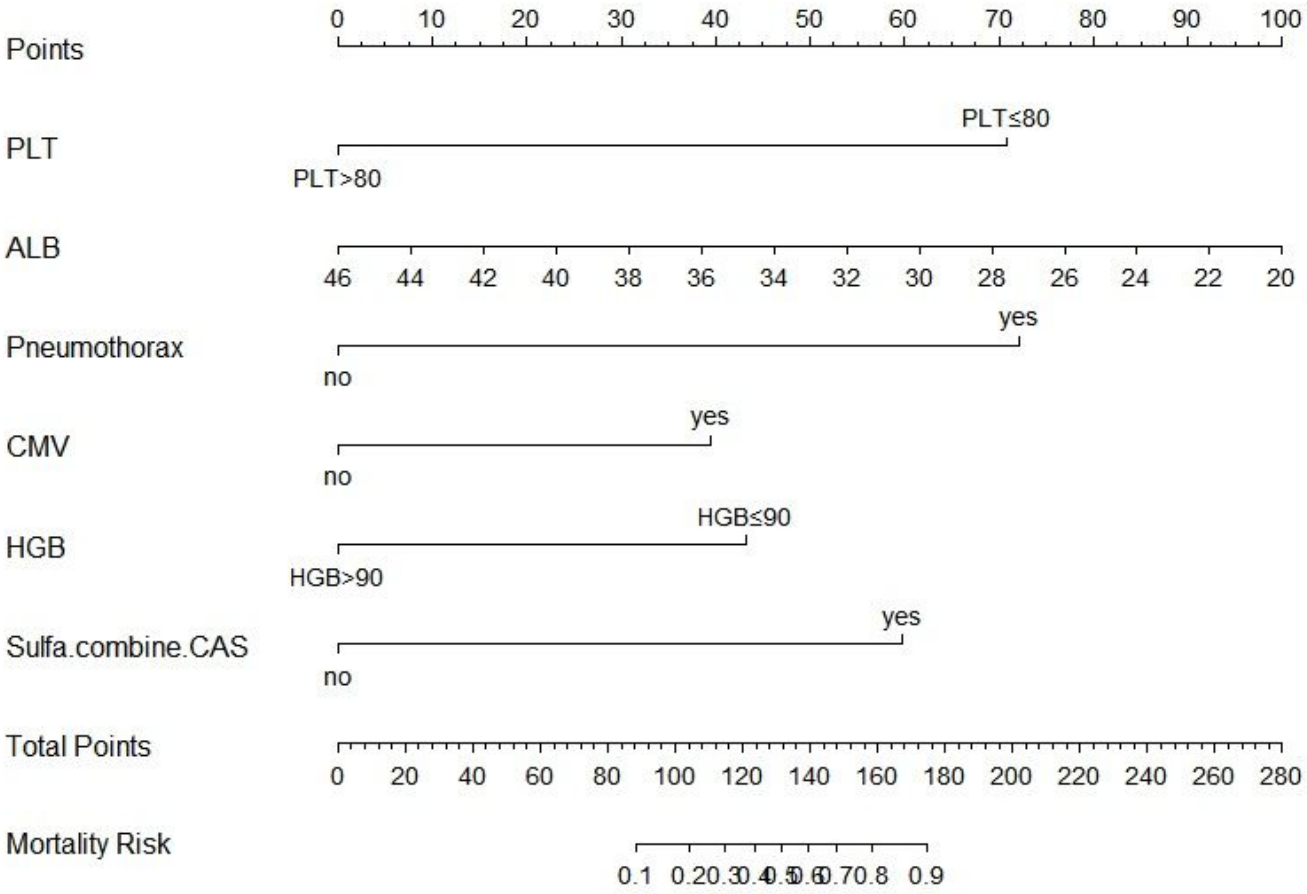

Figure 4

Nomogram for mortality in HIV-PJP group.

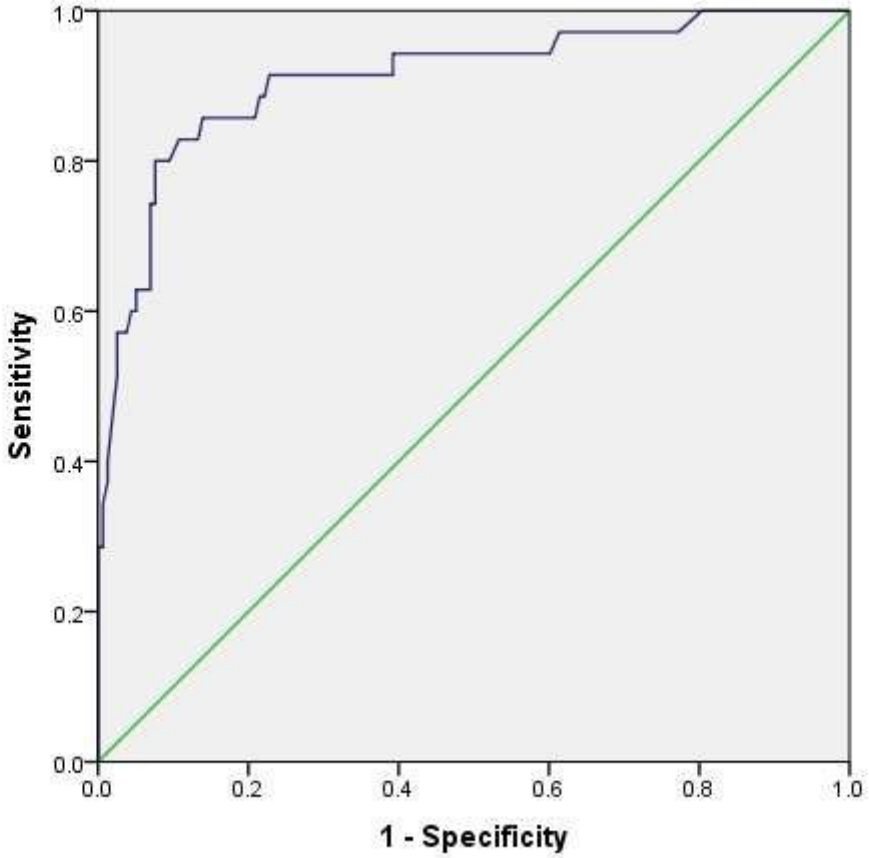

Figure 5

Receiver operating characteristic curve for the prediction model of the HIV-PJP group. The area under the curve was 0.910 (95% confidence interval 0.850-0.970)

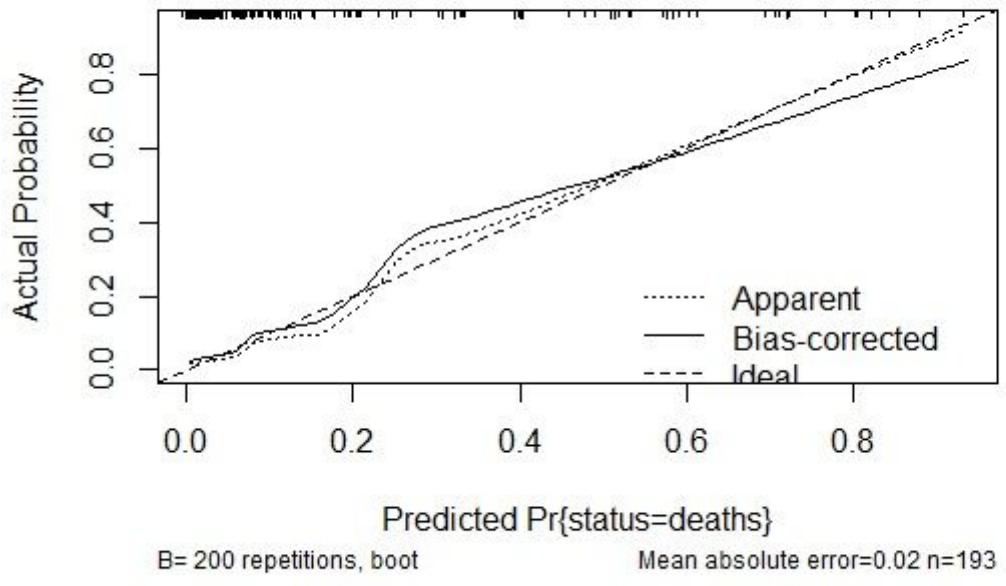

Figure 6

Calibration of the nomogram for mortality of the HIV-PJP group