Prospective Study

A Nomogram Model for Predicting Postherpetic Neuralgia in Patients with Herpes Zoster: A Prospective Study

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Background: Herpes zoster (HZ) and postherpetic neuralgia (PHN) have a negative effect on patients. A simple and practical PHN prediction model is lacking.

Objective: We aimed to investigate risk factors associated with PHN in patients with HZ and develop a predictive model.

Study Design: A prospective observational study.

Setting: This study was conducted at the Department of Pain Management, China-Japan Friendship Hospital in Beijing, People's Republic of China, spanning from August 2020 through March 2022.

Methods: Clinical data of 174 patients with HZ were recorded using a case report form. The patients underwent a 3-month follow-up, which included both in-person visits and telephone follow-ups. Patients were categorized into either a PHN or non-PHN group based on the diagnosis of PHN. Multiple logistic regression analysis was used to identify the predictors of PHN occuring in patients with HZ. Subsequently, a nomogram model was developed to estimate the likelihood of PHN. To validate the prediction model's accuracy, calibration curves, the C-index, and receiver operating characteristic (ROC) curves were utilized.

Results: In this study, a total of 174 patients were divided into 2 groups: the PHN Group, consisting of 52 patients, and the non-PHN Group, consisting of 122 patients based on the follow-up results. Multiple logistic regression analysis revealed 5 significant risk factors for PHN, including being a woman, being more than 50 years old, having prodromal phase pain, having a large rash area, and having great pain severity during the acute phase. The model's performance was excellent, with an area under the ROC curve of 0.81 and a close alignment between the calibration curve and the actual data, signifying high accuracy. The model's accuracy and net benefit were maximized when predicting a prevalence between 6% and 92%.

Limitations: Our study was conducted at a single center and had a limited sample size.

Conclusions: The incidence of PHN is influenced by factors such as being a woman, being more than 50 years old, having prodromal phase pain, having a large rash area, and having great pain severity during the acute stage. The prediction model developed in this study effectively forecasts the occurrence of PHN using these 5 risk factors, making it a valuable tool for clinical practice.

Key words: Herpes zoster, postherpetic neuralgia, risk factors, nomograph, clinical model

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Herpes zoster (HZ) is a painful rash condition resulting from the reactivation of latent varicella-zoster virus within the dorsal root ganglia (1). In certain cases, the pain doesn't subside after the HZ rash has healed; instead, it intensifies and persists for months or even years. This enduring pain is conventionally referred to as postherpetic neuralgia (PHN), which is characterized by persistent neuropathic pain lasting for more than 3 months after the acute rash phase (2,3).

In Europe, North America, and the Asia-Pacific region, the incidence of PHN in patients with HZ ranges from 5% to 30% (4). In The People's Republic of China, the prevalence of HZ and PHN is reported as 7.7% and 2.3%, respectively; the prevalence of PHN in individuals with HZ is as high as 29.8% (5). In stark contrast to the high incidence of PHN, it has a low cure rate, with research indicating that more than half of patients do not experience significant improvement (6). As a result, PHN poses a substantial burden on patients, their families, and society, leading to both direct costs—such as health care resource utilization—and indirect costs, including lost productivity (7,8).

Given the broad effect of this disorder on the general population, recent research on PHN has shifted its focus toward not only treatment, but also prevention. While vaccines can effectively prevent HZ in healthy individuals, they do not provide protection against PHN in patients who already have HZ. Consequently, the emphasis has shifted to secondary prevention of HZ in clinical settings as a critical approach.

In recent years, numerous researchers have initiated investigations into the risk factors associated with PHN and have made efforts to construct predictive models to identify high-risk groups for early prevention, ultimately aiming to reduce the incidence of PHN (9-12). However, most previous studies have primarily involved literature reviews or retrospective research, with a paucity of prospective studies. Moreover, the models that have been developed are typically linear and lack intuitive qualities.

Acknowledging this knowledge gap, our study developed a nomogram model for predicting PHN in patients with acute-phase HZ with the goal of establishing effective preventive strategies.

Methods

Patients and Study Design

Our research comprised a prospective observational study conducted at the Department of Pain Management, China-Japan Friendship Hospital in Beijing, China, spanning from August 2020 through March 2022. All study patients had sought medical attention at the pain department due to neuralgia caused by HZ. The study adhered to the principles outlined in the Declaration of Helsinki and received approval from the Ethics Committee of the China-Japan Friendship Hospital (Ethics approval number: 2019-171-K117). All patients provided written informed consent before their involvement in the study.

Inclusion and Exclusion Criteria.

The inclusion criteria were: 1) aged ≥ 18 years; 2) strictly fulfill features of HZ pathogenesis, i.e., shingles and pain distribution consistent with neuroanatomical features; 3) an HZ duration of less than 14 days; 4) unilateral onset.

The exclusion criteria were: 1) an HZ duration exceeding 14 days; 2) the presence of local skin allergies or other significant skin diseases; 3) concurrent neurological injuries or painful disorders unrelated to HZ; 4) psychiatric disorders or cognitive impairments that could affect somatic sensory testing.

Case Report Form Design

We developed a case report form based on the pathogenesis of HZ and potential risk factors for PHN. We used the form to gather both general information and clinical data from the patients. The study involved 2 visits, including Visit One (on the day of the first attendance) and Visit 2 (3 months following the onset of HZ). The latter 3 follow-ups were conducted through either in-person visits or telephone conversations. The follow-up process was concluded if the patient's rash healed and the pain subsided.

During Visit One, we collected information regarding gender, age, height, weight, time to rash onset, rash area, presence of prodromal phase pain, nerve involvement, pain intensity, and comorbidities. Pain intensity was assessed using the Visual Analog Scale (VAS).

In our study, measurement bias may have occurred when calculating the herpes area. We minimized measurement errors by employing a zonal measurement approach. A physician was specifically assigned to complete the measurements and calculations.

Sample Size

Considering the sample size requirements for establishing a predictive model, it was estimated that if 10 rel-

evant factors were to be included in the model, at least 50 patients with PHN (5-10 times the number of factors) would be required, and at least 168 patients would need to be included in an expected PHN incidence of 29.8%.

Statistical Analyses

Statistical analysis was performed using IBM SPSS Statistics 25.0 (IBM Corporation). Descriptive statistical results are shown as mean ± SD for continuous data, number, and percentage for categorical data. χ^2 tests were used for categorical data, and independent t tests or rank-sum tests were used for continuous data depending on whether the data met the normal distribution and homogeneity of variance. The missing data was culled. $P < 0.05$ indicates that the difference is statistically significant.

Prediction Model Building and Verification

Logistic regression analysis was conducted based on the risk factors identified through single-factor analysis. The model was constructed using the "rms" package in R 4.0.5 software (The R Foundation). Using these risk factors, a nomogram model was developed to predict the likelihood of developing PHN. In the nomogram, each risk factor was assigned a specific point value. The total points are indicative of the risk of developing PHN. A higher cumulative point total corresponds to a greater risk of developing PHN.

We created a calibration curve for the model and calculated the C-index to assess the model's predictive accuracy. Furthermore, we generated a receiver operating characteristic (ROC) curve to evaluate the sensitivity and specificity of the predictive model. To assess the clinical utility of the predictive model, we developed a decision curve, analyzing the net benefit rate under various probabilities within the PHN group.

Results

Basic Information

This study enrolled 179 patients with HZ. Five patients were lost to follow-up, leaving a total of 174 patients who completed the study. Among these patients, 52 of them developed PHN, resulting in an incidence rate of 29.9%. The patients were categorized based on the presence or absence of PHN (Fig. 1).

Feature Selection

Univariate analysis revealed that gender, age, prodromal pain, comorbidities, rash area, and a high VAS score during the acute phase were significantly associated with the occurrence of PHN ($P < 0.05$). Conversely, factors such as involved nerve, body mass index, and duration did not exhibit a significant relationship with PHN occurrence ($P > 0.05$). The results of a univariate analysis are shown in Table 1.

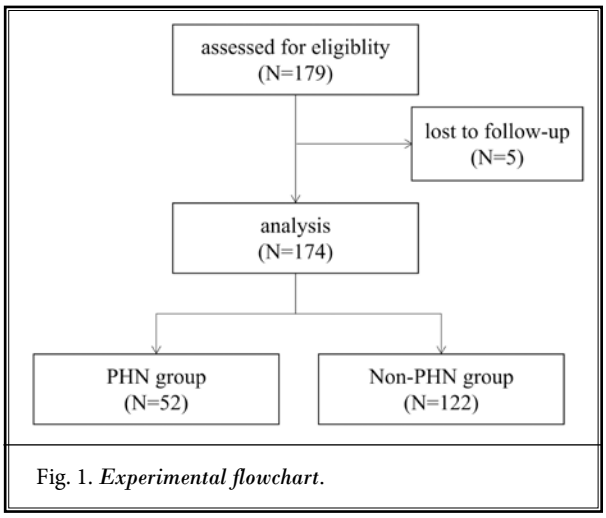

Fig. 1. *Experimental flowchart.*

Logistic Regression Analysis

A logistic regression analysis demonstrated that being a woman, being more than 50 years old, the pain during the prodromal phase, a large rash area, and severe pain in the acute phase are independent risk factors for developing PHN. The results of the logistic regression analysis are shown in Table 2.

Nomogram Design

The 5 factors mentioned were used to construct a logistic regression model in the R programming language, employing the "lrm" function from the rms package. Subsequently, the "plot" function was applied to create a nomogram scoring system. The risk factor with the highest score was "lesion area of 90,000 mm^2," which we awarded 100 points. Following closely, the VAS score in the acute phase was the second highest with 62 points, while "Age > 50 years" ranked third as a risk factor with 32 points. Both gender and the presence of prodromal phase pain received 28 points each (Fig. 2).

Evaluation of the Accuracy and Predictive Effectiveness of the Nomogram Model

To assess the model's accuracy, we calculated the C-index, which yielded a value of 0.81 (95% CI, 0.77-0.95). The model's calibration curve exhibited a strong align-

Table 1. *Comparison of general information and clinical data between the 2 groups.*

Characteristic	PHN	Non-PHN	*P*
Gender, n (%)			
men	12 (23.1)	59 (48.4)	
women	40 (76.9)	63 (51.6)	0.002
Age, n (%)			
> 50 years old	47 (90.4)	86 (70.5)	
≤ 50 years old	5 (9.6)	36 (29.5)	0.005
Prodromal Phase Pain, n (%)			
Yes	39 (75.0)	51 (41.8)	
No	13 (25.0)	71 (58.2)	< 0.001
Comorbidity, n (%)			
Yes	39 (75.0)	63 (51.6)	
No	13 (25.0)	59 (48.4)	0.004
Involved nerve, n (%)			
Trigeminal	10 (19.2)	22 (18.0)	
Cervical	8 (15.4)	16 (13.1)	
Intercostal	24 (46.2)	62 (50.8)	
Lumbosacral	10 (19.2)	22 (18.1)	0.9
BMI, mean (SD)	23.5 ± 3.4	23.2 ± 3.3	0.7
Skin lesion area in mm^2, mean (SD)	6,088.1 ± 10,198.0	15,733.2 ± 19,364.2	0.003
VAS score, mean (SD)	4.9 ± 2.3	6.6 ± 1.9	< 0.0001
Duration in days, mean (SD)	5.2 ± 3.2	6.2 ± 3.6	0.1

BMI = body mass index (kg/m^2); VAS = Visual Analog Scale

Table 2. *Regression analysis of risk factors for PHN in patients with herpes zoster.*

	Regression Coefficient	Odds Ratio	95% CI	*P*
Women	0.979	2.661	1.136-6.230	0.024
Skin lesion area in mm^2	<0.01	1.002	1.001-1.003	<0.01
Prodromal phase pain	0.997	2.711	1.198-6.132	0.017
VAS score	0.021	1.021	1.002-1.041	0.027
> 50 years old	1.107	3.026	0.994-9.212	0.051
Comorbidity	0.631	1.879	0.814-4.340	0.140

ment with the actual curve (Fig. 3). The area under the ROC curve is 0.81 (Fig. 4). The decision curve analysis revealed that the model's accuracy and net benefit were at their peak when the predicted prevalence ranged from 6% to 92%. Beyond this range, the model's accuracy became limited, and the net benefit significantly decreased (Fig. 5).

Discussion

Due to the substantial negative effect of PHN, health care professionals should prioritize HZ management. Patients with a high-risk for PHN should be identified early. To offer clinicians a visual tool for predicting the likelihood of PHN, we developed a nomogram. To the best of our knowledge, our study represents one of the rare and comprehensive attempts to create a predictive model for PHN through a prospective study. This nomogram model has undergone rigorous validation through calibration curve, C-index, and ROC curve analyses, all of which demonstrate its high accuracy. Therefore, we strongly recommend the use of this model, especially in a primary care setting.

This model offers a straightforward means of quickly confirming whether a patient falls into the high-risk population for PHN through a basic physical examination and patient interview. To illustrate, let's consider a 60-year-old man diagnosed with herpes zoster. He reports prodromal phase trunk pain, and has an estimated lesion area of approximately 60,000 mm^2. With the nomogram, one can determine the points associated with each characteristic (age = 32, man = 0, lesion area = 66, prodromal phase pain = 28, acute phase VAS score = 43.4). The total points amount to 169.4, corresponding to an estimated incidence rate of around 80%.

In a previous study, a prediction formula was developed using a random forest plot to calculate the probability of PHN (11). This formula was based on 6 variables: age, Numeric Rating Scale score, Charlson Comorbidity index score, rash site, antiviral therapy, and immunosuppression. Researchers confirmed their formula's accuracy to be 88.33%. However, using the formula requires assigning values to each characteristic and performing computations with a computer. In comparison, our nomogram can estimate PHN incidence through simple manual calculations.

Another model, involving only 2 risk factors, yielded insufficient accuracy (13). An innovative single-center, 12-month, prospective cohort study incorporated the

Self-completed Leeds Assessment of Neuropathic Symptoms and Signs pain scale (S-LANSS) to construct a predictive model; however, this model allows for qualitative rather than quantitative analysis (14).

Our nomogram includes 5 variables: gender, age > 50 years, the presence of prodromal phase pain, a large area, and a high acute phase VAS score. To a certain extent, these variables likely play a role in determining an HZ prognosis. A large lesion area got the most points in this model. This suggests that a large lesion area is the most influential factor in developing PHN.

HZ arises from the reactivation of latent varicella-zoster virus in the dorsal root ganglia of patients

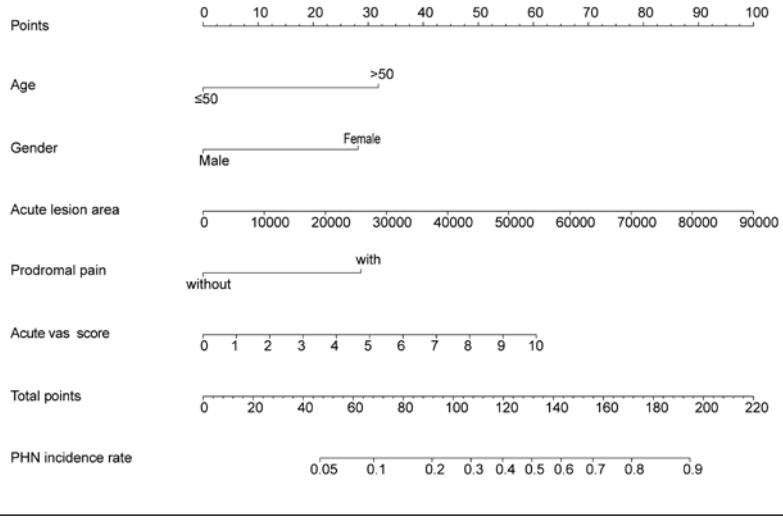

Fig. 2. *Nomogram of postherpetic neuralgia prediction model in patients with herpes zoster. This model comprises 5 factors: age, gender, acute lesion area, Visual Analog Scale score, and the presence of prodromal phase pain. Each factor is associated with a specific point value, and the probability of developing postherpetic neuralgia corresponds to the total points.*

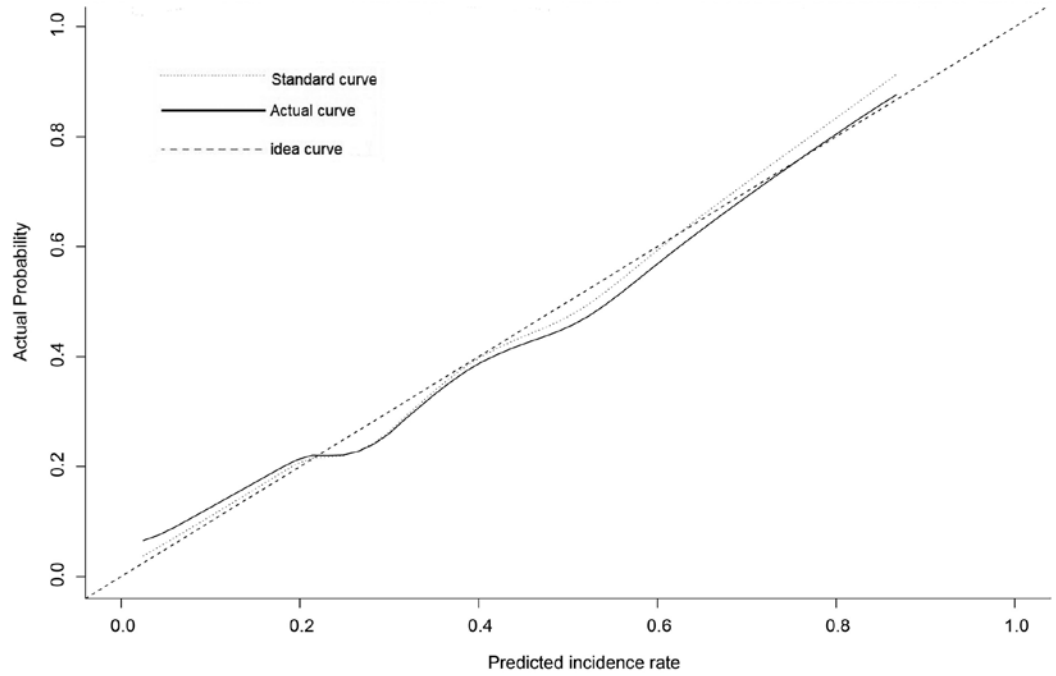

Fig. 3. *Calibration curve of the postherpetic neuralgia prediction model in patients with herpes zoster. The higher the degree of concordance between the standard curve and the actual curve, and the closer it is to the ideal curve, the greater the accuracy of the prediction model.*

(15). Reactivation and continuous replication of the varicella-zoster virus lead to an acute neuroinflammatory response, characterized by hemorrhagic necrosis and demyelination of nerve cells, resulting in neuropathic pain (2,16). The type and area of the rash indicate the level of virus activity. Active viral replication leads to the involvement of more dermatomes, including nonadjacent ones, often accompanied by bleeding or necrosis (17). Simultaneously, more severe nerve damage occurs, leading to prolonged neural repair and continued patient suffering, eventually progressing to chronic pain (18). Importantly, the correlation between rash and PHN remains consistent regardless of age and pain severity. In young patients with less neuralgia, a large lesion area still significantly increases the risk of PHN (19).

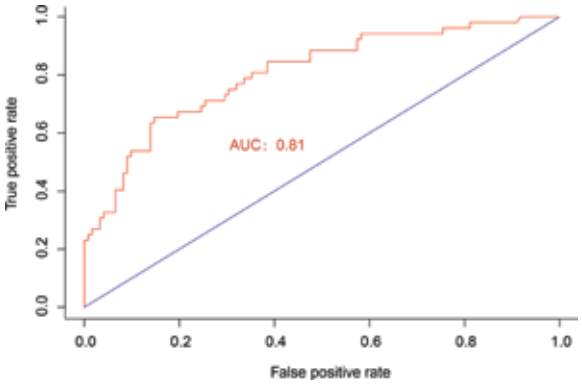

Fig. 4. *Receiver operating characteristic curve to verify the accuracy of the postherpetic neuralgia prediction model in patients with herpes zoster. AUC stands for the area under the curve. The closer it is to one, the greater the prediction accuracy of the model.*

Advanced age is a widely acknowledged risk factor for developing PHN. Reports indicate that approximately 13% of patients with HZ aged 50 years or older will develop PHN (20). An age-related decline in cell-mediated immunity makes older patients more susceptible to PHN (21). Most research has consistently shown that there are gender differences in PHN risk (22). Nevertheless, the psychosocial or biological factors explaining this difference remain unclear. Two explanations for this phenomenon are proposed: first, women's longer average lifespan increases their chances of PHN development; second, women tend to report pain and seek medical advice more frequently.

Furthermore, the presence of prodromal phase

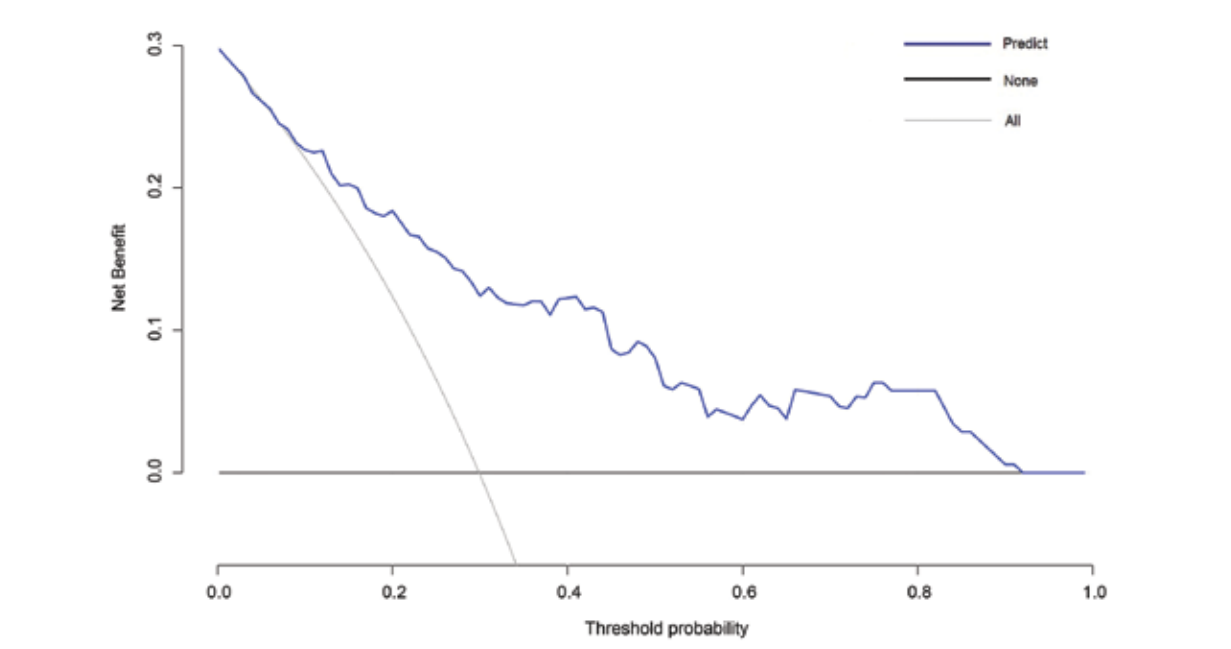

Fig. 5. *Decision curve of the postherpetic neuralgia prediction model patients with herpes zoster. The net benefit is calculated by subtracting the proportion of all patients with a false positive from the proportion of patients with a true positive.*

pain serves as a warning signal. Researchers believe that the presence of prodromal phase pain indicates nerve damage caused by the virus (23). Our study confirms that the presence of prodromal phase pain is associated with an increased risk of developing PHN, which is consistent with previous studies (23,24). Previous research revealed that 24% of patients reporting prodromal phase pain developed PHN, compared to 18% of those without prodromal phase pain (25).

Without a rash, diagnosing HZ becomes considerably challenging, making it harder to detect at a more treatable stage (26). Unilateral pain can result from various diseases before the appearance of a rash, especially in older patients. Pain and difficult-to-diagnose origins can contribute to an increased psychological burden.

Consistent with findings in other studies, prodromal phase pain exhibits a strong correlation with acute herpes zoster pain severity (27). The risk of developing PHN was positively associated with pain severity during the acute phase. Acute pain originates from the neuroinflammatory response triggered by the activation and replication of the virus (28). Intense inflammatory responses increase the likelihood of developing neural plasticity, which in turn is more likely to progress to PHN (29).

Limitations

We acknowledge several limitations in our study. The study was conducted at a single center and had a limited sample size. The small sample size reduces the statistical power of the analyses. In our study, we explored comorbidities as a potential influencing factor and determined that the presence of co-occurring illnesses was not an independent risk factor for PHN. Since each comorbid disorder was not analyzed individually, the results may not align with those of previous studies.

Conclusion

Being a woman, age > 50 years old, prodromal phase pain, a large rash area, and great pain severity in the acute phase affect the incidence of PHN. The prediction model drawn in this study can help physicians identify patients with a high risk of developing PHN and provide aggressive preventive interventions in the acute phase. For low-risk patients, it can also avoid excessive medical treatment, reduce the waste of medical resources, and minimize a patient's economic burden. At the same time, this model is also a practical tool for patients to self-screen.

Data Availability

The data used to support the findings of this study are restricted by the ethics committee of China-Japan Friendship Hospital to protect patient privacy. Data are available only for researchers who meet the criteria for access to confidential data.

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