# Prognostic Nomogram for PJP Patients With HIV and NHIV

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**Research**

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# Abstract

**Background**: This study was to create nomogram models for precise prediction of mortality risk of NHIV-PJP and HIV-PJP cases.

**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 analysis were used to screen out mortality risk factors for creating nomograms. Nomogram models were evaluated by using a bootstrapped concordance index, calibration plots and receiver operating characteristics (ROCs) curve.

**Results**: A total of 167 NHIV-PJP cases and 193 HIV-PJP cases were included in the study. Pneumothorax, febrile days after admission, CD4+ T cells≤100cells/ul and sulfa combine CAS treatment were identified as independent risk factors that could be combined for accurate prediction of mortality result in NHIV-PJP group. We created a nomogram for mortality risk 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. Independent risk factors contained in the nomogram in HIV-PJP group included pneumothorax, PLT≤80×$10^9$/L, HGB≤90g/L, ALB, CMV co-infection and sulfa combine CAS treatment. The nomogram showed good discrimination, with a C-index of 0.904 and good calibration. The area under the curve was 0.910 (95% confidence interval 0.850-0.970).

**Conclusions**: Our nomograms were useful tools for evaluating the poor prognosis in both NHIV-PJP and HIV-PJP cases.


# Background

*Pneumocystis jirovecii* pneumonia (PJP), also known as interstitial plasma cell pneumonia, was 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 was a major cause of morbidity and mortality in patients with AIDS [1].In recent years, with the widespread application of glucocorticoids and cytotoxic drugs, the rapid development of tumor chemoradiotherapy, connective tissue diseases and various organ transplantation, the incidence of PJP in non-AIDS immunosuppressed patients had significantly increased. PJP typically presented with acute and rapid progressive respiratory insufficiency [2]. It had higher mortality in non-HIV patients than in HIV patients (30–60% versus 10–20%) [3, 4].Many risk factors for poor prognosis had been reported [5],however, it was still difficult to predict death rate accurately. More efficient predict tools for estimating prognosis of PJP cases were needed now. The objective of this current study was to combine clinical manifestations, treatment and laboratory variables that were associated with deaths into prediction nomograms.

Nomograms were graphical models that enable users to calculate the overall probability of a specific clinical outcome for an individual patient [6, 7].There were many nomograms used as prediction tools in various diseases, such as cancer [8]. Nomogram facilitated the clinical implementation and probability

calculation of risk factor or other predictor variables. We developed and validated nomograms that predicted death risks in the NHIV and HIV group.

## Patients And Methods

# Study Patients

We conducted a retrospective study to collect clinical data in Beijing Chaoyang Hospital and Beijing Ditan Hospital, Capital Medical University, and the study protocol was approved by the research ethics committee of hospital. Because of the nature of retrospective observation study, without interventional aspect, the informed written consent was waved by ethics committee.

We retrospectively collected the data of these patients who were confirmed PJP and hospitalization for the first time between 1 January 2010 and 31 December 2019 at two centers of the Capital Medical University, Beijing Chaoyang Hospital and Beijing Ditan Hospital, both tertiary care university hospitals in Beijing, China. Through screened the eligible adult patients (age ≥ 18 years old) from a computerized medical charts search system by ICD 10 (International Classification of Diseases, 10th revision), their medical records were reviewed, and data were extracted then registered into the research forms. All of these important data were entered into Excel for preserving. We defined confirmed PCP via 3 criteria: (1) clinical symptoms, like fever, dry cough (occasionally expectorant) and progressive dyspnea; (2) abnormal imaging findings: CT appeared a broad range 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 for an induced sputum [9], low tracheal aspiration or bronchoalveolar lavage fluid (BALF) specimen. We did not include patients for whom only PCR results were positive.

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

# Data collection

The electronic medical charts for each enrolled patient were reviewed to obtain the followings: demographical date, underlying diseases, use of immunosuppressive drugs, clinical manifestations, radiology characteristics, laboratory tests, therapy and hospital mortality. Laboratory data were recorded within 48 hours or the worst values after admission and were used for analysis. Febrile days meant the duration of continue daily temperature > 37.5℃ after admission until discharge or death. Microbiological findings included cytomegalovirus (CMV), Epstein-Barr virus (EBV) and co-infection 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), and the nomograms were constructed using the “rms” package. Measurement data of normal distribution were expressed as mean ± SD, while measurement data of non-normal distribution were expressed as median (interquartile range). Counting variables were expressed as a percentage (%). The independent sample T test was used for the continuous numerical variables obeying normal distribution. Continuous variables that did not follow normal distribution, or grade variables were tested using Mann-Whitney U test, and the categorical variables were compared by using Pearson Chi-Square test. $P < 0.05$ was statistically significant. The variables with statistical significance were selected for the binary logistic regression analysis related to 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 multivariate logistic regression analysis model, nomograms for hospital mortality risks were created based on the multivariate logistic regression model. The performance of the nomogram was evaluated using a 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 were probable PJP without microbiological results. The following 40 patients were excluded: sulfa drug allergy in 26,hospitalized less than 1 week in 34. Finally, 360 cases were eventually included in the study, 167 cases in the NHIV-PJP group and 193 cases in the HIV-PJP group.

# Patient Characteristics

We compared demographics, clinical characteristics, and auxiliary examination of both groups (Table 1), and recorded the underlying diseases in NHIV-PJP group (Table 2). HIV-PJP patients were predominantly men (97.4% vs. 61.7%; $P < 0.001$), less smoking (22.80% vs. 35.3%; $P = 0.009$) and younger (38.12 ± 10.53 vs. 53.69 ± 16.32 years; $P < 0.001$) compared to NHIV-PJP patients. There was no difference in blood type between NHIV-PJP and HIV-PJP group except O type. One NHIV-PJP patient was Rh-negative (rhesus factor). Underlying diseases in the NHIV-PJP group, included SOT (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), hematological malignancy (n = 8; non-Hodgkin’s lymphoma 4, myelodysplastic syndrome 1, multiple myeloma 1, Chronic Lymphocytic Leukemia 1 and autologous hematopoietic stem cell transplantation 1), solid tumor (n = 14; lung cancer 6, esophageal 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, the past diseases included cardiovascular disease 10, diabetes mellitus 2, asthma 2, chronic hepatitis B 1 and schizophrenia 1.

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

| Characteristic | NHIV-PJP( n = 167) | HIV-PJP(n = 193) | *P*-Values |
|---|---|---|---|
| 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, dyspnea | 99(59.3) | 99(51.3) | 0.129 |
| Febrile days before admission, d | 7(3–10) | 10(4–15) | **0.004** |
| Highest temperature, ℃ | 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 (x$10^9$/L) | 8.43 ± 3.88 | 6.64 ± 3.31 | **< 0.001** |
| Lymphocyte count (x$10^9$/L) | 0.81 ± 0.55 | 0.78 ± 0.48 | **0.475** |
| Platelet (x$10^9$/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** |

| Characteristic | NHIV-PJP( n = 167) | HIV-PJP(n = 193) | *P*-Values |
|---|---|---|---|
| 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 24h | 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, medians (interquartile ranges) or No. (%). *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

Table 2
Underlying diseases at diagnosis of NHIV-PJP

| Underlying disease | Number of patients | |
|---|---|---|
| Hematological malignancy | 8 | (4.79) |
| Solid tumors | 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

Both NHIV-PJP and HIV-PJP patients had symptoms of the commonest fever (89.8% vs. 86.0%, P = 0.27), the rarer chest pain (3.60% vs. 3.10%, P = 0.79), the triad of symptoms: fever, cough, dyspnea (59.3% vs. 51.3%, P = 0.12). These manifestations were no differences between two groups. However, obviously shorter duration of fever before admission [7(3–10) vs. 10(4–15) days, P = 0.004], higher temperature [39(38.3–39.5) vs. 38.5(37.6–39.0)℃,P < 0.001], much more patients had lung rale (54.5% vs. 15.0%, P < 0.001), and fewer patients loss of weight (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. Glucocorticoid alone was 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 PJP diagnosis was 186 days (range: 99–372 days). Laboratory data including blood routine, β-D-Glucan, CD4 + T cells, CD8 + T cells, CD4/CD8 ratio, procalcitonin (PCT), C-reactive protein (CRP), lactic dehydrogenase, albumin (ALB) and oxygenation index were available from all 360 patients. The value of platelet (PLT), hemoglobin (HGB), CD8 + cell counts, CRP, ALB and

oxygenation index were much lower in the NHIV-PJP group than in the HIV-PJP group, the difference was statistically significant. Oppositely these variants of CD4 + T cells, 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 ≤ 100cells/ul, pneumothorax, and sulfa combine caspofungine (CAS) 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 ≤ 90g/L, ALB, CMV co-infection, pneumothorax and sulfa combine CAS.

Co-infections 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. Positive serum assay for CMV was identified in 241 patients in both NHIV-PJP and HIV-PJP groups [112(67.1%) vs.129(66.5%)], EBV in 101 patients [97(58.1%) vs. 4(2.1%)], respectively. 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 pneumonia [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%)], atypical pathogens [n = 4; 2(2.1%) vs. 2(1.0%)], and H1N1 virus [n = 3; 2(1.2%) vs.1(0.5%)], respectively. Co-infections in blood: Cytomegalovirus virusemia [n = 6, 0 (0.0%) vs. 6 (3.1%)], Gram-positive cocci septicemia [n = 14, 9 (5.4%) vs. 5 (2.6%)], Gram-negative bacilli septicemia [n = 9, 7 (4.2%) vs. 2 (1.0%)].

# Treatment and outcome

354 patients received TMP-SMX (720 mg of trimethoprim, 3600 mg of sulfamethoxazole daily), 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 = 0.50], but this difference did not reach statistical significance. 15 patients stopped taking TMP-SMX due to drug intolerance. 351 patients received suitable antibiotic treatment according to antimicrobial susceptibility tests of respiratory samples or empiric antibiotic therapy. 275 patients received systemic corticosteroids as adjunctive therapy.

NHIV-PJP caused more severe oxygenation impairment (oxygenation index, 287.57 ± 119.28vs. 310.78 ± 100.68mmHg, p = 0.046), and transfer to the ICU [93 (55.69%) vs. 53(27.46%), p < 0.001], even extracorporeal membrane oxygenation therapy [12 (7.2%) vs. 2 (1.0%), p = 0.04].

# Nomogram for mortality prediction

We investigated the association between clinical factors and all-cause mortality in univariate analysis in both groups. Febrile days after admission, PLT ≤ 80($x10^9$/L), HGB ≤ 90g/L, CD4 + T cells ≤ 100cells/ul, PCT, LDH ≥ 500U/L, ALB, CMV co-infection, EBV co-infection, pneumothorax, Sulfa combine CAS, ICU days, and ECMO were significantly associated with mortality in the NHIV-PJP group (Table 3). We

performed multivariate logistic regression analysis with these associated factors then. We identified febrile days after admission, CD4 + cells ≤ 100cells/ul, pneumothorax and Sulfa combine CAS as independent risk factors and that a combination of these factors most precisely predicted mortality (Table 4). We then created a nomogram for mortality by using 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 well calibrated (Fig. 6).

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

| | NHIV-PJP | | HIV-PJP | |
|---|---|---|---|---|
| | Crude OR(95%CI) | *P*-Values | Crude OR(95%CI) | *P*-Values |
| 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 ≤ 90g/L | 2.038(0.944–4.398) | 0.070 | 4.463(1.398–14.245) | **0.012** |
| CD4 + T cells ≤ 100cells/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** |

| | NHIV-PJP HIV-PJP | | | |
|---|---|---|---|---|
| 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) | |

Table 4
Multivariate regression analysis for independent death factors after admission

| | NHIV-PJP patients | | HIV-PJP patients | |
|---|---|---|---|---|
| | Adjusted OR(95%CI) | *P*-Values | Adjusted OR(95%CI) | *P*-Values |
| 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 ≤ 90g/L | 2.46(0.29–20.61) | 0.40 | 29.54(2.21-394.29) | **0.010** |
| CD4 + ≤ 100cells/ul | 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** |

# Discussion

To our knowledge, this is the first study that create predictive nomogram models to accurately calculate mortality in the PJP patients. This retrospective study describes the clinical characteristics and outcome between the NHIV-PJP cases and the HIV-PJP cases. The results show that the PJP populations suffering from HIV and non-HIV immunosuppression are different according to baseline data, these HIV-negative patients were older than those in studies of HIV-positive patients, similarly to previous report[11].Co-infections, most notably with viruses, especially CMV co-infection, were considerably more prevalent among NHIV-PJP patients than HIV-PJP patients in our study, which was consistent with published studies [12].PJP presents with atypical symptoms usually, such as fever, dry cough, and dyspnea, occurring in up to 86%, 76%, and 81%, respectively [13].The same to ours, the fever rate in the HIV-PJP and NHIV-PJP groups was 86% vs. 89.8% respectively. In the multivariate regression analysis, febrile days after admission was an independent death factor in NHIV-PJP patients. The result suggested us that

continuous fever as a predictive factor could enable clinicians to recognize the risk of PJP earlier and avoid further deterioration in the patient's condition.

The main risk factors for immunosuppression in our study are drug related immunosuppression and transplant, which are obviously related with the deficiencies in cellular immunity. Our study shows that almost 1/3 of PJP patients were renal transplant recipients, 141(84.4%) patients had low level CD4 + T cells in the NHIV group. This largely correlates to those patients who becoming Organ transplant recipients remained 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 hormone and cytotoxic drugs simultaneously, which aggravated the immunity deficiency. Glucocorticoid treatment is a well-known risk factor for PJP in non-HIV cases, and accounts for 55–97% of published cases [14, 15] and 88.0% in our study. The mechanism could be a decrease of peripheral CD4 + T cells due to glucocorticoid therapy [14]. Immunosuppressive agents such as thiopurine could reduce the absolute numbers of lymphocytes by inhibiting cell proliferation, tacrolimus and cyclosporine could inhibit lymphocytes activation and cytokine could inhibit lymphocyte function.

The main radiologic features of PJP identified through CT scanning were extensive ground-glass opacity (GGO) and reticulation [16, 17]. In our study, the rate of GGO remained high (59.9%) in the non-HIV-PJP group and (88.1%) in the HIV-PJP group. Pneumothorax is an unresolved problem in PJP until now, because PJ had enough time to grow in the subpleural spaces and was thus difficult to eradicate by treatment [18].For adults, incidence of pneumothorax ranges from 4–36% [19].When barotrauma occurred, it usually indicated a poor prognosis and a high mortality rate 50%-100% [20–22].Our study showed that pneumothorax rate was 10.2% and 4.7% in the two groups respectively. Nearly all of the poor prognosis patients developed pneumothorax. Especially in 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 lower than normal and that (1,3)-β-D-glucan and lactate dehydrogenase (LDH) level were elevated in PJP patients. WBC count was normal in these patients. These findings were consistent with other studies [23].Previous studies demonstrated that hypoalbuminemia had a positive correlation to 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 HIV-PJP patients than NHIV-PJP patients, but both groups were lower than normal. We showed that the serum albumin level was a significant independent poor prognosis factor in only HIV-PJP group, but not in NHIV-PJP group. This finding was similar with Kim et al. who showed hypoalbuminemia was not considered as an independent predictor of mortality [26]. These results suggested that ALB levels might be a predicting factor to be used in the prognosis of PJP patients. Overall, these results reflected that treatment strategies for HIV-PJP patients should raise awareness of the serum albumin level to a potentially fatal warning of increasing incidence. Low oxygenation index had also been associated with poor outcomes in PJP patients with immunosuppressive disease [27]. In our study, oxygenation index in the NHIV-PJP and HIV-PJP groups

were 287.57 ± 119.28 vs. 310.78 ± 100.68 respectively. The lower oxygenation index, which was also a representative of ventilation-perfusion abnormality, was related to death in both groups.

A decrease in hemoglobin indicates anemia, and a decrease in hemoglobin below 90 indicates moderate to severe anemia. It can also be defined as a lowered ability of the blood to carry oxygen. So we thought that anemia might cause worse prognosis in PJP patients. Through our study, we found that HGB ≤ 90g/L was obviously associated with the poor outcomes in the two groups and an independent risk factor for death in HIV-PJP patients.

Despite presenting intolerance and adverse events, TMP-SMZ is still the first-line therapeutic regiment for PJP [9, 28, 29].In our study, 55.1% NHIV-PJP patients and 88.6% HIV-PJP patients were initially treated with TMP-SMZ within 24 hours, but aggressive medicine does not improve prognosis. Caspofungin was recognized as second-line regimen, known as echinocandins. Echinocandins were reported to inhibit the enzyme 1,3-β glucan synthase, and caspofungin was reported to improve overall mortality in patients with AIDS-PJP [30].However, some studies reported failure of salvage therapy using echinocandins to improve survival among non-AIDS patients [31, 32].The same to our study, we found that sulfa combine CAS treatment was identified as independent risk factors for death in multivariate analysis in both groups. This event reminded us to aware of the combination two kinds of drugs for PJP treatment.

The overall mortality rate in NHIV-PJP patients is 31%, up to almost 100% when PJP is not properly and readily treated [33, 34]. In several studies, PJP was more often fatal in non-HIV-infected patients than in HIV-positive patients[11, 20].We also observed mortality rate of 29.3% in the non-HIV group was higher than 18.1% in the HIV group, in which rates in the order of 30–60% in the former and 10–20% in the later that had been reported. However, several studies had also reported mortality rates in the range of 7 to 14% [35, 36]. In order to calculate the precise mortality rate of these PJP patients, we constructed the model of nomogram with these independent factors.

Meanwhile, there remains some limitation. First, it is a retrospective study of two centers with a small population. Retrospective studies may be bias in terms of the data collected, such as physical examination data and normal range in lab test. A prospective study which includes larger sample sizes is necessary. Second, the underlying diseases are composed mostly with kidney transplants in the NHIV group which was not very representative. Third, it only includes these PJP patients who were hospitalized more than 7 days. Some patients would not be enrolled into this study if they left within 7 days after admission due to any reasons.

# Conclusions

Our nomogram models provided a useful, conveniently and applicable tool to evaluate the prognosis of mortality both in NHIV-PJP group and HIV-PJP group.

# 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. Q-YF and J-JH contributed to the review and edited the manuscript. Q-YF contributed to the 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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# Figures

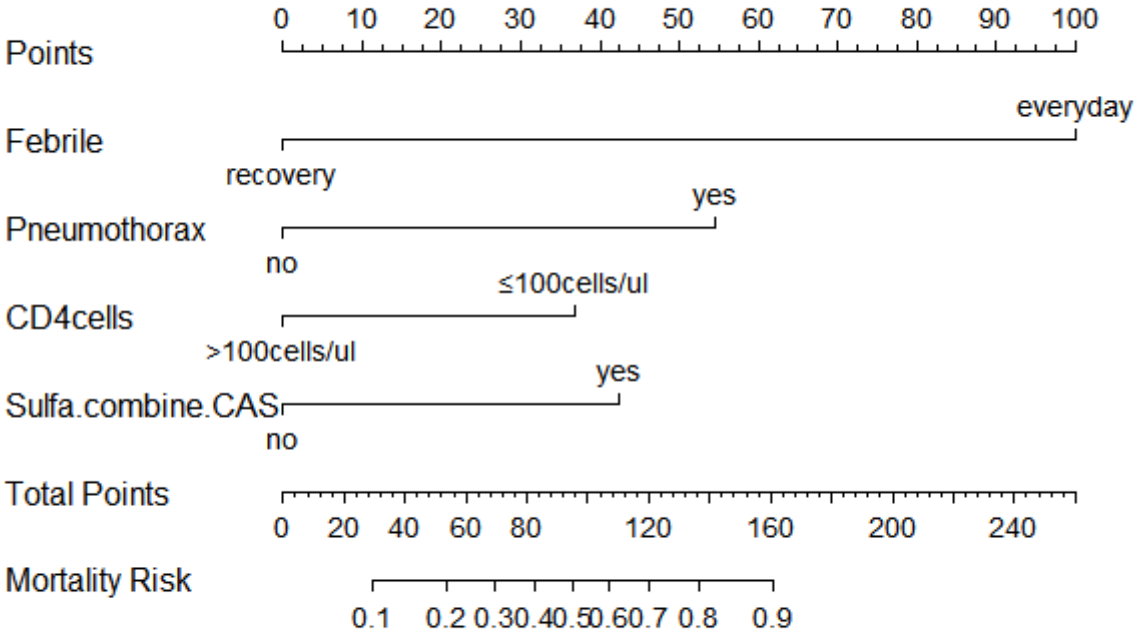
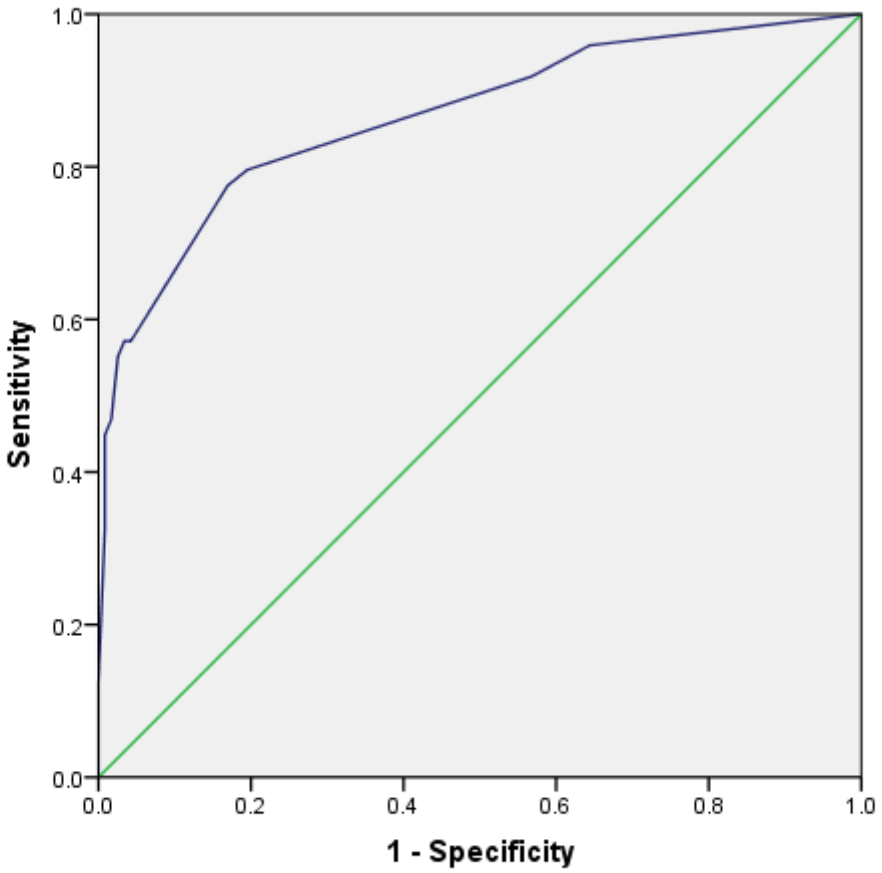



**Figure 1**

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




## Figure 2

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

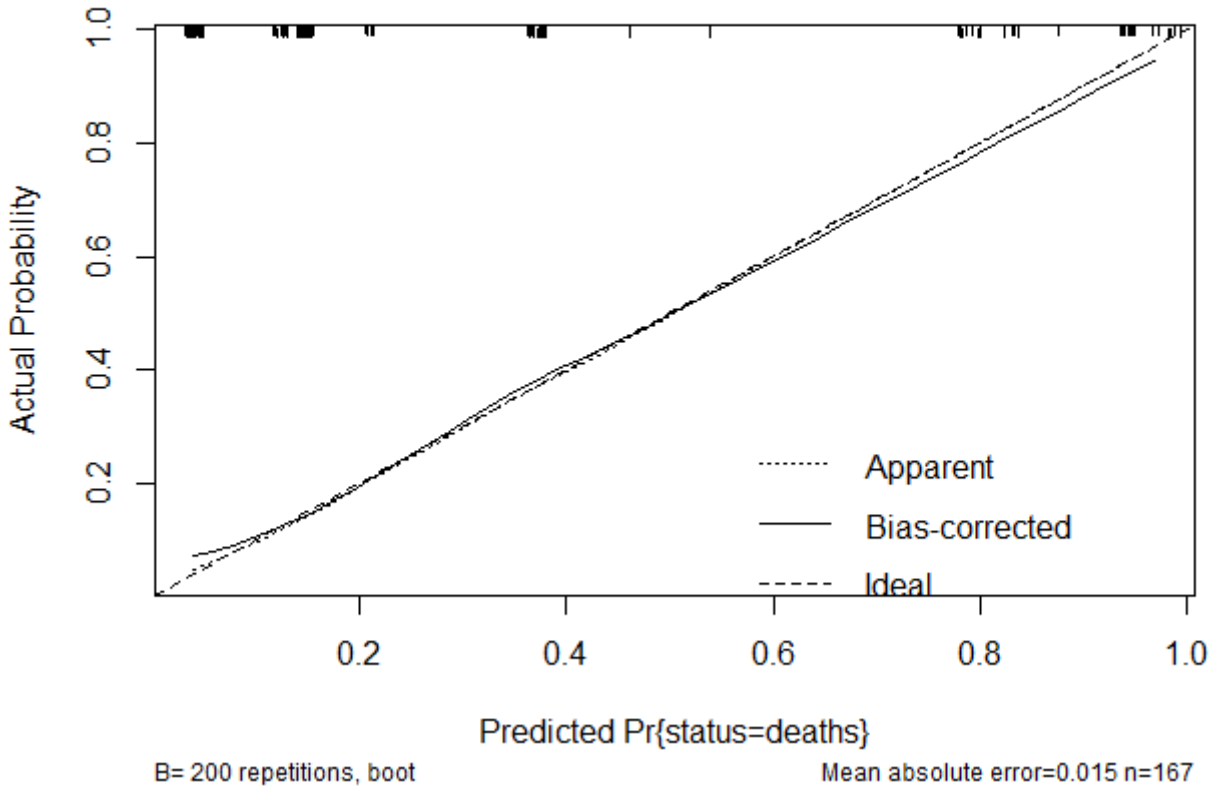
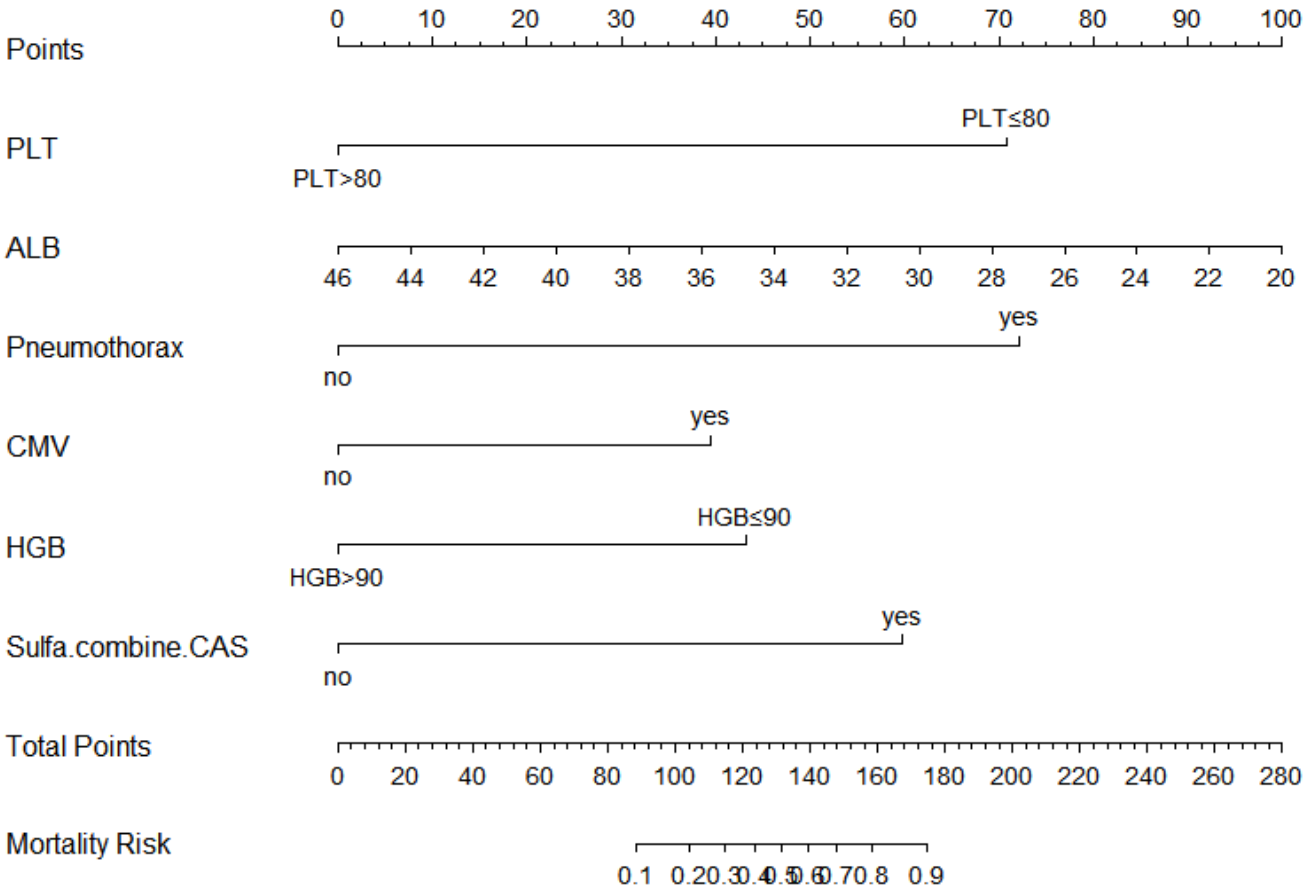


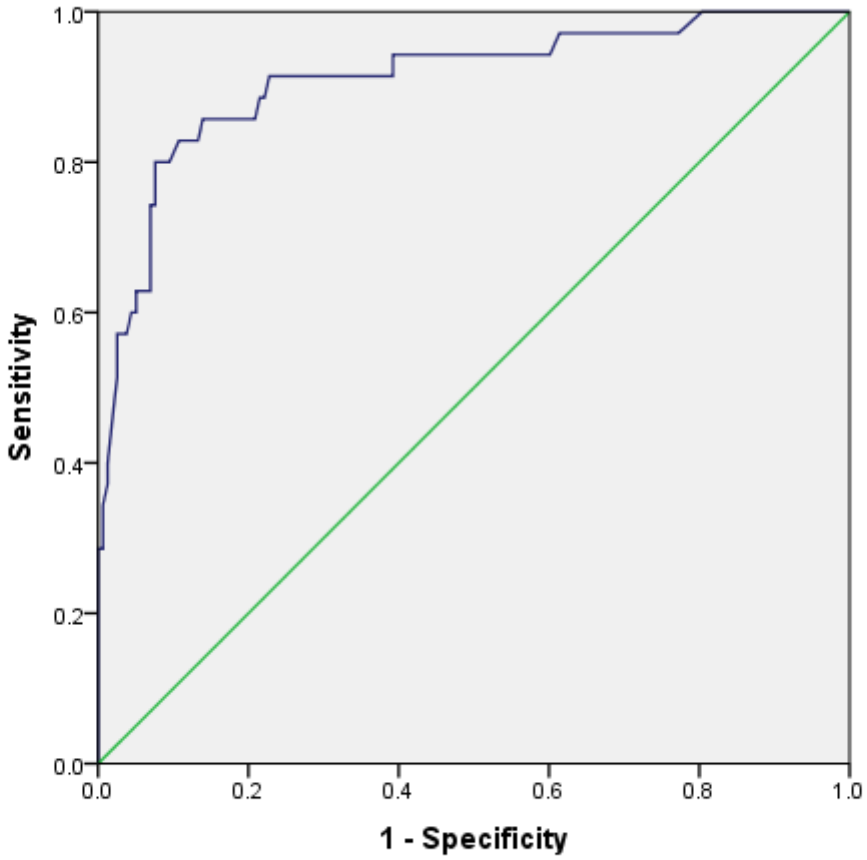

**Figure 3**

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. Area under the curve was 0.910 (95% confidence interval 0.850-0.970)

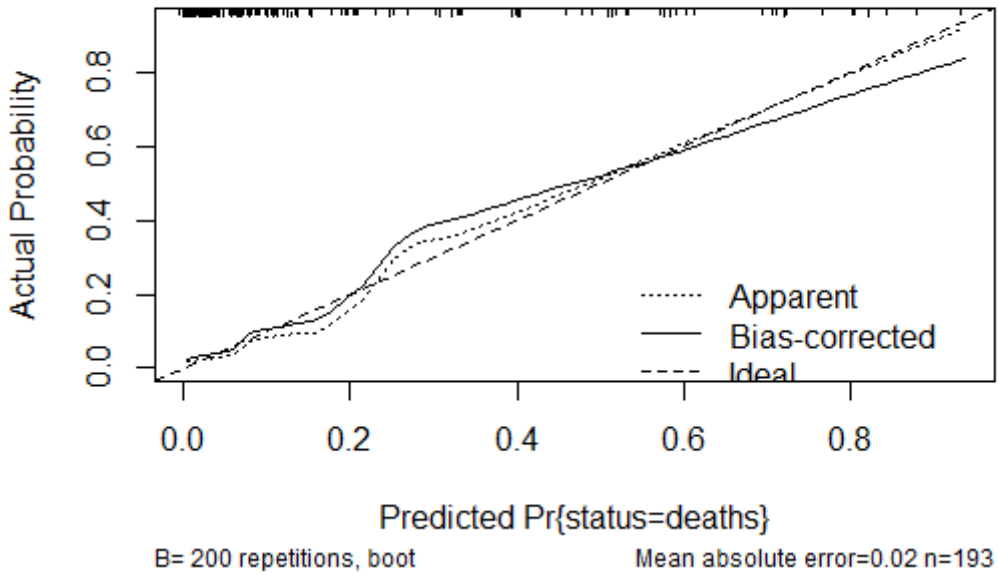



**Figure 6**

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