

Risk Factors and Nomogram-Based Prediction of the Risk of Postherpetic Neuralgia in Patients with Herpes Zoster

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Objective: Postherpetic neuralgia (PHN) is considered as the most common complication of herpes zoster, and its incidence is increasing. The aim of this study was to explore the risk factors of postherpetic neuralgia (PHN) (ICD-10: B02.29) and to construct a predictive line graph model for early identification and prevention of PHN.

Methods: In this study, we focused on a cohort of 650 patients who had been diagnosed with herpes zoster (HZ) (ICD-10: B02) and subsequently admitted to Wuhan Fourth Hospital over a span of seven years, specifically from January 2018 to June 2025. The study cohort was randomly divided into a training set (n=458) and a validation set (n=192), with an average age of 57.31±12.64 years in both groups. The Nomogram model, designed to predict the elevated risk of PHN in individuals with HZ was constructed through the R4.2.1 software “rms” package. The nomogram model's predictive performance was evaluated using the decision curve, while the calibration curve was utilized for internal validation. The model was also externally validated using a validation set of data.

Results: The logistic regression analysis revealed that independent risk factors for PHN included age, the course of HZ, herpes in specific areas, VAS score, severity of skin damage, and temperature rising >1°C. The proposed Nomogram model, developed with the previously mentioned indicators, exhibits ROC curve area values of 0.943 for the training set and 0.900 for the validation set. The correction curve suggests that the model maintains high accuracy. Furthermore, the DCA outcomes reveal that the model possesses enhanced clinical utility at risk thresholds ranging from 0 to 0.99 for the training data and from 0.04 to 0.89 for the validation data.

Conclusion: Our study confirms that age, the course of herpes zoster, herpes in special sites, VAS score, the severity of skin lesions, and a temperature increase of >1°C are independent risk factors for the occurrence of Postherpetic neuralgia (PHN). The nomogram model established based on these six indicators demonstrates good developmental potential and exhibits high discriminative predictive performance for Postherpetic neuralgia (PHN) in patients with herpes zoster.

Keywords: postherpetic neuralgia, nomogram model, prediction, risk factors, herpes zoster

Introduction

Herpes zoster (HZ) is an acute viral infectious disease that arises from the varicella zoster virus (VZV). The initial infection of the varicella-zoster virus is more commonly acquired during childhood and can lead to either varicella or a latent infection. Latent in the body, when the immune system is weakened or due to aging, the virus may become reactivated, leading to the occurrence of herpes zoster.¹ The aging population has led to a rise in the occurrence of herpes zoster, which has become a global public health concern. A comprehensive study carried out by Marra et al has shown a notable increase in the incidence of herpes zoster in Canada over a defined period. Specifically, the rates rose from 3.2 cases per 1000 person-years in 1997 to 4.5 cases per 1000 person-years by the year 2012.² In China, it was determined that the rates of HZ and PHN were 7.7% and 2.3%, respectively. Additionally, within the population of individuals diagnosed with HZ, the prevalence of PHN was found to be 29.8%.³ Overall, it was observed that 20–30% of people experience HZ at some point in their lifetime. PHN refers to persistent pain lasting for a duration of one month or more after the healing of an acute herpes zoster rash. It is the most commonly observed complication of HZ, affecting

approximately 10% to 35% of patients who have had HZ.⁴ The treatment of postherpetic neuralgia usually includes anti-neuralgia drug therapy, anti-depressive drug therapy, dorsal root ganglion pulse radiofrequency therapy and traditional Chinese medicine acupuncture therapy.⁵ However, according to the study, over 50% of patients with PHN did not experience significant symptom relief after treatment, which can be attributed to the challenges in treating the condition.⁶ Not only does PHN impact the physical and mental well-being of individuals, but it also creates a financial strain on public health care systems. Approximately 43% of patients with PHN show moderate anxiety or depression, severely affecting daily life and even suicidal in severe cases.⁴ A research investigation on herpes zoster conducted in Latin America,⁷ the direct cost per case of postherpetic neuralgia cases was \$1227.67 and the indirect cost was \$773.46, resulting in a cumulative cost of \$2,001.13. An Italian study showed that the cost of postherpetic neuralgia cases was 5400 euros per case.⁸ In 2011, the total cost of hospitalization for 50 years in Sweden was 11.01 million crowns.⁹ In view of its serious adverse consequences and huge economic burden, more and more scholars began to seek risk factors for the pathogenesis of PHN in recent years. Previous studies have shown that advanced age, larger areas of herpes and higher pain scores are risk factors for postherpetic neuralgia.^{10,11} Nonetheless, an intuitive and precise approach to easily evaluate the likelihood of developing PHN in patients with HZ is still lacking. The Nomogram model is a graphical statistical analysis tool that can intuitively indicate the connection between particular diseases and their associated risk factors without complicated mathematical calculation, by integrating different prognostic-related variables, risk probability of a clinical disease or complication can be generated.¹² Based on the aforementioned strengths, our study aimed to investigate the risk factors associated with PHN through a retrospective study and to establish a more intuitive and accurate incidence of PHN through a nomogram Predictive model to identify high-risk patients of PHN to early treatment and minimize the incidence of PHN as much as possible.

Methods and Materials

Research Design and Patient Selection

After strict inclusion and exclusion criteria screening, we finally retrospectively analyzed 650 patients with herpes zoster who were hospitalized at our facility from January 2018 to June 2025. Based on Hyun Kang's research,¹³ a prior power analysis was conducted using G*Power 3.1.9.2 for sample size calculation. When the effect size $f=0.5$, $\alpha=0.05$, and $1-b=0.95$, the required sample size was 210 participants. This study included 650 patients in its training set and validation set, meeting the sample size requirements. A posterior power analysis was performed on the included sample size, demonstrating that when achieving an effect size $d=0.5$, $\alpha=0.05$, and $1-b=0.99994$, the sample size could achieve favorable statistical results. All participants' diagnosis was independently completed by two deputy chief physicians or above from the Department of Pain Medicine, Wuhan Fourth Hospital, and the diagnosis was verified before being included in the study. The entire cohort was then randomly divided into a training set ($n=458$) and a validation set ($n=192$), following a 7 to 3 ratio. Based on the study of Hu and Cai et al, we formulated the inclusion and exclusion criteria.^{14,15} Inclusion criteria: (1) In alignment with a diagnosis of herpes zoster, the skin appears clusters of integrated blisters, distributed along the nerve, arranged in a ribbon; (2) Age ≥ 18 years and ≤ 85 years; (3) All patients have complete clinical data and can communicate normally. Exclusion criteria: (1) herpes zoster patients during pregnancy and lactation; (2) Patients with mental disorders; (3) Combining with other categories pain disorders that would affect the assessment of PHN; (4) Patients with low immunity such as tumors or HIV (5) Patients with Communication impairments, including language impairments, preexisting neurologic disorders, and psychiatric disorders. All research subjects provided informed consent for this study. Our research is consistent with the Declaration of Helsinki, The Ethics Committee of Wuhan Fourth Hospital gave its approval for this retrospective research (Ethics Approval Number: KY2025-127-01).

Data Collection

We collected the clinical data of the patients through the case report form (CRF), including factors such as age, gender, body mass index (BMI), smoking history, Course of the acute phase of herpes zoster (The time from symptom onset to treatment), VAS score, Severity of skin damage (Acute skin lesions covering more than 5% of the total body skin area with bullae, gangrene, bleeding, and panepidema), whether the body temperature increase is greater than 1 degree Celsius (It was defined as the skin temperature of herpes area increased by more than 1°C after infrared thermography detection in HZ patients),

Blood glucose level and herpes in special sites (trigeminal nerve distribution area, perineum, limbs, etc). The information is sourced from the hospital information system (HIS), the laboratory information management system (LIS), medical image information management system (PACS). We created a dedicated database based on the CRF to collect the clinical data. For improving input data quality, all data were independently checked and entered into the database by two researchers.

Statistical Analysis

Statistical analysis of the collected data was performed using the SPSS software, specifically version 26.0. Initially, all data underwent testing for normality through the application of non-parametric tests. For measurement data following a normal distribution, we present results in the format “mean $\pm$ standard deviation” ($\bar{x} \pm s$). For data not following a normal distribution, we use the format “median (lower quartile, upper quartile)” or abbreviate it as [M (P25, P75)]. Furthermore, categorical variables were presented as counts and percentages (n%). In the analysis, continuous variables exhibiting a normal distribution were compared using the independent *t*-test, whereas continuous variables that did not follow a normal distribution were evaluated with the Mann–Whitney *U*-test. Categorical variables were examined using the chi-square test. It is important to note that all *p*-values were calculated as two-sided, and a *p*-value of less than 0.05 was deemed statistically significant.

Establishment and Verification of Nomogram Model

For the construction of the prediction model, univariate logistic regression was used for preliminary screening of research variables, and the obtained clinical research variables with significant differences were included as independent variables into multivariate Logistic regression, and the development of PHN in patients diagnosed with HZ was used as the dependent variable to screen out independent predictors of PHN. Based on the independent predictors, a model formula for predicting PHN risk was constructed, and a visual nomogram model for predicting PHN risk was constructed using R4.2.1. The nomogram collected points assigned to each risk factor, and mapped the predictive probability to 0 to 100 points for scale points, the sum of the scores corresponds to the corresponding risk, with a high level of score indicating a higher risk of PHN. To assess the performance of the nomogram, both internal and external validation methods were employed. The receiver operating characteristic (ROC) curve was plotted, and the area under the curve (AUC) was computed to evaluate the model’s discriminatory ability. Additionally, a calibration curve was created to assess the model’s calibration accuracy. The Decision Curve Analysis (DCA) was utilized to examine the clinical applicability and advantages of the prediction model. The internal validation of the obtained prediction model is through the bootstrapping with 1000 resamples and the calibrated mean absolute error is calculated. The external validation is done with validation set data.

Results

Following rigorous inclusion and exclusion criteria, a total of 650 patients diagnosed with herpes zoster were ultimately enrolled in this research. Among these patients, 225 experienced progression to postherpetic neuralgia (PHN), resulting in an incidence rate of 34.6%. The cohort was randomly divided into a training set ($n=458$, including 155 PHN patients and 303 simple HZ patients) and a validation set ($n=192$, including 70 PHN patients and 122 simple HZ patients) with an average age of 57.31 ± 12.64 years. Statistical analysis showed no obvious difference in clinical characteristics between the two sets ($p > 0.05$), as presented in [Table 1](#).

Independent Risk Factors Selection

Single factor logistic regression was employed as a preliminary method to screen the variables within the training set and a total of 7 research variables with significant differences were screened out, namely: Age, Herpes in special sites, course of HZ, VAS Score, Severity of skin damage, Blood glucose level and temperature rising $>1^{\circ}\text{C}$, and then, the research variables obtained from the preliminary screening of single-factor logistic regression were incorporated into a multi-factor logistic regression, and to identify the independent predictive factors that influence the occurrence of postherpetic neuralgia (PHN) in patients, the Enter method was employed during this analysis. The results suggested: Age, course of HZ, Herpes In special sites, VAS Score, Severity of skin damage, and temperature rising $>1^{\circ}\text{C}$ had significant statistical differences, which can be considered as independent risk factors for PHN ([Table 2](#)).

Table 1 Comparison of Clinical Characteristics Between Training Set and Validation Set

Variables	Verification Set (n=192)	Training Set (n=458)	X ² /Z/T value	P value
Gender (male/female)	128/69 (64.1%)	308/150 (67.2%)	0.615	0.43
Age (years)	58.57±11.87	56.79±12.91	1.642	0.10
BMI (kg/m ²)	24.70±4.15	24.94±3.49	-0.779	0.437
Course of HZ (days)	6.96±4.91	6.85±4.50	0.293	0.77
History of smoking	101/91 (52.6%)	238/220 (52%)	0.02	0.88
Temperature rising >1°C (0or1)	84/108 (43.8%)	174/284 (38%)	1.874	0.17
HbA1c (%)	8.98±2.47	8.64±2.23	1.725	0.085
VAS (0–10)	6.66±1.76	6.57±1.59	0.067	0.497
Herpes in special sites (0or1)	77/115 (40.1%)	175/283 (38.2%)	0.205	0.65
Severity of skin damage (0or1)	81/111 (42.2%)	197/261 (43%)	0.038	0.85

Table 2 The Results of Multivariate Logistic Analysis

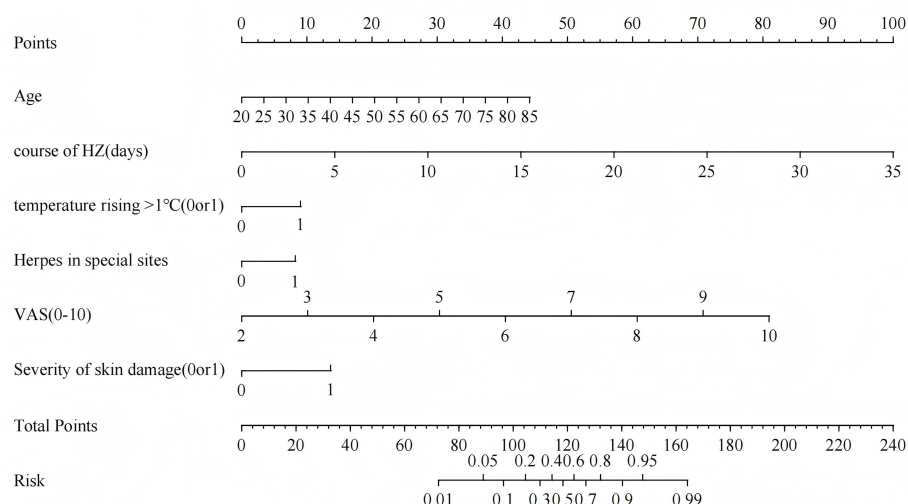
Variables	β	SE	Wald	P	OR (95 % CI)
Age	0.068	0.014	22.888	<0.001	1.071 (1.041, 1.101)
Course of HZ (days)	0.286	0.051	31.266	<0.001	1.331 (1.204, 1.471)
Herpes in special sites	0.824	0.319	6.662	0.01	1.439 (1.235, 1.820)
VAS (0–10)	1.014	0.139	53.096	<0.001	2.757 (2.099, 3.621)
Severity of skin damage (0or1)	1.367	0.324	17.855	<0.001	1.255 (1.135, 1.480)
Temperature rising >1°C (0or1)	0.905	0.327	7.655	0.006	1.405 (1.213, 1.768)

The Establishment and Application of Nomogram Model

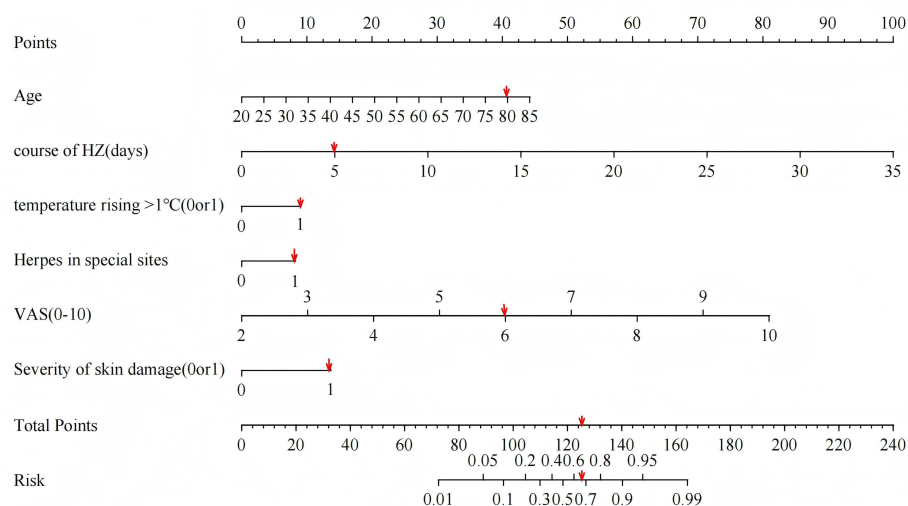
A nomogram predicting PHN was established based on the six variables of Age, course of HZ, Herpes In special sites, VAS Score, Severity of skin damage, and temperature rising >1°C, each variable is followed by a scale, and the scale corresponds to the corresponding value. Each independent risk factor of each patient draws an upward vertical line on the corresponding scale, and the score obtained by each risk factor can be obtained, and the scores corresponding to the 6 factors are added and drawn on the total score scales a downward vertical line, the risk probability of developing PHN for this patient could be quickly obtained. The left endpoints of each scoring line correspond to 0 points, and the right endpoints from Age to course of HZ, Herpes In special sites, VAS Score, Severity of skin damage, and temperature rising >1°C are 44, 100, 9, 8, 91, 14 points, respectively, the total score is 164 points showed as [Figure 1A](#). For example, if a Patients with HZ is 80 years old and has Herpes in special sites, VAS score is 6 points, skin damage is severe, body temperature rising >1°C, and the course of HZ is 5 days, the probability of PHN is evaluated to be 68% ([Figure 1B](#)). The red arrow shows the corresponding values of the patient's risk factors in the Nomogram and the overall risk prediction rate for PHN occurrence.

Nomogram Model Verification

The Nomogram model was rigorously evaluated using several statistical methods, including the area under the receiver operating characteristic (ROC) curve (AUC), the calibration curve constructed through the Bootstrap method, which involved 1000 repeated samplings of the original dataset, and the decision curve analysis (DCA) curve. These techniques were employed to provide an internal validation of the nomogram model based on data from the training set. For external validation, we utilized a separate validation set. The findings revealed impressive results: the AUC for the training set was 0.943 (with a 95% confidence interval of 0.922 to 0.964), while the AUC for the validation set was 0.900 (with a 95% confidence interval of 0.852 to 0.974), as illustrated in [Figure 2A](#) and [B](#). Moreover, both of the calibration curves derived from the training and validation sets demonstrated strong alignment with the ideal curves, reinforcing the model's reliability as depicted in [Figure 3A](#) and [B](#). The clinical applicability of the nomogram was further assessed using the DCA curve. The results indicated that the model



A



B

Figure 1 A Nomogram model for predicting the risk of PHN in herpes zoster patients (A) and a dynamic nomogram (B). The predictors used in the nomogram include Age, course of HZ, Herpes in special sites, VAS Score, Severity of skin damage, temperature rising $>1^{\circ}\text{C}$. Note: Herpes in special sites: 1, no Herpes in special sites: 0; Severity of skin damage: 1, no Severity of skin damage: 0; temperature rising $>1^{\circ}\text{C}$: 1, no temperature rising $>1^{\circ}\text{C}$: 0, the red arrow shows the corresponding values of the patient's risk factors in the Nomogram and the overall risk prediction rate for PHN occurrence.

exhibited the highest clinical predictive value when the risk threshold probabilities for postherpetic neuralgia (PHN) ranged from 0 to 0.99 in the training set and from 0.04 to 0.89 in the validation set, as shown in Figure 4A and B.

Discussion

PHN is the most common complication of HZ. Previous literature has shown that older age, higher VAS score, longer duration of herpes zoster, lower immune function, gender, etc. can. In this research, we gathered clinical data from 650 patients with herpes zoster who were hospitalized in our facility. The primary aim of our study was to identify the independent risk factors that contribute to the development of postherpetic neuralgia (PHN) in these patients. Using this information, we proceeded to construct and rigorously validate a Nomogram model. This predictive tool is designed to

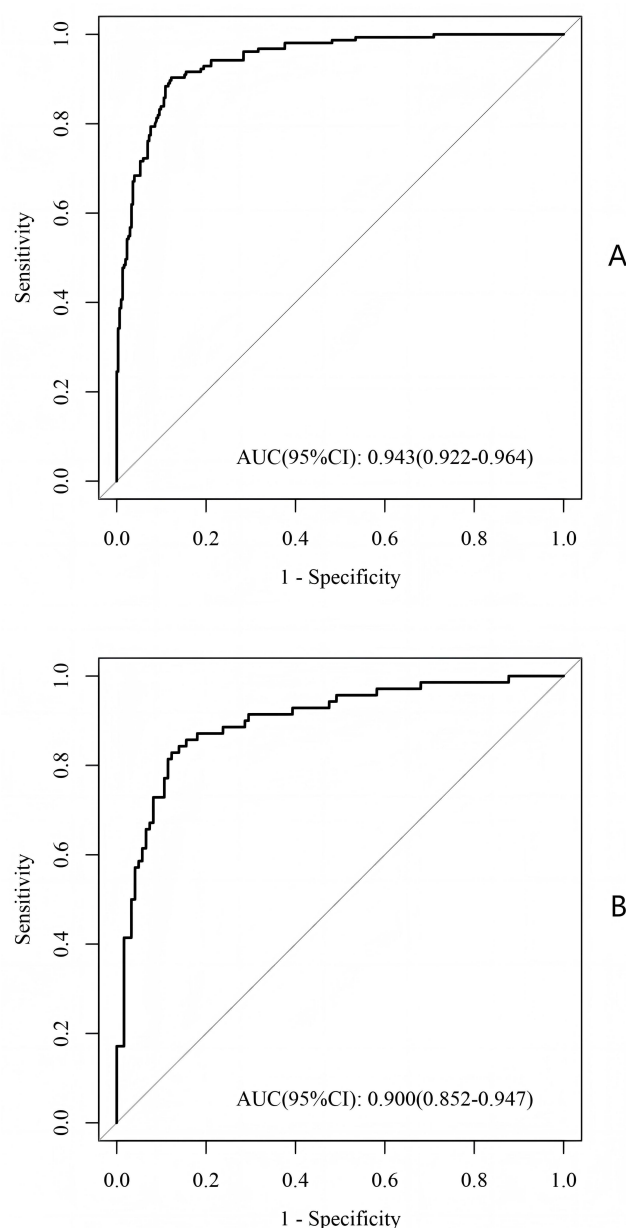


Figure 2 ROC curves for the risk model of PHN occurrence. The area under the ROC curve (AUC) of 0.5 indicates that the model can distinguish PHN patients with a probability of 50%, while an AUC of 1 indicates a 100% probability. An increased AUC value signifies a more robust ability of the model to differentiate. The training dataset reached an AUC of 0.943, with a confidence interval of 95% spanning from 0.852 to 0.947 (**A**). Conversely, the verification dataset exhibited an AUC value of 0.900, accompanied by a 95% confidence interval ranging from 0.852 to 0.947 (**B**). On the other hand, the verification set's AUC value was 0.900 with a 95% confidence interval ranging from 0.852 to 0.947.

assess and forecast the likelihood of PHN occurrence in individuals diagnosed with herpes zoster, thereby aiding healthcare providers in making more informed decisions regarding patient management and intervention strategies.

In this research involving 650 patients diagnosed with herpes zoster, 155 patients in the training set ($n=458$) suffered from PHN, with an incidence rate of 33.8%, and 70 patients in the validation set ($n=192$) suffered from PHN, with an incidence rate of 36.4%, which is consistent with the findings reported by Yang F et al.³ The study identifies several independent risk factors that contribute to the onset of PHN, including age, duration of herpes zoster, presence of herpes in specific anatomical areas, visual analog scale (VAS) scores, the degree of skin damage, and a rise in temperature exceeding 1°C. These findings align with those of Shijuan Wei et al.¹⁶ Age is generally recognized as a significant risk factor for the development of PHN.¹⁷ PHN tends to occur in middle-aged and elderly herpes zoster (HZ) patients over 50

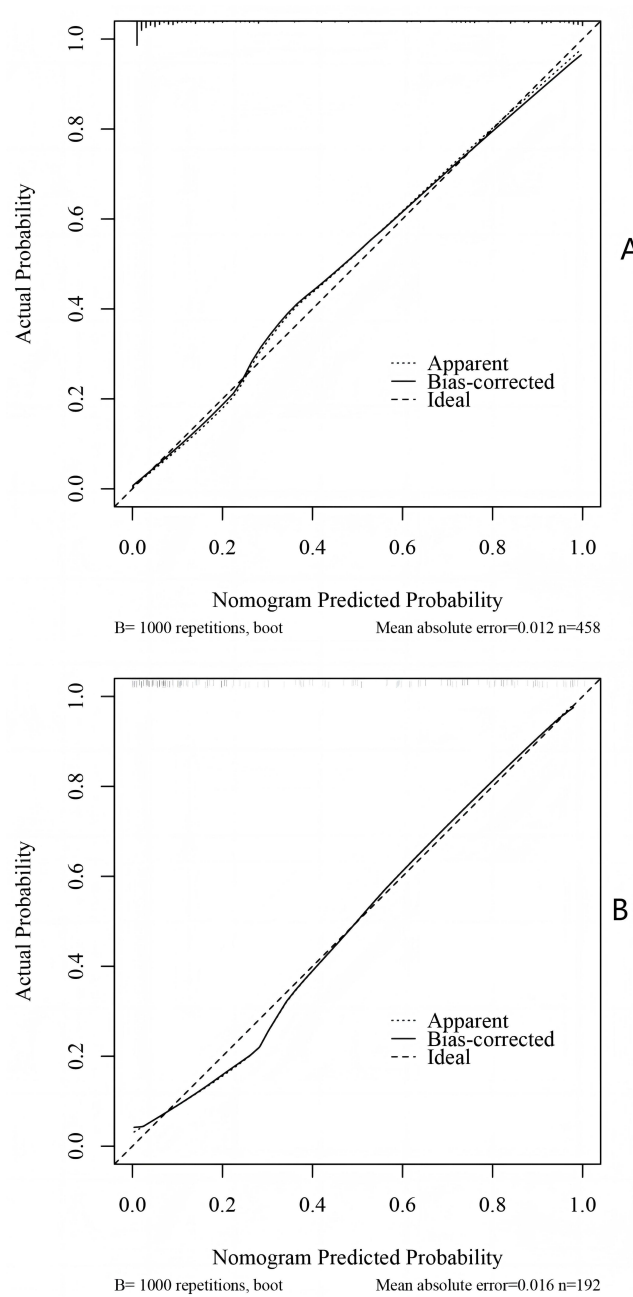


Figure 3 This study showcases the calibration curves relevant to the prediction of PHN risk utilizing nomogram analysis. The ideal prediction is represented by the thick dotted line, while the predictive ability of the nomogram is represented by the thin dotted line. The better the fit between the thick and thin dotted lines, the higher the predictive accuracy of the nomogram. The calibration curves of the training set (A) and verification set (B) both demonstrate a strong correlation between the predicted probability and actual probability, with a mean absolute error of 0.016, which is less than 0.05.

years old, with an average occurrence rate of 14.33%,¹⁸ and it is significantly related to age. Among them, the incidence rate of HZ patients aged 50–59 is about 12.28%. 17.54% of patients over 70 years old, and 33% of HZ patients over 79 years old.¹⁹ Compared with young people, the elderly are more prone to PHN because their cell-mediated immunity decreases with age.²⁰ In addition, due to the decline of immune function in the elderly, this particular virus, which is known to remain inactive within the dorsal root ganglia after an individual has experienced chickenpox, is more likely to become activated and cause disease. At the same time, due to the reduced nerve repair ability of the elderly, the nerve tissue repair process is slow, and it is easier to develop into PHN.²¹

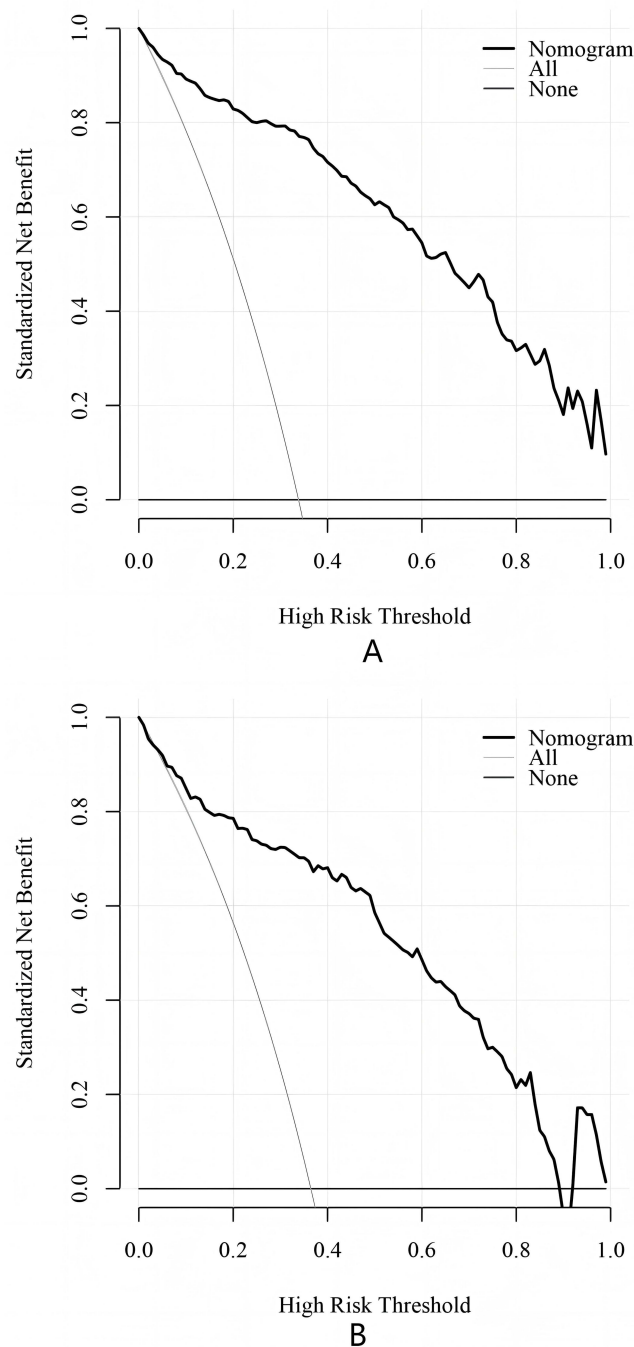


Figure 4 This study utilized decision curve analysis (**A**) (training set) and (**B**) (validation set) to evaluate the PHN risk nomogram. The y-axis of the graph measured the net benefit, with the light color thin solid line representing the assumption that all patients had PHN and the dark color thin solid line representing the assumption that all patients did not have PHN. The dark color solid line on the graph represented the risk nomogram.

Previous studies^{22,23} have confirmed that for patients with acute herpes zoster, the more severe the pain, the more likely to progress to PHN, and a consistent result was also observed in our study. The pain in the acute phase is caused by skin damage and peripheral nerve inflammation,²⁴ which can activate the varicella-zoster virus and replicate in large quantities, causing nerve fiber damage. Necrosis and remodeling changes of the nerves. In patients with HZ, the severity of the pain can mean severe nerve damage. The damage, repair, remodeling, and central sensitization of nerve tissue are currently recognized theories of PHN formation. The degree of pain changes the early physiological and pathological changes of the nerves, which directly affects the development of the disease. The prolongation of the course of herpes zoster (Initial treatment time) will also

aggravate the nerve damage of the patient, and irreversible ganglion necrosis will occur, which will eventually lead to an increased incidence of postherpetic neuralgia,²⁵ the results of our study also proved that.

In our study, we found that having herpes at a particular location was an autonomous risk factor for PHN in patients with HZ. Herpes zoster in special sites includes the trigeminal nerve distribution area (especially the eyes), perineum, limbs, etc. Because these parts are special, they have a great impact on the function of the body. If the treatment is not timely, it is easier to develop into PHN. Herpes zoster that occurs in the distribution area of the trigeminal nerve is extremely painful and affects the appearance and function of the patient, especially the herpes zoster of the eye can be more harmful to the body. Ocular HZ can cause severe pain in the ipsilateral forehead, nasociliary nerve distribution area, upper eyelid, migraine, etc. It has even been reported that ocular herpes zoster causes blindness in patients.²⁶ Herpes zoster in the perineum can affect the urine and defecation of patients. Due to the inconvenience of nursing, it often leads to aggravated infection, prolonged course of disease, and a higher incidence of PHN. Herpes zoster of the extremities often causes muscle weakness and affects the activities of the extremities. Early treatment is advocated in clinical practice, which is effective in preventing HZ patients from progressing to PHN.

In addition, we found that the severity of skin damage (the number of vesicles or papules > 50) is also one of the independent risk factors for the occurrence of PHN, and according to the study of Gross et al.²⁷ It may be that the greater the number of blisters or papules, the more severe the virus infection, the greater the viral load, and thus the greater the risk of PHN.

Our research also revealed that the occurrence of PHN in HZ patients increased significantly when the body temperature of herpes patients increased by more than 1 degree Celsius. A manuscript published by Park et al²⁸ reported that in the acute stage of herpes zoster, the occurrence of fever or the greater the change in body temperature is, the greater the possibility of PHN occurring. When the body temperature changes from 0.5°C to 1.0°C, the probability of PHN is increased by 8.25 times, and the change in body temperature > 1.0°C, the probability of PHN increased by 30.26 times, the mechanism perhaps is relevant to the stronger immune response and more serious nerve damage in patients with HZ with high body temperature.²⁹

In this study, a nomogram model was created with the objective of predicting the risk of developing postherpetic neuralgia. This particular model underwent both internal and external validation processes to ensure its reliability. Calibration curves were employed for the internal validation, while data from a separate validation set were used for external validation. The findings from these validations revealed that the model demonstrated impressive performance, with an area under the curve (AUC) of 0.943 in the training set and a slightly lower AUC of 0.900 in the validation set. These values underscore the model's effectiveness in accurately assessing the risk of postherpetic neuralgia, reinforcing its potential utility in clinical settings. The calibration curves provided compelling evidence of the predictive model's high accuracy, as they revealed that the predicted probabilities closely mirrored the actual occurrences of differential diagnosis (DF) in both the training and validation sets. This alignment signifies that the model is proficient at forecasting DF occurrences based on the available data. Furthermore, the Decision Curve Analysis (DCA) curves for both the training and validation sets underscored the model's significant clinical utility.

The study confirmed that Age, course of HZ, Herpes in special sites, VAS Score, Severity of skin damage, temperature rising >1°C were independent risk factors for the development of PHN. A risk model for predicting PHN in HZ patients was preliminarily established based on these indicators. The model was evaluated and found to have good discrimination, calibration, and clinical applicability. This model can provide clinical staff with a reference value to predict and prevent the occurrence of PHN at an early stage.

However, there are still some areas for improvement in our research. First, this research is a retrospective case analysis, and the parameter variables of the study are not comprehensive, and more risk factors need to be included in further prospective studies to enhance the model's accuracy. Second, the object of this study is a Compared with outpatients, inpatients with herpes zoster may have a more serious condition and a higher probability of developing postherpetic neuralgia. Therefore, there is a certain selection bias, and the research results may not be fully applicable to outpatients. Finally, the established prediction model is the research result of a single center, whether it is generally applicable to HZ patients still needs to be further confirmed by multi-center research.

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Disclosure

The authors report no conflicts of interest in this work.

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