Research Square

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Influencing factors analysis and clinical prediction model construction of high voltage long-term pulsed radiofrequency in the treatment of herpes zoster associated pain

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Article

Keywords: Herpes zoster-associated pain, High-voltage long-duration pulsed radiofrequency, Influencing factors of therapeutic efficacy, Clinical prediction model

Posted Date: March 13th, 2026

DOI: https://doi.org/10.21203/rs.3.rs-8505280/v1

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Additional Declarations: No competing interests reported.

Abstract

Background

Herpes zoster-associated pain (ZAP) imposes a substantial burden with frequently suboptimal treatment outcomes. High-voltage long-duration pulsed radiofrequency (HL-PRF)) has emerged as a promising treatment. This study explored HL-PRF's application in ZAP, identified efficacy-influencing factors, and established a clinical prediction model.

Methods

Retrospective analysis of 128 ZAP patients treated with HL-PRF (Department of Anesthesiology and Pain Medicine, First Affiliated Hospital of Wannan Medical College, Mar 2023–Dec 2024) was done. Independent predictors of treatment inefficacy were identified via univariate and multivariate logistic regression. A predictive model was developed utilizing a nomogram. Model performance was evaluated using area under the curve (AUC), calibration curves, Hosmer-Lemeshow test, and decision curve analysis (DCA).

Results

HL-PRF demonstrated 60% efficacy at 3-month follow-up. Univariate analysis identified significant associations ($P < 0.05$) between HL-PRF efficacy and multiple factors, including age, disease duration, prolonged hormone use, early non-utilization of antiviral medications, use of antiepileptic drugs, tramadol use, coexisting connective tissue disorders, concurrent malignancy, coexisting cerebral infarction, acute-phase VAS score, and the CD4+/CD8 + T-cell ratio. Multivariate regression confirmed 7 risk factors for reduced efficacy (age, disease duration, connective tissue disease, malignant tumors, long-term hormone use, acute-phase VAS score, CD4+/CD8 + T-cell ratio; $P < 0.05$). The predictive model exhibited excellent discriminatory power(AUC = 0.988, 95%CI:0.976-1.000), good fit (Hosmer-Lemeshow $P = 0.969$), and high accuracy (93.0% overall accuracy, 90.7% sensitivity, 96.2% specificity).

Conclusion

HL-PRF is safe and effective for ZAP but affected by multiple factors. Older patients, prolonged disease duration, comorbidities (connective tissue disease/malignant tumors), long-term hormone use, acute-phase VAS > 7, and low CD4+/CD8 + ratio may have suboptimal outcomes. Future research should focus on individualized HL-PRF protocols.

Why carry out this study?

This study aimed to explore the influencing factors of high-voltage long-term pulsed radiofrequency (HL-PRF) in the treatment of herpes zoster associated pain (ZAP), and build a clinical prediction model to improve the treatment effect. Research questions focus on clarifying the clinical and biological influencing factors of PRF efficacy, and solving the problem of inaccurate prognosis evaluation in current treatment.

What was learned from the study?

This prediction model can effectively individualize the evaluation of HL-PRF efficacy, provide a quantitative tool for clinical decision-making, and optimize the precision treatment strategy for ZAP patients.

Introduction

Herpes zoster-associated pain (ZAP) presents as unilateral chronic pain occurring in one or more dermatomes following a herpes zoster (HZ) infection. This condition impairs patients' quality of life and causes severe discomfort. Beyond conventional treatment such as oral antiepileptic drugs, non-steroidal anti-inflammatory drugs, and opioids, interventional treatments offer innovative alternatives. These include epidural injections of local anesthetics and corticosteroids, pulsed radiofrequency (PRF) or radiofrequency ablation, and spinal cord stimulation. Among these interventional approaches, PRF shows particular promise as an effective therapeutic strategy.

PRF is a non-thermal, minimally invasive, and targeted therapeutic technique that modulates the electrophysiological properties of nerves through pulsed current, maintaining temperatures below 42°C [7] to prevent nerve damage. Consequently, PRF has a favorable safety profile and is widely used for treating postherpetic neuralgia (PHN) [8]. Studies have identified that patients with PHN exhibit degenerative changes in C fibers, which may lead to the reorganization of pain signal pathways in the central nervous system, activation of fiber reflexes, and reduction of pain thresholds, thereby exacerbating neuropathic pain [9]. PRF works by applying a rapidly varying electric field to the nerve cell membrane, inducing electrolyte conduction and depolarization, which alleviates pain and protects nerves [10]. Recently, high-voltage long-duration PRF (HL-PRF) has garnered attention in pain management. HL-PRF modulates the ion channels of nerve cell membranes, alters nerve excitability, inhibits pain signal conduction, and thereby achieves the dual objectives of pain relief and enhancement of nerve function [11].

Previous research has identified age, pre-existing comorbidities (such as diabetes and immune-related diseases), and pain intensity as risk factors for the development of postherpetic neuralgia following herpes zoster infection [12]. However, few studies have analyzed the factors influencing HL-PRF therapeutic efficacy in managing herpes zoster-related neuralgia or developed clinical prediction models. Therefore, this study aims to evaluate the clinical efficacy of HL-PRF in treating herpes zoster-related neuralgia, investigate the determinants affecting therapeutic outcomes, and develop a clinical prediction model. This study will provide an evidence base for clinical treatment strategies.

Methods

Study Design and Population

This single-center retrospective observational study was conducted at the Department of Anesthesiology and Pain Medicine of the First Affiliated Hospital of Wannan Medical College, spanning the period from January 2023 to October 2023. Ethical approval for the study was granted by the Medical Ethics Committee of the First Affiliated Hospital of Wannan Medical College, located in Wuhu, Anhui Province, China (approval number: 2023-LSX-08). The treatment protocols were executed by two experienced attending physicians within the department. Data were systematically reviewed and extracted from the electronic medical records of all patients who received HL-PRF treatment, primarily for the management of herpes zoster associated pain.

Clinical procedure

All procedures were performed under computed tomography (CT) guidance[7]. Patients were positioned supine or prone on the unaffected side. After sterile draping and disinfection of the chest and back, the affected ganglion segment plus one adjacent segment were identified. The puncture point was located 5–6 cm lateral to the spinous process on the affected side. Under local anesthesia with 2% lidocaine, a 10mm bare-tip radiofrequency puncture needle was inserted at a 50–60° angle to the puncture plane. CT guidance was used to adjust needle direction and confirm positioning at the target intervertebral foramen. Sensorimotor testing was performed (100 Hz, 0.1-0.5V) to confirm nerve paresthesia at the pain site. Treatment parameters were: temperature 55℃, frequency 2 Hz, pulse width 20ms, starting voltage 70V (gradually increased to 90 V as deeded), duration 900 seconds. the needle was withdrawn after the operation and covered with sterile dressing. After needle removal, a sterile dressing was applied. Patients returned to the ward after 15 minutes of observation with stable vital signs.

Data Collection

The primary outcome measure was the VAS scores, assessed at baseline prior to PRF treatment and subsequently at 1-, 4-, 8-, and 12-weeks post-treatment. Secondary outcomes included Pittsburgh Sleep Quality Index (PSQI), Quality of Life assessments using the SF-36 instrument, total efficiency rate, and adverse events.

Total efficiency rate:

The VAS score was employed to assess the therapeutic efficacy of HL-PRF at 12 weeks post-treatment. Based on the VAS score, the treatment outcomes were categorized into four levels: excellent (VAS reduction ≥ 75%), good (VAS reduction between 50% and 75%), poor (VAS reduction between 25% and 50%), and ineffective (VAS reduction < 25%). The total effective rate (%) was calculated as the sum of the excellent and good outcomes divided by the total number of cases.

Adverse Events:

Adverse events, encompassing a range of postoperative complications such as nerve damage, hematoma, local infection, and other serious complications, were documented following PRF treatment.

Data Processing

To facilitate computational analysis, data were coded as follows: Gender (male = 1, female = 2); Education (illiteracy = 1, primary school = 2, middle school = 3, college and above = 4); Comorbidities and prior medications (yes = 1, no = 0); Disease duration (within 1 month = 1, 1–3 months = 2, > 3 months = 3); Affected areas (head/face = 1, neck/upper limbs = 2, chest = 3, lumbosacral = 4); Working voltage (60-70V = 1, 70-80V = 2, 80-90V = 3); Pulse duration (10 minutes = 1, 15 minutes = 2); Treatment effectiveness (ineffective = 0, effective = 1).

Statistical Analysis

In this study, data analysis was conducted using SPSS version 25.0 and R version 4.1.2. The primary outcome variable was the effectiveness of the treatment, with ineffective treatment considered as the positive outcome. Independent variables included sociodemographic characteristics, disease-related indicators, and treatment-related information, which were analyzed to identify key factors associated with treatment efficacy. The analytical methods employed were as follows: For continuous data following a normal distribution, results were presented as mean ± standard deviation (Mean ± SD), and comparisons between groups were performed using the t-test. For continuous data not following a normal distribution, results were reported as median (interquartile range), and the Mann-Whitney U test was used for group comparisons. Categorical data were expressed as frequency and percentage (n(%)), with group comparisons conducted using the chi-square test (χ^2 test) or Fisher's exact test, as appropriate.Variables with $P < 0.1$ were further analyzed to identify independent predictors by forwarding stepwise multivariate logistic regression. Results from logistic regression analysis were expressed as odds ratios (ORs) with 95% CIs. A nomogram based on the multivariate model was then established. To assess the calibration of the model, a smoothed non-parametric calibration curve and a fitted logistic calibration curve were depicted. To evaluate the discrimination of the model, the area under the receiver operating characteristic (ROC) curve (AUC) or the c-index was calculated. To assess the clinical utility of the model, a decision curve analysis was performed. The decision curve was used to quantify the clinical utility of the model, displaying standardized net benefit against risk threshold probability. The clinical impact curve showed the number of judged high-risk patients for different threshold probabilities and the number of true positives.A significance level of $P < 0.05$ was established for all statistical tests.

Results

Baseline Characteristics of Patients

Of 148 patients screened, 128 were included in the final analysis after excluding 16 patients with > 20% missing data and 4 lost to follow-up. The cohort comprised 75 males (58.6%) and 55 females (41.4%), with a mean age of 70.98 ± 10.29 years.

The distribution of affected areas was as follows: chest and abdomen (n = 87, 68.0%), neck/shoulders/upper limbs (n = 17, 13.3%), head/face (n = 14, 10.9%), and lower limbs (n = 10, 7.8%). Disease duration varied: <1 month (n = 55, 43.0%), 1–3 months (n = 24, 18.7%), and > 3 months (n = 49, 38.3%).

The overall treatment efficacy rate at 3 months post-HL-PRF was 60%. Significant differences ($P < 0.05$) between effective and ineffective treatment groups were observed in multiple variables: age, disease duration, long-term hormone use, absence of early antiviral therapy, antiepileptic drug use, tramadol use, presence of connective tissue disease, malignancy, cerebral infarction, kidney disease, lesion location, nerve involvement, acute phase VAS score, and CD4+/CD8 + T lymphocyte ratio. No significant differences were found in other clinical characteristics (Table 1).

Table 1
Baseline Characteristics

Variables	Total (n = 128)	Negative (n = 75)	Positive (n = 53)	Statistic	*p-Value*
Age, Mean ± SD	70.98 ± 10.29	67.65 ± 10.67	75.70 ± 7.61	t=-4.98	**< .001**
BMI, Mean ± SD	23.01 ± 2.44	22.99 ± 2.49	23.04 ± 2.39	t=-0.12	0.908
$CD4^+T/CD8^+T$, n(%)				χ^2=28.06	**< .001**
Almost constant	67 (52.34)	54 (72.00)	13 (24.53)		
Significantly lower	61 (47.66)	21 (28.00)	40 (75.47)		
Stage of herpes zoster, n(%)				χ^2=22.33	**< .001**
<1 month	55 (42.97)	45 (60.00)	10 (18.87)		
1–3 months	49 (38.28)	22 (29.33)	27 (50.94)		
>3 months	24 (18.75)	8 (10.67)	16 (30.19)		
Oral corticosteroids, n(%)				χ^2=26.43	**< .001**
No	99 (77.34)	70 (93.33)	29 (54.72)		
Yes	29 (22.66)	5 (6.67)	24 (45.28)		
VAS in Acute phase, n(%)				χ^2=45.34	**< .001**
<7	67 (52.34)	58 (77.33)	9 (16.98)		
≥7	61 (47.66)	17 (22.67)	44 (83.02)		
CTD, n(%)				χ^2=9.93	**0.002**
No	111 (86.72)	71 (94.67)	40 (75.47)		
Yes	17 (13.28)	4 (5.33)	13 (24.53)		
Cancer, n(%)				χ^2=19.07	**< .001**
No	103 (80.47)	70 (93.33)	33 (62.26)		
Yes	25 (19.53)	5 (6.67)	20 (37.74)		
Early antiviral treatment, n(%)				χ^2=9.69	**0.002**
No	43 (33.59)	17 (22.67)	26 (49.06)		

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Variables	Total (n = 128)	Negative (n = 75)	Positive (n = 53)	Statistic	*p-Value*
Yes	85 (66.41)	58 (77.33)	27 (50.94)		
Sex, n(%)				χ^2=0.20	0.657
Male	73 (57.03)	44 (58.67)	29 (54.72)		
Female	55 (42.97)	31 (41.33)	24 (45.28)		
Education level, n(%)				-	0.296
Illiteracy	37 (28.91)	17 (22.67)	20 (37.74)		
Elementary school level	63 (49.22)	39 (52.00)	24 (45.28)		
Junior high school	11 (8.59)	5 (6.67)	6 (11.32)		
Senior high school	9(7.03)	5(6.67)	4(7.55)		
University and above	8 (6.25)	5 (6.67)	3 (5.66)		
Pregabalin, n(%)				χ^2=17.90	**< .001**
No	35 (27.34)	10 (13.33)	25 (47.17)		
Yes	93 (72.66)	65 (86.67)	28 (52.83)		
Methylcobalamin tablets, n(%)				χ^2=0.13	0.714
No	13 (10.16)	7 (9.33)	6 (11.32)		
Yes	115 (89.84)	68 (90.67)	47 (88.68)		
Tramadol, n(%)				χ^2=11.21	**< .001**
No	46 (35.94)	18 (24.00)	28 (52.83)		
Yes	82 (64.06)	57 (76.00)	25 (47.17)		
NSAIDs, n(%)				χ^2=1.99	0.158
No	93 (72.66)	58 (77.33)	35 (66.04)		
Yes	35 (27.34)	17 (22.67)	18 (33.96)		
Cardiovascular disease, n(%)				χ^2=1.23	0.268
No	63 (49.22)	40 (53.33)	23 (43.40)		
Yes	65 (50.78)	35 (46.67)	30 (56.60)		

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Variables	Total (n = 128)	Negative (n = 75)	Positive (n = 53)	Statistic	*p-Value*
Diabetes, n(%)				χ^2=0.00	0.975
□	94 (73.44)	55 (73.33)	39 (73.58)		
Yes	34 (26.56)	20 (26.67)	14 (26.42)		
Cerebral infarction, n(%)				χ^2=9.16	**0.002**
No	105 (82.03)	68 (90.67)	37 (69.81)		
Yes	23 (17.97)	7 (9.33)	16 (30.19)		
Chronic kidney disease, n(%)				χ^2=5.06	**0.024**
No	123 (96.09)	75 (100.00)	48 (90.57)		
Yes	5 (3.91)	0 (0.00)	5 (9.43)		
Rash site, n(%)				χ^2=10.56	**0.014**
Head	14 (10.94)	4 (5.33)	10 (18.87)		
Cervical	14 (10.94)	5 (6.67)	9 (16.98)		
Thoracic	90 (70.31)	59 (78.67)	31 (58.49)		
Lumbosacral	10 (7.81)	7 (9.33)	3 (5.66)		
Voltage of PRF, n(%)				χ^2=5.03	0.081
60-70V	58 (45.31)	28 (37.33)	30 (56.60)		
71-80V	45 (35.16)	29 (38.67)	16 (30.19)		
81-90V	25 (19.53)	18 (24.00)	7 (13.21)		
Time of PRF, n(%)				χ^2=0.02	0.877
10min	59 (46.09)	35 (46.67)	24 (45.28)		
15min	69 (53.91)	40 (53.33)	29 (54.72)		
Number of nerve blocks, n(%)				-	0.436
0	5 (3.91)	1 (1.33)	4 (7.55)		
1	65 (50.78)	41 (54.67)	24 (45.28)		
2	38 (29.69)	22 (29.33)	16 (30.19)		

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Variables	Total (n = 128)	Negative (n = 75)	Positive (n = 53)	Statistic	*p-Value*
3	17 (13.28)	9 (12.00)	8 (15.09)		
4	3 (2.34)	2 (2.67)	1 (1.89)		

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Univariate logistic regression analysis

Factors associated with HL-PRF treatment outcomes were screened using univariate logistic regression. The results showed that patient demographics (age, disease duration), treatment history (corticosteroid use, early antiviral therapy, antiepileptic/tramadol use), comorbidities (connective tissue disease, malignancy, cerebral infarction), clinical presentation (acute-phase VAS score), and immunologic profile (CD4+/CD8 + ratio) were all significant predictors ($P < 0.05$), as detailed in Table 2.

Table 2
Univariate analysis of possible risk factors for.

Variables	β	S.E	Z	*P*	OR (95%CI)
$CD4^+T/CD8^+T$					
Almost constant					1.00 (Reference)
Significantly lower	2.07	0.41	5.05	**< .001**	7.91 (3.54 ~ 17.67)
Stage of ZAP					
<1 month					1.00 (Reference)
1–3 months	1.71	0.45	3.78	**< .001**	5.52 (2.28 ~ 13.41)
>3 months	2.20	0.56	3.95	**< .001**	9.00 (3.02 ~ 26.79)
Oral corticosteroids					
No					1.00 (Reference)
Yes	2.45	0.54	4.55	**< .001**	11.59 (4.03 ~ 33.32)
VAS in Acute phase					
<7					1.00 (Reference)
≥7	2.81	0.46	6.14	**< .001**	16.68 (6.80 ~ 40.94)
CTD					
No					1.00 (Reference)
Yes	1.75	0.60	2.90	**0.004**	5.77 (1.76 ~ 18.88)
Cancer					
No					1.00 (Reference)
Yes	2.14	0.54	3.94	**< .001**	8.48 (2.93 ~ 24.58)
Early antiviral treatment					
No					1.00 (Reference)
Yes	-1.19	0.39	-3.06	**0.002**	0.30 (0.14 ~ 0.65)
Sex, n					
Male					1.00 (Reference)
Female	0.16	0.36	0.44	0.657	1.17 (0.58 ~ 2.39)

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Variables	β	S.E	Z	*P*	OR (95%CI)
Education level					
Illiteracy					1.00 (Reference)
Elementary school level	0.67	0.80	0.84	0.401	1.96 (0.41 ~ 9.43)
Junior high school	0.03	0.78	0.03	0.974	1.03 (0.22 ~ 4.68)
Senior high school	-0.34	0.88	-0.38	0.702	0.71 (0.13 ~ 3.99)
Pregabalin					
No					1.00 (Reference)
Yes	-1.76	0.44	-4.02	**< .001**	0.17 (0.07 ~ 0.41)
Methylcobalamin tablets					
No					1.00 (Reference)
Yes	-0.22	0.59	-0.37	0.714	0.81 (0.25 ~ 2.55)
Tramadol					
No					1.00 (Reference)
Yes	-1.27	0.39	-3.28	**0.001**	0.28 (0.13 ~ 0.60)
NSAIDs					
No					1.00 (Reference)
Yes	0.56	0.40	1.40	0.160	1.75 (0.80 ~ 3.84)
Cardiovascular disease					
No					1.00 (Reference)
Yes	0.40	0.36	1.11	0.269	1.49 (0.73 ~ 3.03)
Diabetes					
					1.00 (Reference)
Yes	-0.01	0.41	-0.03	0.975	0.99 (0.45 ~ 2.19)
Cerebral infarction					
No					1.00 (Reference)
Yes	1.44	0.50	2.89	**0.004**	4.20 (1.59 ~ 11.13)

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Variables	β	S.E	Z	*P*	OR (95%CI)
Chronic kidney disease					
No					1.00 (Reference)
Yes	17.01	1073.11	0.02	0.987	24455251.23 (0.00 ~ Inf)
Rash site					
Head					1.00 (Reference)
Cervical	0.80	0.77	1.04	0.297	2.22 (0.50 ~ 9.96)
Thoracic	-0.97	0.84	-1.14	0.253	0.38 (0.07 ~ 1.99)
Lumbosacral	-0.71	0.54	-1.33	0.185	0.49 (0.17 ~ 1.40)
Voltage of PRF					
60-70V					1.00 (Reference)
71-80V	-0.66	0.41	-1.63	0.103	0.51 (0.23 ~ 1.14)
81-90V	-1.01	0.52	-1.96	0.050	0.36 (0.13 ~ 1.00)
Time of PRF					
10min					1.00 (Reference)
15min	0.06	0.36	0.15	0.877	1.06 (0.52 ~ 2.14)
Number of nerve blocks					
0					1.00 (Reference)
1	-1.92	1.15	-1.68	0.094	0.15 (0.02 ~ 1.39)
2	-1.70	1.17	-1.46	0.143	0.18 (0.02 ~ 1.78)
3	-1.50	1.22	-1.23	0.217	0.22 (0.02 ~ 2.42)
4	-2.08	1.66	-1.25	0.210	0.13 (0.00 ~ 3.22)
Age	0.09	0.02	4.05	**< .001**	1.10 (1.05 ~ 1.15)
BMI	0.01	0.07	0.12	0.907	1.01 (0.87 ~ 1.17)

BMI:Body mass index; ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases; NSAIDs:Nonsteroidal anti-inflammatory drugs; PRF:Pulsed radio frequency;

Multivariate Logistic Regression Analysis

In this study, the therapeutic effect was designated as the dependent variable, categorized as 1 for effective and 0 for ineffective outcomes. To identify independent predictors, multivariate logistic

regression was performed. The final model demonstrated that patient age, disease duration, long-term corticosteroid use, acute-phase VAS score, connective tissue disease, malignancy, and the CD4+/CD8 + T-cell ratio were all independently associated with treatment efficacy (all $P < 0.05$; Table 3).

Table 3
Multivariate analysis of independent risk factors for

Variables	**β**	**S.E**	**Z**	***P***	**OR (95%CI)**
Intercept	-24.07	8.36	-2.88	**0.004**	0.00 (0.00 ~ 0.00)
$CD4^+T/CD8^+T$					
Almost constant					1.00 (Reference)
Significantly lower	4.17	1.44	2.89	**0.004**	64.52 (3.83 ~ 1087.41)
Stage of ZAP					
<1 month					1.00 (Reference)
1–3 months	3.65	1.39	2.62	**0.009**	38.61 (2.51 ~ 593.49)
>3 months	3.21	2.07	1.55	0.120	24.86 (0.43 ~ 1430.01)
Oral corticosteroids					
No					1.00 (Reference)
Yes	4.58	2.11	2.17	**0.030**	97.83 (1.57 ~ 6105.21)
VAS in Acute phase					
<7					1.00 (Reference)
≥7	7.17	2.52	2.84	**0.004**	1303.75 (9.30 ~ 182735.32)
CTD					
No					1.00 (Reference)
Yes	6.71	2.91	2.31	**0.021**	822.34 (2.74 ~ 246389.83)
Cancer					
No					1.00 (Reference)
Yes	5.16	1.93	2.67	**0.008**	174.40 (3.94 ~ 7729.06)
Early antiviral treatment					
No					1.00 (Reference)
Yes	-0.57	1.33	-0.43	0.667	0.56 (0.04 ~ 7.60)
Pregabalin					
No					1.00 (Reference)
ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases;					

Variables	β	S.E	Z	*P*	OR (95%CI)
Yes	-0.10	1.19	-0.09	0.932	0.90 (0.09 ~ 9.24)
Tramadol					
No					1.00 (Reference)
Yes	-2.04	1.25	-1.63	0.103	0.13 (0.01 ~ 1.51)
Cerebral infarction					
No					1.00 (Reference)
Yes	1.50	1.68	0.89	0.372	4.46 (0.17 ~ 119.03)
Rash site					
Head					1.00 (Reference)
Cervical	-0.57	2.02	-0.28	0.777	0.56 (0.01 ~ 29.47)
Thoracic	0.77	1.62	0.47	0.636	2.15 (0.09 ~ 51.31)
Lumbosacral	4.07	3.37	1.21	0.226	58.76 (0.08 ~ 43000.67)
Age	0.17	0.07	2.31	**0.021**	1.19 (1.03 ~ 1.38)
ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases;					

Construction and validation of nomogram prediction model

Based on the findings from the multivariate logistic regression analysis, a nomogram prediction model for clinical outcomes was developed, incorporating age, disease duration, coexisting connective tissue disease, coexisting malignant tumor, long-term hormone use, acute phase VAS, and the CD4+/CD8 + T lymphocyte ratio as predictive factors. Detailed information is presented in Fig. 1. To use it, the value for each predictor is located on its corresponding axis, and a line drawn upward determines the points received. The sum of all points is then projected downward to the total points axis, yielding the predicted probability of treatment failure.

Performance of the Prediction Model

The prediction model demonstrated excellent performance. It showed outstanding discriminatory power, with an area under the receiver operating characteristic curve (AUC) of 0.988 (95% CI: 0.976–1.000, Fig. 2). The Hosmer-Lemeshow test yielded a non-significant *P*-value of 0.969, indicating excellent calibration between predicted and observed probabilities (Fig. 3). Decision curve analysis indicated that when the threshold probability of risk ranged from 5% to 95%, the net benefit associated with the application of the nomogram model was significantly greater than that of both the "no intervention" and "full intervention" strategies. This finding suggests that the nomogram exhibits substantial clinical effectiveness. The nomogram within this predictive model demonstrates acceptable predictive capability

(Fig. 4). Furthermore, the model demonstrated a sensitivity of 90.7%, a specificity of 96.2%, and an overall accuracy of 93% (Table 4).

Table 4
ROC index of nomogram

AUC (95%CI)	Accuracy (95%CI)	Sensitivity (95%CI)	Specificity (95%CI)
0.988 (0.976-1.000)	0.930 (0.871–0.967)	0.907 (0.841–0.973)	0.962 (0.911–1.000)
AUC: Area under curve;			

Discussion

This study analyzed 128 ZAP patients treated with HL-PRF at the First Affiliated Hospital of Wannan Medical College. Univariate logistic regression analysis identified factors such as patient age, duration of the disease, prolonged use of corticosteroids, initial non-administration of antiviral medications, utilization of antiepileptic drugs, consumption of tramadol tablets, presence of concurrent connective tissue disease, coexisting malignancies, concurrent cerebral infarction, acute phase VAS score, and the CD4+/CD8 + T lymphocyte ratio were significantly associated with the treatment efficacy of HL-PRF for ZAP ($P < 0.05$). Further analysis using both univariate and multivariate logistic regression identified seven independent predictors of treatment failure: age, disease duration, acute phase VAS score, long-term hormone use, connective tissue disease, malignant tumors, and CD4+/CD8 + T lymphocyte ratio ($P < 0.05$). The resulting nomogram prediction model demonstrated excellent performance with an AUC of 0.988 (95% CI: 0.976-1.000), sensitivity of 90.7%, specificity of 96.2%, and overall accuracy of 93%.$P < 0.05$).

ZAP develops through three main mechanisms[13, 14]: (1) Nerve damage impairs nociceptive pain signal inhibition, lowering pain thresholds and causing spontaneous discharges; (2) Small fiber damage sensitizes C fibers, reducing action potential thresholds and increasing discharge frequency; (3) Combined large and small fiber damage with central nervous system changes causes pain allodynia in areas with sensory loss. PRF alleviates neuropathic pain by reducing the excitability of nociceptive fibers, boosting endogenous opioid precursor mRNA, and inactivating microglia in the spinal dorsal horn[15]. Song *et al*[16] reported 74.7% overall effectiveness with HL-PRF for acute/subacute trigeminal neuralgia (82.98% acute, 63.89% subacute). I Our study showed 60% effectiveness in ZAP patients, with lower rates possibly due to inclusion of PHN patients with chronic pain, indicating severe nerve damage and central sensitization. Chronic pain can lead to spinal neuron remodeling, complicating PRF's ability to reverse pain pathways, while long-term inflammation may cause perineural fibrosis, affecting PRF's electromagnetic field. Subgroup analysis revealed effective rates of 81.82% (< 1 month), 55% (1–3 months), and 33.33% (> 3 months), confirming early treatment improves outcomes[17].

Aging weakens cell-mediated immunity against VZV, increasing the severity and frequency of herpes zoster. Multiple studies confirm age as an independent risk factor for PHN [18–21], consistent with our

finding that HL-PRF is less effective in older ZAP patients. The potential reasons could involve these mechanisms: (1) In the elderly, decreased levels of key neurotransmitters in the central nervous system may alter pain signal transmission and neural regulation[22]; (2) Aging disrupts noradrenergic and serotonergic pain inhibitory pathways that PRF normally enhances [23, 24]; (3) Persistent low-grade inflammation in the elderly may counteract PRF's anti-inflammatory effect[25].These factors may contribute to a reduction in the neural repair capacity and immune function of elderly patients, thereby influencing the recovery process of nerve injuries and the efficacy of HL-PRF in neural regulation. Future research should investigate the influence of age-related epigenetic modifications, such as DNA methylation, on PRF target molecules like TRPV1 and P2X3 receptors and optimize PRF parameters, including temperature and frequency, for elderly patients.

Severe acute pain is a recognized risk factor for PHN alongside age. Acute pain severity correlates with nerve damage extent, suggesting herpes zoster pain results from peripheral nerve deafferentation and central sensitization [29–31]. Pain severity also correlates with anxiety, depression, and reduced quality of life in herpes zoster patients[26].Another study examined the link between ZAP and immune response, revealing that cell-mediated immunity inversely relates to the severity of skin damage and pain in herpes zoster, while antibody levels show no such relationship [27]. This indicates that cell-mediated immunity is crucial in managing herpes zoster symptoms. Additionally, voiding dysfunction due to herpes zoster is strongly linked to pain severity, with longer pain relief times in patients experiencing voiding issues, particularly when herpes zoster affects the sacral region [28]. Severe pain indicates greater nerve damage, intense neuroinflammation, high viral load, and strong inflammatory response with elevated IL-6 and TNF-α levels, which disrupt the blood-nerve barrier and cause persistent nociceptor sensitization [32–34]. Our study confirmed high acute phase VAS score as an important predictor of poor HL-PRF treatment outcomes in ZAP patients.

Multiple studies demonstrate higher herpes zoster prevalence in patients with immune-compromising conditions. Kim *et al.* [35] demonstrated that the prevalence of solid tumors, hematological malignancies, autoimmune diseases, and chronic kidney diseases was significantly higher in patients experiencing recurrent herpes zoster. Additionally, Wang *et al.* [36] identified connective tissue diseases and malignant tumors as independent PHN risk factors. Furthermore, it has been reported that the prevalence of herpes zoster is notably elevated among individuals with rheumatic diseases, with the incidence rate in patients with rheumatoid arthritis (RA) being at least double that of the general healthy population [37]. In patients with systemic lupus erythematosus, the incidence rate is even higher, reaching up to 91 per 1,000 person-years [38]. Our study found reduced HL-PRF efficacy in ZAP patients with connective tissue diseases or malignant tumors. This may result from autoimmune responses, chronic inflammation, autoantibodies targeting neural tissues, and prolonged immunosuppressant therapy compromising immune function. Furthermore, patients with connective tissue diseases often undergo prolonged immunosuppressant therapy, which may further compromise the immune system and diminish the effectiveness of PRF. Our research also identified the long-term use of corticosteroids as a significant predictor of reduced treatment efficacy.

Our study found that a lower CD4+/CD8 + T lymphocyte ratio in peripheral blood is a risk factor for the reduced effectiveness of HL-PRF. Previous research links PHN with host immune response, showing CD4 + and CD8 + T cell changes correlate with pain scores [39–41]. Wang *et al.*[40] demonstrated that age and CD4+/CD8 + ratio are independent PHN risk factors, indicating significant cellular immune dysregulation in older HZ patients. This study suggests that HZ patients with normal acute immune function, particularly those who are older and more susceptible to PHN, exhibit significant cellular immune dysregulation. Peng *et al.*[41] found elevated PD-1CD4 T cells and TNF-α production in PHN patients. TNF-α promotes neuroinflammation, activates calcium signaling in dorsal root ganglion neurons, and exacerbates pain transmission. Jiang *et al.* [42] demonstrated that PRF (20 ms pulse width, 2 Hz frequency, 2-minute duration) alleviated mechanical allodynia and thermal hyperalgesia. They observed decreased IL-1β and TNF-α levels, suggesting an anti-inflammatory effect that may reduce various neuromuscular pains. PRF modulates pain signaling, immune activity, synaptic function [43], and affects ion channels, neurotransmitters, and postsynaptic receptors in chronic neuropathic pain [44].

Limitations

This study has several limitations. First, although the predictive model showed strong internal validation performance, external validation is needed to confirm its robustness across diverse clinical settings. Previous studies demonstrate that models often perform well internally but may show reduced efficacy in external validation [45]. Second, this study utilizes retrospective data from a single center, potentially constraining the generalizability of its findings. Multi-center studies with diverse patient populations would provide more comprehensive evaluation of model reliability. An illustrative example is a study that assessed the prediction of gastric cancer survival rates through external validation using data from a mid-sized center. The findings revealed that, although the model exhibited strong discriminatory power, the observed survival rates were marginally higher than those predicted. This underscores the necessity of accounting for population differences when applying the model across various centers [46]. Third, the techniques employed to address missing variables during the development and validation phases of predictive models can substantially influence their performance. Empirical evidence indicates that multiple imputation methods are superior to simple variable omission strategies for managing missing data, thereby offering valuable insights for the advancement of future models [47]. Subsequent research should prioritize multi-center data and external validation to enhance the model's applicability and reliability.

Conclusions

HL-PRF is an effective treatment for ZAP, its efficacy is substantially influenced by specific patient factors. Our study identified that older age, prolonged disease duration, comorbidities (connective tissue disease or malignancy), long-term corticosteroid use, high acute-phase pain intensity (VAS > 7), and a low CD4+/CD8 + T-cell ratio are key predictors of poorer outcomes. The clinical prediction model developed in this study provides a tool for individualizing patient management. Future research should

focus on developing individualized treatment protocols to improve the precision and effectiveness of HL-PRF treatment.

Declarations

Ethics approval and consent to participate

This retrospective study was conducted in compliance with the World Medical Association Declaration of Helsinki. The study was designed and reported in alignment based on the TRIPOD guidelines. The study received approval from the Ethics Committee of the First Affiliated Hospital of Wannan Medical College, located at No. 2 Zhe Shan Street, Wuhu, Anhui, China (Approval No: 2023-LSX-08). Written informed consent was obtained from all participants prior to the commencement of study procedures.

Consent for publication

Not applicable.

Competing interests

The authors declare no conflicts of interest.

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Funding

The present work was supported by grants from the Anhui Provincial Special Project Fund for Clinical Medical Research and Translational Studies(202527c10020015).

Author Contribution

Dr. Yongquan Chen and Huaichang Wen contributed to the study design. Weijian Zhang and Mengjuan Dong wrote the manuscript, collected the data and performed the data analysis. Dr. Yongquan Chen,Weijian Zhang, Mengjuan Dong and Bin Wang reviewed the final draft. All authors read and approved the final manuscript.

Acknowledgement

The authors thank Dr. Hao Cheng, Department of Anesthesiology and Pain Medicine, First Affiliated Hospital of Wannan Medical College, Wuhu, China., for the clinical work support.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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Figures

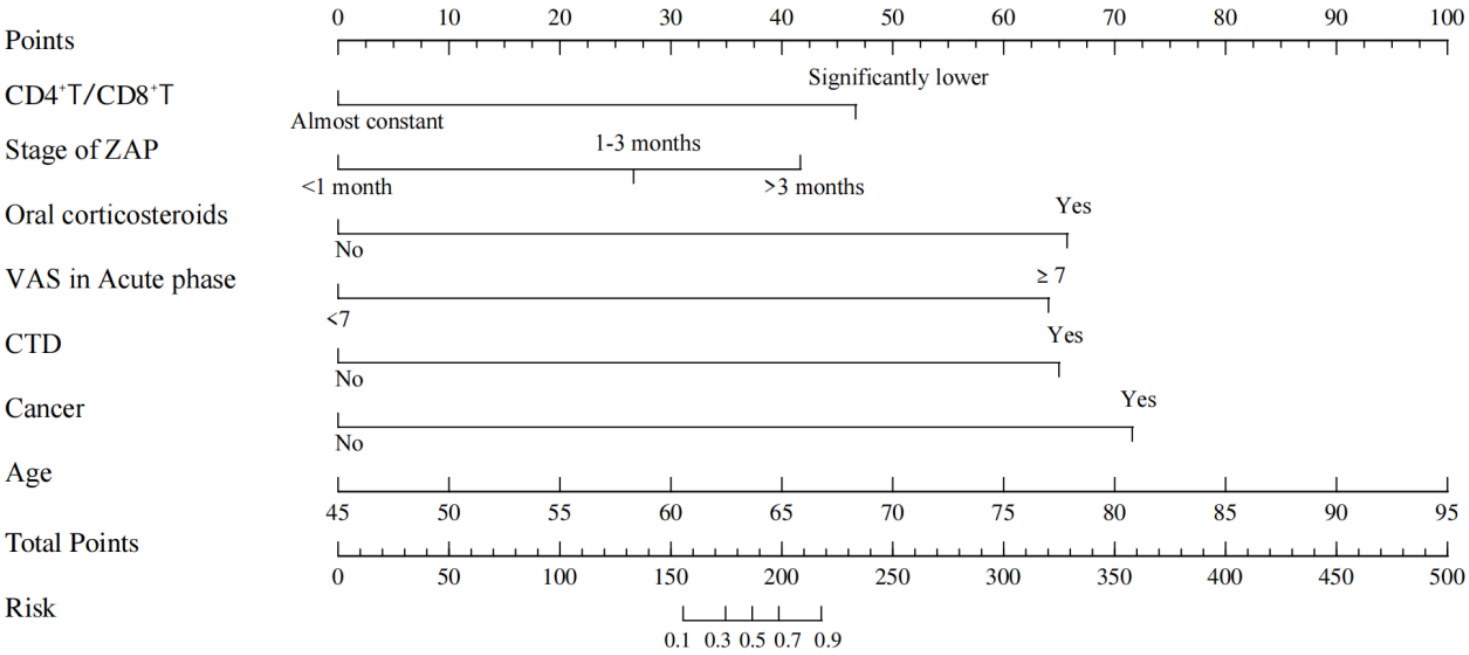


Figure 1

Predictive nomogram for efficacy of HL-PRF in the treatment of ZAP□ZAP:Herpes zoster associated pain; CTD:Connective tissue diseases;

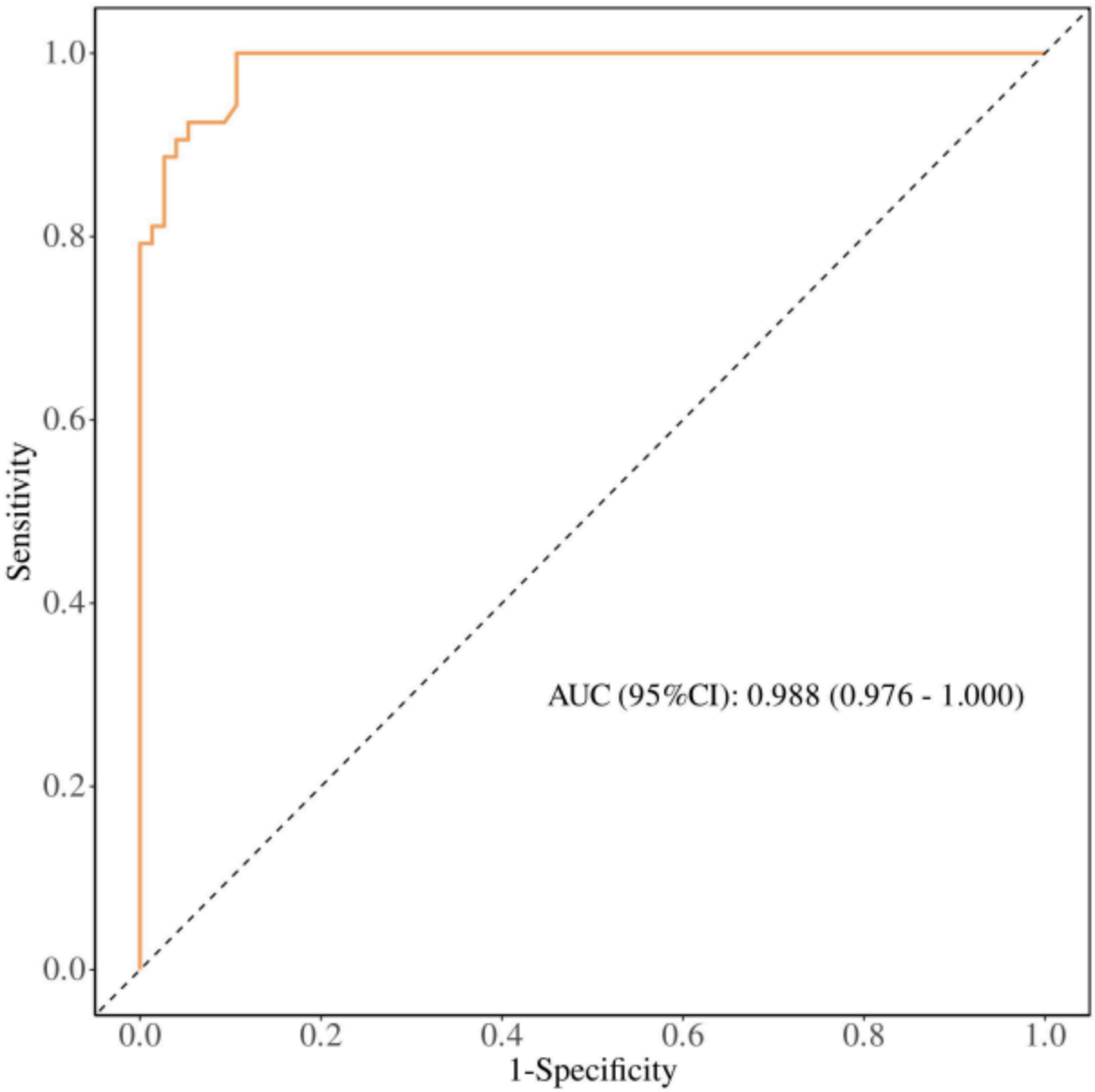


Figure 2

Receiver operating characteristic curve to verify the

accuracy of predictive nomogram

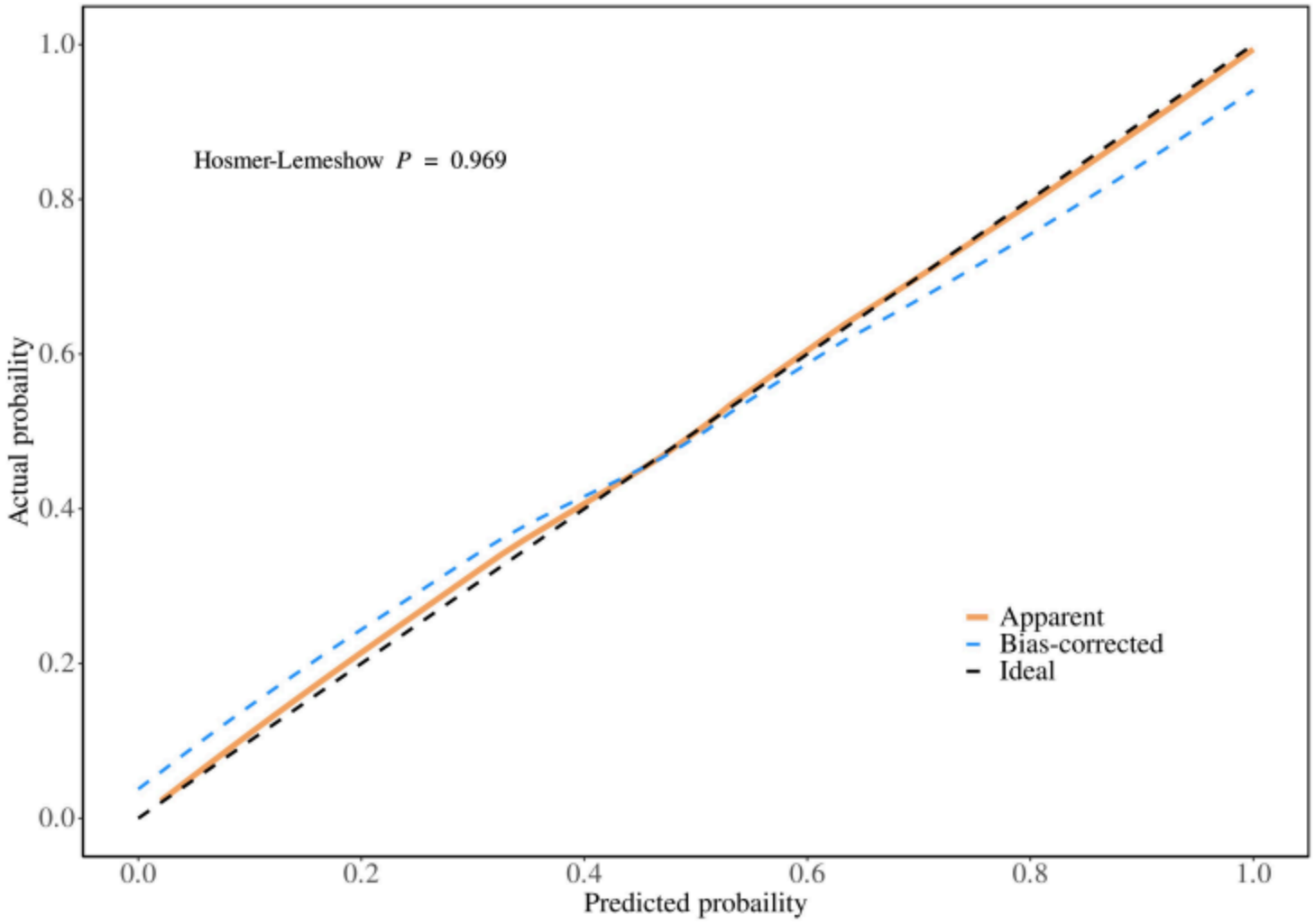


Figure 3

Calibration curve of nomogram

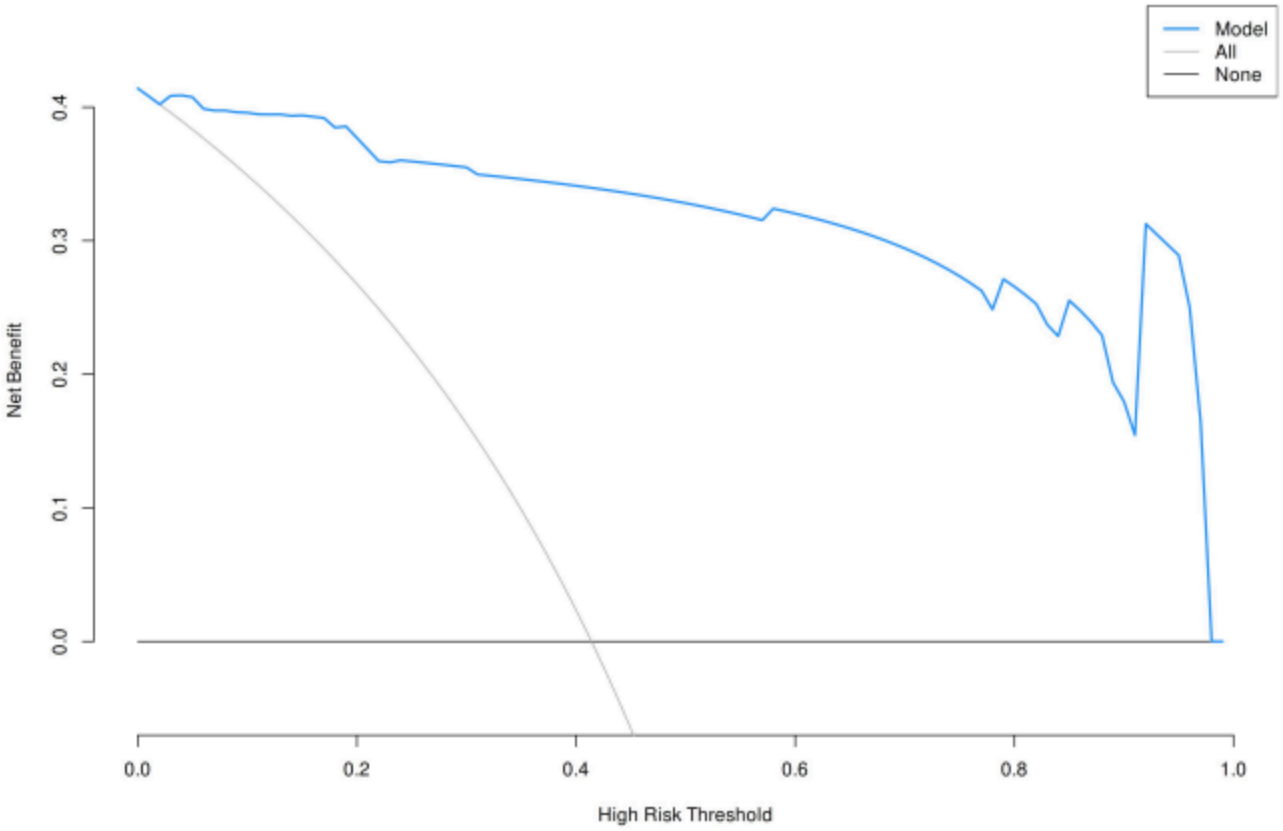


Figure 4

Clinical decision analysis curve of nomogram