Retrospective Study

Development and Validation of a Novel Clinical Prediction Model for Postherpetic Neuralgia: Integrating Inflammatory and Coagulation Biomarkers

YanPi Li, MMed[1], NaiChong Hu, MMed[1], BiFa Fan, MD, PhD[2], XiYun Wang, MMed[1], Botao Liu, PhD[2], Peng Mao, PhD[2], Yi Zhang, PhD[2], and YiFan Li, PhD[2]

From: [1]Beijing University of Chinese Medicine, Beijing, 100029, People's Republic of China; [2]Department of Pain Management, China-Japan Friendship Hospital, Beijing, 100029, People's Republic of China

Address Correspondence: Yifan Li, PhD 2 Yinghuayuan East Street Chaoyang District Beijing, People's Republic of China E-mail: liyifan1214@126.com

Disclaimer: YP Li and NC Hu contributed equally to this work. This work was supported by the National High Level Hospital Clinical Research Funding (Numbers 2024-NHLHCRF-PY -22, Clinical Research Funding-2025-NHLHCRF-XKJS-A-04, and 2022-NHLHCRF-YSPY-02) and the National Key Research and Development Program of China (2022YFC3602201).

Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted article.

Article received: 04-03-2025
Revised article received: 06-16-2025
Accepted for publication: 08-08-2025

Free full article: www.painphysicianjournal.com

Background: Postherpetic neuralgia (PHN) is the most common and debilitating complication of herpes zoster, yet predicting PHN occuring remains challenging.

Objectives: Our study aimed to develop and validate a clinical prediction model for PHN based on key demographic, serological, and clinical parameters.

Study Design: Retrospective cohort study.

Setting: This study included 202 patients with herpes zoster treated at the China-Japan Friendship Hospital from December 2023 through November 2024.

Methods: Eligible patients were classified into PHN (n = 89) and non-PHN (n = 113) groups. Clinical and laboratory data were extracted from electronic medical records. Univariate logistic regression ($P < 0.20$) identified candidate predictors, which were further refined using least absolute shrinkage and selection operator regression. A multivariate logistic regression model was constructed, and a predictive nomogram was developed. Model performance was evaluated using the area under the receiver operating characteristic curve (AUC), calibration plots, and decision curve analysis.

Results: Four independent predictors were identified: age ≥ 60 years (odds ratio [OR] = 8.45; 95% CI. 3.94–18.12; $P < 0.001$), higher pain intensity measured by the Numeric Rating Scale (OR = 1.31; 95% CI, 1.07–1.61; $P = 0.009$), elevated D-dimer levels (D-dimer > 0.5 mg/L) (OR = 2.19; 95% CI, 1.10–4.36; $P = 0.026$), and lower neutrophil-to-lymphocyte ratio (≤ 3) (OR = 0.22; 95% CI, 0.10–0.49; $P < 0.001$). The final model demonstrated robust predictive accuracy (AUC = 0.83; 95% CI, 0.78–0.89) and good calibration (Hosmer-Lemeshow test, $P = 0.326$). A decision curve analysis confirmed the model's clinical utility within a risk threshold range of 8%–85%.

Limitations: Our study is limited by its single-center design and small sample size.

Conclusion: Our study developed a reliable and clinically applicable nomogram for PHN prediction in patients with herpes zoster. The model incorporates age, pain intensity, D-dimer level, and neutrophil-to-lymphocyte ratio,, enabling early risk stratification and optimized patient management. Future prospective studies are warranted to validate this model's utility across diverse populations.

Key words: Postherpetic neuralgia, herpes zoster, predictive model, nomogram, risk factors, D-dimer, neutrophil-to-lymphocyte ratio, retrospective cohort study

Pain Physician 2026: 29:E229-E237

Postherpetic neuralgia (PHN) is the most common chronic complication of herpes zoster (HZ) (1). It is characterized by persistent pain lasting more than 90 days after complete resolution of cutaneous lesions (2). The lifetime incidence of HZ ranges from 10% to 30% (3), with 5% to 35% of affected patients developing PHN (4).PHN-related pain is typically severe and may persist for months or even years (1,2), severely compromising a patients' quality of life, disrupting sleep, and imposing substantial physical, psychological, and financial burdens (5-8). Existing treatments are ineffective for nearly half of patients with PHN (9), but timely and effective interventions for HZ can significantly reduce its incidence (10). Therefore, accurate and intuitive prediction of PHN occuring is crucial for facilitating timely and proactive interventions.

Chronic pain pathophysiology is closely linked to inflammation (11,12). The coagulation cascade has also been implicated in neurological disorders (13,14). Measuring inflammatory and coagulation markers in peripheral blood is an objective, quantifiable, well established, convenient, and cost-effective approach (15). While some studies have explored the association between inflammatory markers and PHN, research on coagulation factors and pathways remains limited (16,17). Our retrospective cohort study analyzed data from 202 patients with HZ, integrating clinical factors with peripheral blood inflammatory and coagulation markers to assess their feasibility and reliability in predicting PHN.

Methods

Study Design and Population

Our retrospective cohort study analyzed 202 patients with HZ who were treated in the inpatient departments of the China-Japan Friendship Hospital from December 2023 through November 2024. The study protocol was approved by the Ethics Committee of the China-Japan Friendship Hospital (approval number 2023-KY-343), and written informed consents were obtained. Our research adhered to the ethical guidelines outlined in the Declaration of Helsinki (October 2013).

Inclusion and Exclusion Criteria

The inclusion criteria were: 1) age ≥ 18 years; 2) diagnosed with HZ; 3) within 14 days of HZ onset.

The exclusion criteria were: 1) incomplete clinical data; 2) cognitive impairment or psychiatric disorders affecting data reliability; 3) recent use (within 2 months pre-enrollment) of anticoagulants, antiplatelet agents, antibiotics, corticosteroids, or estrogen-based medications known to alter hematologic/coagulation parameters; 4) invasive procedures within the past month; 5) active smoking (≥ 1 cigarettes/d) or daily ethanol intake (> 12 g/d) within the past 6 months; 6) concurrent infectious diseases (excluding HZ) within 30 days; 7) comorbidities potentially influencing hematologic/coagulation profiles, including diabetes, hypertension, cardiovascular/cerebrovascular diseases, malignancies, thyroid dysfunction, autoimmune disorders, hematologic diseases, or organ dysfunction; 8) pregnancy or lactation.

Data Collection

Clinical data were extracted from the hospital's electronic medical record system using the ICD-10 diagnostic code for herpes zoster (B02.9). All patients included in the analysis were hospitalized for acute herpes zoster. The presence of PHN was assessed through follow-up, based on telephone interviews and review of follow-up documentation in both inpatient and outpatient electronic medical records. The dataset was categorized into 3 domains: 1) demographics: date of clinical visit, age, gender, body mass index (BMI), and mean arterial pressure; 2) Disease characteristics: pain intensity (Numeric Rating Scale [NRS-11]), dermatomal distribution of lesions (categorized as cranial, cervical, thoracic, or lumbosacral nerve involvement), and Traditional Chinese Medicine therapeutic engagement. (3) Serological biomarkers: neutrophil-to-lymphocyte ratio (NLR), derived neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, monocyte-to-neutrophil ratio, systemic immune-inflammation index, hemoglobin, mean platelet volume, prothrombin activity, international normalized ratio, activated partial thromboplastin time, fibrinogen, thrombin time, D-dimer, and fibrinogen degradation products.

Definitions

HZ was clinically diagnosed by board-certified physicians based on characteristic vesicular eruptions and associated neuropathic pain. PHN was strictly defined as persistent pain lasting ≥ 3 months after complete resolution of cutaneous lesions. Clinician-diagnosed HZ and PHN exhibited high diagnostic accuracy.

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics 26.0 (IBM Corporation) and R 4.3.2 (The R Foundation). A two-sided *P* value < 0.05 was considered statistically significant.

Descriptive Statistics

Continuous variables following a normal distribution were presented as mean (SD) and compared using an independent samples t test. Non-normally distributed continuous variables were expressed as median (interquartile range) and analyzed using the Mann-Whitney U test. Categorical variables were summarized as frequencies (percentages) and compared using the χ^2 test or Fisher's exact test, as appropriate.

Model Development

Multicollinearity among candidate predictors was assessed using variance inflation factors. A variance inflation factor > 10 indicated significant collinearity, necessitating variable exclusion. Potential predictors of PHN were initially identified via univariate logistic regression ($P < 0.20$). Feature selection and optimization were subsequently performed using least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation to mitigate overfitting. Variables retained under the one-standard-error criterion (λ.1se) were incorporated into a multivariate logistic regression model to develop a clinical prediction nomogram.

Model performance was assessed using receiver operating characteristic curves, with the area under the curve quantifying discriminative ability. Calibration accuracy was evaluated through calibration plots with bootstrapping (1,000 resamples), while clinical utility was assessed using decision curve analysis.

Sample Size Estimation

The required sample size was estimated based on the 10 events per variable criterion for multivariate analysis. Assuming 3–5 candidate predictors in the final model, at least 50 PHN events were necessary. Given the reported PHN incidence rate of 29.8% among Chinese patients with HZ, the minimum calculated sample size was ≥ 168. Ultimately, a total of 202 eligible patients were included, ensuring adequate statistical power for model development.

Results

Baseline Characteristics

A total of 260 patients were initially enrolled, with 58 excluded due to incomplete data or loss to follow-up, yielding a final cohort of 202 patients. PHN developed in 89 patients (44.06%), who were classified into the PHN group, while the remaining 113 constituted the non-PHN group. The cohort included 68 men and 134 women. The average age of the patients was 62.84 ± 11.98 years. All patients received antiviral and neurotrophic therapy. A detailed flowchart of patient recruitment and data processing is presented in Fig. 1.

A comparative analysis revealed significant intergroup differences ($P < 0.05$) in NRS-11 score, platelet-to-lymphocyte ratio, age, NLR and D-dimer level. No statistically significant differences ($P \geq 0.05$) were observed in other variables. Demographic and baseline characteristics are provided in Table 1.

Variables Selection

In the univariate logistic regression analysis, variables with $P < 0.2$, including NRS-11 score, derived neutrophil-to-lymphocyte ratio, platelet-to-lymphocyte ratio, systemic immune-inflammation index, prothrombin activity, international normalized ratio, activated partial thromboplastin time, dermatomal distribution of lesions, body mass index, age, D-dimer level, and NLR, were selected for further analysis using LASSO regression (Supplement Table 1). Variables with $P \geq 0.2$, such as gender, Traditional Chinese Medicine, monocyte-to-

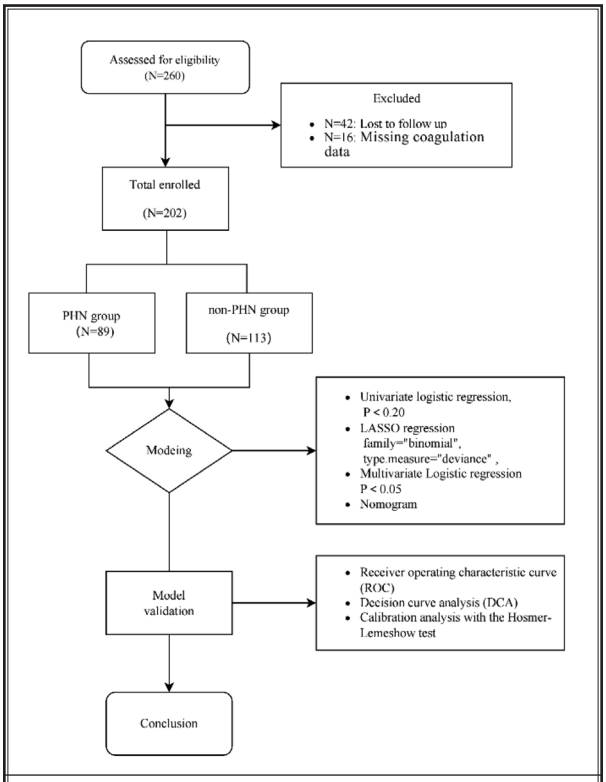

Fig. 1. *Study flowchart.*

Table 1. *Baseline and clinical data of the study population.*

Variables	Total (n = 202)	Non-PHN Group (n = 113)	PHN Group (n = 89)	Statistic	*P*
Age, n(%)				χ^2 = 43.87	< 0.001
< 60 years	79 (39.11)	67 (59.29)	12 (13.48)		
≥ 60 years	123 (60.89)	46 (40.71)	77 (86.52)		
Gender, n (%)				χ^2 = 0.08	0.773
Women	134 (66.34)	74 (65.49)	60 (67.42)		
Men	68 (33.66)	39 (34.51)	29 (32.58)		
BMI, n(%)				χ^2 = 4.46	0.216
BMI < 18.5 kg/m²	9 (4.46)	3 (2.65)	6 (6.74)		
18.5kg/m² ≤ BMI < 24 kg/m²	101 (50.00)	63 (55.75)	38 (42.70)		
24kg/m² ≤ BMI < 28 kg/m²	72 (35.64)	37 (32.74)	35 (39.33)		
28kg/m² ≤ BMI	20 (9.90)	10 (8.85)	10 (11.24)		
MAP, Mean ± SD	91.38 ± 11.00	91.27 ± 10.89	91.52 ± 11.19	t = -0.16	0.875
NRS-11, M (IQR)	4.00 (3.00–5.50)	4.00 (3.00–5.00)	5.00 (4.00–6.00)	Z = -4.25	<.001
Dermatomal distribution of lesions, n (%)				χ^2 = 2.70	0.441
Cranial	60 (29.70)	29 (25.66)	31 (34.83)		
Cervical	26 (12.87)	17 (15.04)	9 (10.11)		
Thoracic	69 (34.16)	41 (36.28)	28 (31.46)		
Lumbosacral	47 (23.27)	26 (23.01)	21 (23.60)		
TCM therapeutic engagement, n(%)				χ^2 = 0.12	0.730
No	132 (65.35)	75 (66.37)	57 (64.04)		
Yes	70 (34.65)	38 (33.63)	32 (35.96)		
NLR, n (%)				χ^2 = 10.61	0.001
≤ 3	147 (72.77)	72 (63.72)	75 (84.27)		
> 3	55 (27.23)	41 (36.28)	14 (15.73)		
dNLR, M (IQR)	1.33 (1.24–1.46)	1.34 (1.26–1.50)	1.33 (1.23–1.43)	Z = -1.30	0.193
PLR, M (IQR)	120.12 (92.43–160.59)	129.91 (96.99–166.48)	112.66 (87.17–146.59)	Z = -1.99	0.046
MNR, M (IQR)	0.12 (0.09–0.15)	0.11 (0.09–0.15)	0.12 (0.10–0.14)	Z = -0.71	0.475
SII, M (IQR)	386.13 (277.23–592.13)	386.56 (289.16–624.18)	367.05 (269.46–529.61)	Z = -1.51	0.131
HGB, Mean ± SD	131.74 ± 14.49	131.81 ± 14.28	131.65 ± 14.83	t = 0.07	0.941
MPV, M (IQR)	9.90 (9.12–10.50)	9.70 (9.20–10.30)	10.10 (9.00–10.70)	Z = -1.33	0.183
PTA, M (IQR)	102.00 (95.00–108.00)	103.00 (97.00–109.00)	100.00 (95.00–108.00)	Z = -1.46	0.146
INR, M (IQR)	0.99 (0.96–1.02)	0.98 (0.95–1.01)	0.99 (0.96–1.03)	Z = -1.39	0.164
APTT, M (IQR)	34.05 (32.50–36.38)	34.00 (32.50–35.90)	34.20 (32.60–36.80)	Z = -1.08	0.281
FIB, M (IQR)	3.34 (2.97–3.82)	3.24 (2.97–3.86)	3.45 (2.99–3.80)	Z = -0.66	0.506
TT, M (IQR)	16.80 (16.30–17.40)	16.90 (16.30–17.40)	16.80 (16.30–17.40)	Z = -0.72	0.471
D-dimer, n (%)				χ^2 = 7.81	0.005
≤ 0.5 mg/L	113 (55.94)	73 (64.60)	40 (44.94)		
> 0.5 mg/L	89 (44.06)	40 (35.40)	49 (55.06)		
FDP, M (Q_1, Q_3)	1.00 (1.00, 2.53)	1.00 (1.00, 2.28)	1.00 (1.00, 2.88)	Z = -1.43	0.154

Abbreviations: PHN, postherpetic neuralgia; BMI, body mass index; MAP, mean arterial pressure; SD, standard deviation; NRS, Numerical Rating Scale; IQR, interquartile range; TCM, Traditional Chinese Medicine; NLR, neutrophil to lymphocyte ratio; dNLR, derived neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; MNR, monocyte to neutrophil ratio; SII, systemic immune inflammation index; HGB, hemoglobin; MPV, mean platelet volume; PTA, prothrombin activity; INR, international normalized ratio; APTT, activated partial thromboplastin time; FIB, fibrinogen; TT, thrombin time; FDP, fibrinogen degradation products; t, t test; Z, Mann Whitney test; χ^2, Chi square test; M, Median.

neutrophil ratio, hemoglobin, mean platelet volume, mean arterial pressure, thrombin time, fibrinogen degradation products, activated partial thromboplastin time, and fibrinogen, were excluded. LASSO regression with 10-fold cross-validation was performed to identify key predictors, determining the optimal regularization parameter (λ) using both the minimum criteria and the one-standard-error (1.se) rule. Four noncollinear predictors—age, D-dimer level, NLR, and NRS-11 score—were retained (λ.1.seE = 0.06289906) (Figs. 2A, 2B). Subsequent multivariate logistic regression analysis confirmed that age (β = 2.13; *P* < 0.001; odds ratio [OR] = 8.45; 95% CI, 3.94–18.12), D-dimer level (β = 0.78; *P* = 0.026; OR = 2.19; 95% CI, 1.10–4.36), and NRS-11 score (β = 0.27; *P* = 0.009; OR = 1.31; 95% CI, 1.07–1.61) were significant risk factors, while NLR (β = -1.52; *P* < 0.001; OR = 0.22; 95% CI, 0.10–0.49) was inversely associated with the outcome. The model intercept was -2.86 (*P* < 0.001) (Table 2).

Predictive Model Construction

Figure 3 presents a nomogram for predicting PHN in patients with HZ, incorporating 4 key predictors: age, D-dimer level, NLR, and NRS-11 score. The nomogram assigns individual scores to each variable and maps the total score to the corresponding PHN risk probability. Specifically, each one point increase in NRS-11 adds 12.5 points, while age > 60 years, D-dimer level > 0. 5mg/L, and NLR ≤ 3 contribute 98.61, 36.11, and 70.37 points, respectively. For instance, a patient aged ≥ 60 years with an NRS-11 score of 7, NLR ≤ 3, and D-dimer level > 0.5 mg/L would have an estimated PHN probability of 85.7%.

Evaluation

The predictive performance of the model was assessed using multiple validation metrics. The area under the curve was 0.83 (95% CI, 0.78–0.89) (Fig. 4), indicating strong discriminative ability. Calibration analysis with the Hosmer-Lemeshow test showed a good fit (*P* = 0.326, Fig. 5), demonstrating close alignment between predicted and actual probabilities. A decision curve analysis identified an optimal risk threshold range of 8%–85% (Fig. 6), reinforcing the model's clinical applicability.

Discussion

PHN is a major complication of HZ that severely affects a patient's quality of life. While various predictive models have been proposed, most rely primarily on clinical symptoms, with limited incorporation of objective serological markers. Our study is the first to integrate coagulation factors into PHN risk assessment, highlighting their potential role in disease development. We developed and validated a novel predictive model incorporating age, NRS-11 score, D-dimer level, and the NLR, demonstrating strong discriminative ability (area under the curve = 0.83) and clinical applicability.

Our findings not only reinforce existing risk stratification frameworks, but also provide new insights into the interplay between coagulation, inflammation, and neuropathic pain. The predictive nomogram established in our study offers a practical tool for early identification of high-risk patients, facilitating timely intervention and improved clinical management.

Advanced age has been confirmed by multiple

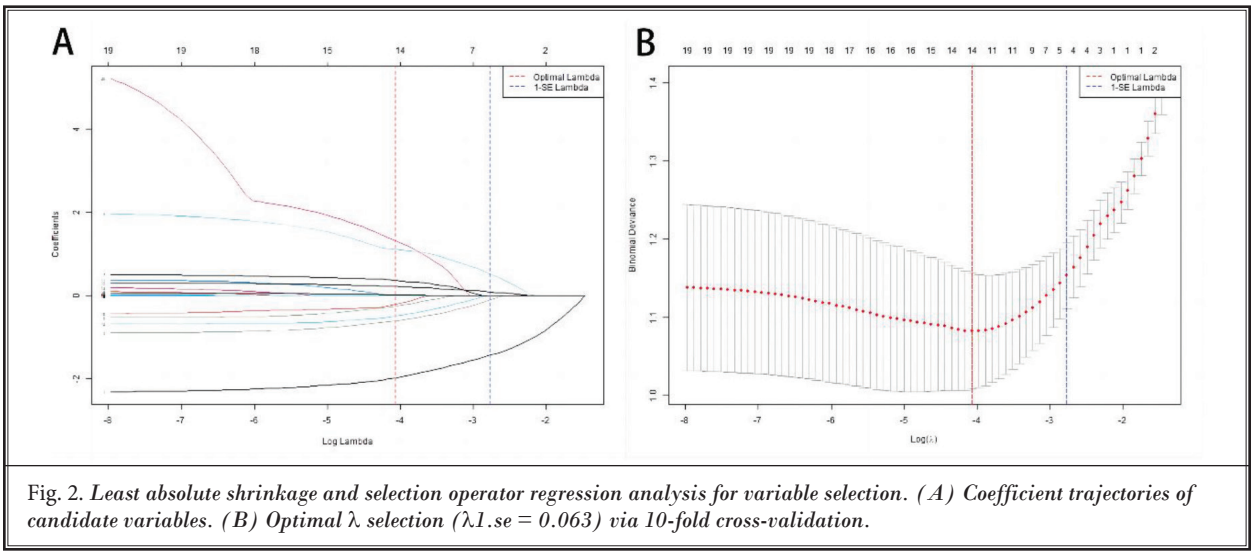

Fig. 2. *Least absolute shrinkage and selection operator regression analysis for variable selection. (A) Coefficient trajectories of candidate variables. (B) Optimal λ selection (λ1.se = 0.063) via 10-fold cross-validation.*

studies as an independent risk factor for PHN and is significantly associated with its occurrence (18–20). In the overall study population, the incidence of PHN increases with age (18), with the risk of PHN rising by 1.52-fold per decade (21), particularly among individuals older than 60 (16), which aligns with our findings. Our study revealed that the prevalence of PHN in patients older than 60 (86.52%) was significantly higher than in those younger than 60 (13.48%). This may be attributed to age-related decline in cellular immune function, impairing the body's ability to effectively clear the varicella-zoster virus and exacerbating nerve damage (18,22).

Pain is one of the common clinical manifestations of acute HZ, and the NRS-11 scale is often used to assess pain severity in patients with HZ. A possible mechanism is that the severity of pain in the acute phase positively correlates with the degree of nerve damage; more severe nerve damage increases PHN risk (20). Another study found that among patients with HZ who have malignancies, higher NRS-11 scores, indicating greater pain severity, were associated with an elevated PHN risk (23).

Table 2. *Multivariable logistic regression analysis.*

Variables	β	S.E	Z	*P*	OR (95% CI)
Intercept	-2.86	0.58	-4.96	< 0.001	0.06 (0.02–0.18)
Age					
< 60 years					1.00 (Reference)
≥ 60 years	2.13	0.39	5.48	< 0.001	8.45 (3.94–18.12)
NRS-11	0.27	0.11	2.59	0.009	1.31 (1.07–1.61)
NLR					
≤ 3					1.00 (Reference)
> 3	-1.52	0.41	-3.68	< 0.001	0.22 (0.10–0.49)
D-dimer					
≤ 0.5 mg/L					1.00 (Reference)
> 0.5 mg/L	0.78	0.35	2.23	0.026	2.19 (1.10–4.36)

OR: Odds Ratio, NRS-11: Numeric Rating Scale, NLR: neutrophil to leukocyte ratio

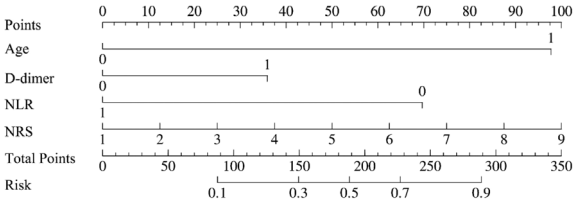

Fig. 3. *Nomogram prediction model.*
NLR: neutrophil to leukocyte ratio, NRS-11: Numeric Rating Scale

Our study observed a negative correlation between the NLR and PHN risk. However, previous studies have reported that elevated NLR is associated with an increased risk of PHN (11). A study on living donor liver transplantation found that a higher preoperative NLR significantly increased the risk of postoperative HZ and PHN (24). While some studies have not directly examined NLR, they have demonstrated that lymphopenia significantly increases PHN incidence (25,26).

An elevated NLR reflects an increase in neutrophils and/or a decrease in lymphocytes, indicating a heightened systemic inflammatory response and impaired humoral and cellular immunity, which may contribute to PHN development (11,27). However, other studies have suggested no significant association between the NLR and PHN risk (28). A recent machine-learning-based predictive model found that the median NLR was higher in patients who did not have PHN compared to those who developed PHN, supporting our findings (29).

The inconsistency in NLR-PHN associations may stem from differences in study populations, research design, or the complex pathophysiology of PHN. Our cohort consisted exclusively of hospitalized patients, who are more likely to receive aggressive treatment. Early interventions, such as antiviral therapy, may have mitigated immune dysfunction and lymphopenia,

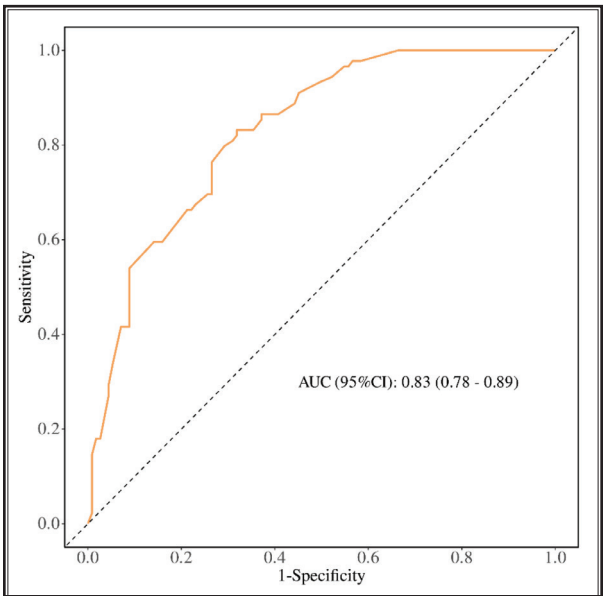

Fig. 4. *Receiver operating characteristic curve of the Postherpetic Neuralgia Prediction Model.*
AUC: area under the curve

potentially influencing NLR levels. Moreover, while baseline neutrophil counts in older adults are generally stable, their stress-induced neutrophil response may be impaired, suggesting a unique immune balance in this population. Future research should control potential confounders, systematically assess treatment effects, and conduct multicenter, large-scale clinical and mechanistic studies.

Our study identified D-dimer level as a potential risk factor for the progression of HZ to PHN. As a soluble fibrin degradation product generated during thrombus breakdown, D-dimer level serves as a biomarker of activated coagulation and fibrinolysis (30). Elevated D-dimer levels have been associated with various adverse conditions, including painful diabetic peripheral neuropathy (31), malignancies (32), pulmonary embolism (33), and coronary heart disease (34). Although no direct studies have linked D-dimer levels to PHN, evidence suggests that increased D-dimer levels correlate with the severity of nerve damage and poor prognosis (35,36). Additionally, in vitro studies indicate an association between D-dimer levels and neuroinflammatory cytokines (37), implying that enhanced fibrinolysis and elevated D-dimer levels may impair nerve repair. Given the complex interplay between coagulation, inflammation, and immune responses, the D-dimer level may serve as an indirect marker reflecting their involvement in PHN progression (38,39).

Mechanistically, D-dimer level may represent a critical link between coagulation dysregulation and neuroimmune interactions. The varicella-zoster virus can spread to vascular structures, leading to varicella-

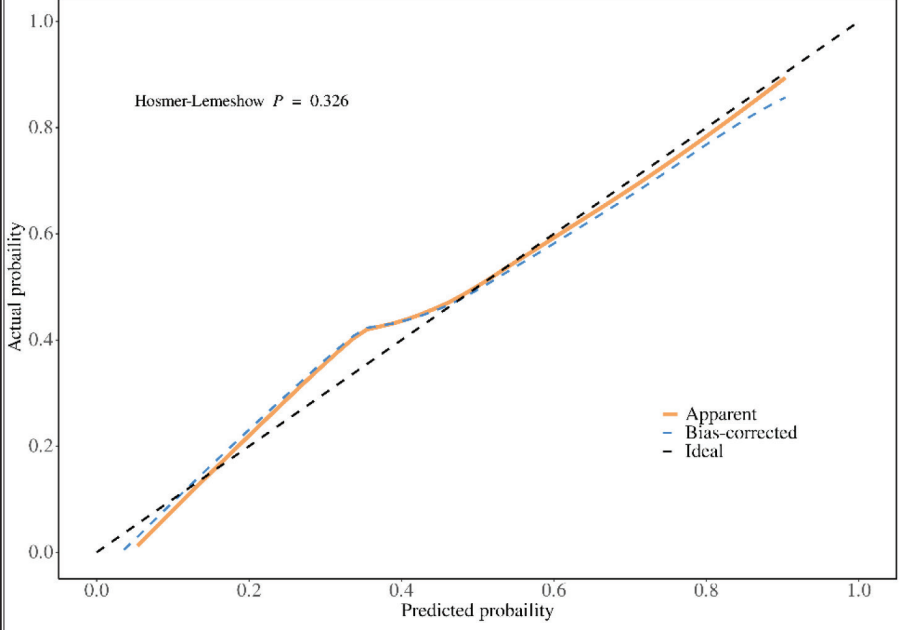

Fig. 5. *Calibration plot of the Postherpetic Neuralgia Prediction Nomogram.*

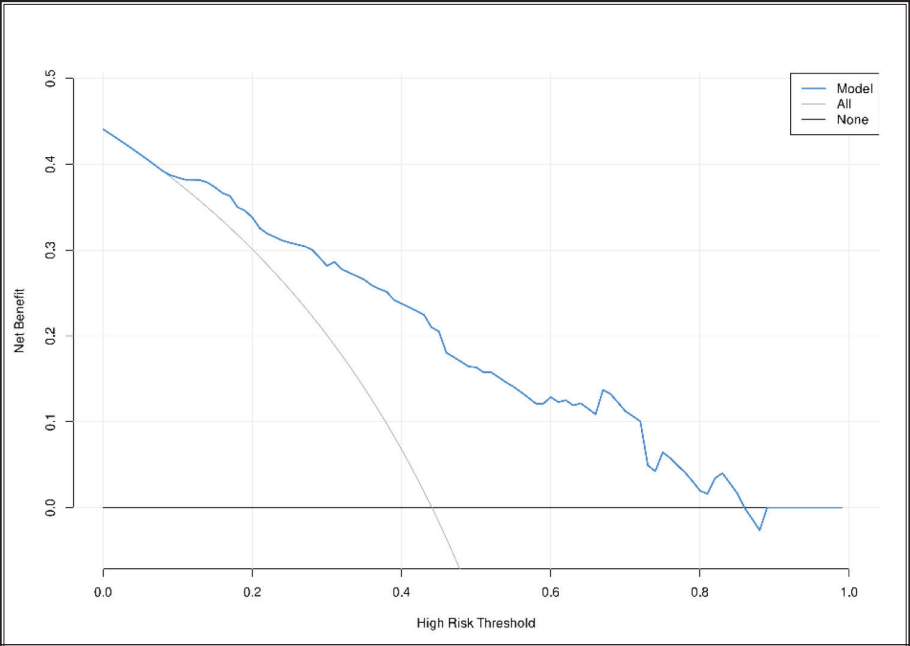

Fig. 6. *Decision curve analysis of the Postherpetic Neuralgia Risk Nomogram.*

zoster virus-induced vasculopathy, which may further amplify thromboinflammatory cascades, hinder neural repair through fibrinolytic activation, and exacerbate neuroinflammation. Moreover, we hypothesize that D-dimer activates protease-activated receptors, thereby inducing the release of pro-inflammatory cytokines such as interleukin-6 and tumor necrosis factor-α, as well as glial cell activation in the dorsal horn, ultimately promoting central sensitization (37,40). This aligns with the studies that reported that beyond peripheral skin dissemination, varicella-zoster virus may also invade arterial structures, contributing to vascular pathology and further complicating the progression of PHN (41).

Limitations and Outlook

Our study has several limitations. First, the single-center design, limited sample size, and strict inclusion and exclusion criteria may reduce statistical power and limit the external validity of the model, particularly in older or more clinically complex populations. Second, all patients were hospitalized, which may introduce selection bias, as their pain severity and PHN risk could be higher than in the general population. Third, the retrospective design is inherently subject to bias, underscoring the need for prospective validation in independent, multicenter cohorts across diverse ethnic and geographic backgrounds.

Future research should focus on validating our findings in larger, prospective, and multicenter cohorts that better reflect real-world populations. Incorporating novel biomarkers and imaging indicators may further improve the model's predictive performance. Additionally, studies should explore early interventional strategies—such as optimized antiviral timing and immunomodulatory therapies—to enhance PHN prevention and support personalized patient management.

Conclusions

Our findings suggest that age, NRS-11 score, NLR and D-dimer level are independent predictors of PHN in patients with HZ. These findings may help clinicians stratify high-risk patients early, enabling proactive interventions such as optimized analgesia or targeted antiviral therapy to mitigate PHN development. Future studies should validate these biomarkers in multicenter cohorts and explore whether modulating these predictors (e.g., anticoagulation for elevated D-dimer levels) could reduce PHN incidence, potentially informing novel therapeutic strategies.

Acknowledgments

We would like to thank all the patients of this project and investigators for collecting the data.

Author Contributions

Yanpi Li and Naichong Hu were responsible for data collection, data analysis, and manuscript writing. Bifa Fan contributed to study conception, design, and funding acquisition. Xiyun Wang participated in data collection, data analysis, and manuscript revision. Botao Liu assisted with data collection and provided funding support. Yifan Li performed manuscript review and editing, and secured research funding.

Consent for Publication

All authors gave consent for the publication of the article.

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.

Ethical approval and consent to participate

this study's protocol was approved by the Ethics Committee of China-Japan Friendship Hospital (ethics approval number: 2023-KY-343); written informed consent was obtained.

References

1. Johnson RW, Rice ASC. Clinical practice. Postherpetic neuralgia. *N Engl J Med* 2014; 371:1526-1533.
2. Johnson RW, Alvarez-Pasquin MJ, Bijl M, et al. Herpes zoster epidemiology, management, and disease and economic burden in Europe: a multidisciplinary perspective. *Ther Adv Vaccines* 2015; 3:109-120.
3. Thomas SL, Hall AJ. What does epidemiology tell us about risk factors for herpes zoster? *Lancet Infect Dis* 2004; 4:26-33.
4. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: Towards a global perspective. *BMJ Open* 2014; 4:e004833.
5. Bugden S, Friesen K, Falk J, Alessi-Severini S, Chateau D. Price of pain: Population-based cohort burden of disease analysis of medication cost of herpes zoster and postherpetic neuralgia. *JPR* 2016; 9:543-550.
6. Chen P, Chen Z, Xiao Y, et al. Characteristics and economic burden of hospitalized patients with herpes zoster

in China, before vaccination. *Hum Vaccin Immunother* 2023; 19:2268990.

7. Johnson RW, Bouhassira D, Kassianos G, Leplège A, Schmader KE, Weinke T. The impact of herpes zoster and post-herpetic neuralgia on quality-of-life. *BMC Med* 2010; 8:37.
8. Södergren E, Mårdberg K, Nishimwe M, et al. Incidence and burden of herpes zoster in Sweden: A regional population-based register study. *Infect Dis Ther* 2024; 13:121-140.
9. Forbes HJ, Bhaskaran K, Thomas SL, et al. Quantification of risk factors for postherpetic neuralgia in herpes zoster patients: A cohort study. *Neurology* 2016; 87:94-102.
10. Fan HR, Zhang EM, Fei Y, Huang B, Yao M. Early Diagnosis of Herpes Zoster Neuralgia: A Narrative Review. *Pain Ther*. 2023;12(4):893-901.
11. Li Y, Jin J, Kang X, Feng Z. Identifying and evaluating biological markers of postherpetic neuralgia: A comprehensive review. *Pain Ther* 2024; 13:1095-1117.
12. Sommer C, Leinders M, Üçeyler N. Inflammation in the pathophysiology of neuropathic pain. *Pain* 2018; 159:595-602.
13. De Luca C, Virtuoso A, Maggio N, Papa M. Neuro-coagulopathy: Blood coagulation factors in central nervous system diseases. *IJMS* 2017; 18:2128.
14. Gofrit S, Shavit-Stein E. The neuro-glial coagulonome: The thrombin receptor and coagulation pathways as major players in neurological diseases. *Neural Regen Res* 2019; 14:2043.
15. Moukas SI, Kasimir-Bauer S, Tewes M, et al. Ratios of monocytes and neutrophils to lymphocytes in the blood predict benefit of CDK4/6 inhibitor treatment in metastatic breast cancer. *Sci Rep* 2023; 13:21262.
16. Cai M, Yin J, Zeng Y, Liu H, Jin Y. A prognostic model incorporating relevant peripheral blood inflammation indicator to predict postherpetic neuralgia in patients with acute herpes zoster. *JPR* 2024; 17:2299-2309.
17. Lin Z, Yu L yan, Pan S yi, Cao Y, Lin P. Development of a prediction model and corresponding scoring table for postherpetic neuralgia using six machine learning algorithms: A retrospective study. *Pain Ther* 2024; 13:883-907.
18. Forbes HJ, Thomas SL, Smeeth L, et al. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016; 157:30-54.
19. Wang C, Song X, Liu J, Song Y, Gao J. Analysis of risk factors and development and validation of a dynamic nomogram for postherpetic neuralgia: A retrospective study. *JPR* 2024; 17:3935-3948.
20. Zhou H, Wang Z, Jin H, Chen X, Lei L. A systematic review and meta-analysis of independent risk factors for postherpetic neuralgia. *Ann Palliat Med* 2021; 10:12181-12189.
21. Ding S, Wen S, Kang H, Zhang H, Guo H, Li Y. Association of the incidence of postherpetic neuralgia with early treatment intervention of herpes zoster and patient baseline characteristics: A systematic review and meta-analysis of cohort studies. *Int J Infect Dis* 2024; 147:107181.
22. Liu Q, Han J, Zhang X. Peripheral and central pathogenesis of postherpetic neuralgia. *Skin Res Technol* 2024; 30:e13867.
23. Li H, Gong G, Wang J, et al. Analysis of risk factors for postherpetic neuralgia in patients with postmalignancy herpes zoster. *Pain Physician* 2023; 26:E397-E403.
24. Sim JH, Moon YJ, Kim SH, et al. Association between neutrophil-lymphocyte ratio and herpes zoster infection in 1688 living donor liver transplantation recipients at a large single center. *Biomedicines* 2021; 9:963.
25. Yue J, Yao M. Humoral cytokine levels in patients with herpes zoster: A meta-analysis. *JPR* 2024; 17:887-902.
26. Peng Z, Guo J, Zhang Y, et al. Development of a model for predicting the effectiveness of pulsed radiofrequency on zoster-associated pain. *Pain Ther* 2022; 11:253-267.
27. Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *BLL* 2021; 122:474-488.
28. Kim JY, Park GH, Kim MJ, et al. Usefulness of inflammatory markers for the prediction of postherpetic neuralgia in patients with acute herpes soster. *Ann Dermatol* 2018; 30:158.
29. Park SJ, Han J, Choi JB, Min SK, Park J, Choi S. Deciphering risk factors for severe postherpetic neuralgia in patients with herpes zoster: An interpretable machine learning approach. *Reg Anesth Pain Med* 2025; https://rapm.bmj.com/content/early/2025/01/08/rapm-2024-106003.long
30. Weitz JI, Fredenburgh JC, Eikelboom JW. A test in context: D-dimer. *J Am Coll Cardiol* 2017; 70:2411-2420.
31. Zhuang L, Yu C, Xu F, et al. Increased plasma D-dimer levels may be a promising indicator for diabetic peripheral neuropathy in type 2 diabetes. *Front Endocrinol* 2022; 13:930271.
32. Lei X, Zhang T, Deng Z, Jiang T, Hu Y, Yang N. Coagulation markers as independent predictors of prostate cancer aggressiveness: A retrospective cohort study. *Sci Rep* 2023; 13:16073.
33. Kearon C, De Wit K, Parpia S, et al. Diagnosis of pulmonary embolism with D-dimer adjusted to clinical probability. *N Engl J Med* 2019; 381:2125-2134.
34. Danesh J, Whincup P, Walker M, et al. Fibrin D-dimer and coronary heart disease: Prospective study and meta-analysis. *Circulation* 2001; 103:2323-2327.
35. Fujiwara G, Okada Y, Sakakibara T, Yamaki T, Hashimoto N. The association between D-dimer levels and long-term neurological outcomes of patients with traumatic brain injury: An analysis of a nationwide observational neurotrauma database in Japan. *Neurocrit Care* 2022; 36:483-491.
36. Zhang J, He M, Song Y, Xu J. Prognostic role of D-dimer level upon admission in patients with traumatic brain injury. *Medicine (Baltimore)* 2018; 97:e11774.
37. Robson SC, Shephard EG, Kirsch RE. Fibrin degradation product D-dimer induces the synthesis and release of biologically active IL-1β, IL-6 and plasminogen activator inhibitors from monocytes in vitro. *Br J Haematol* 1994; 86:322-326.
38. De Los Reyes-García AM, Aroca A, Arroyo A, et al. Neutrophil extracellular trap components increase the expression of coagulation factors. *Biomed Rep* 2019; 10:195-201.
39. Gaertner F, Massberg S. Blood coagulation in immunothrombosis—At the frontline of intravascular immunity. *Semin Immunol* 2016; 28:561-569.
40. Kawasaki Y, Zhang L, Cheng JK, Ji RR. Cytokine mechanisms of central sensitization: Distinct and overlapping role of interleukin-1β, interleukin-6, and tumor necrosis factor-α in regulating synaptic and neuronal activity in the superficial spinal cord. *J Neurosci* 2008; 28:5189-5194.
41. Nagel MA, Bubak AN. Varicella zoster virus vasculopathy. *J Infect Dis* 2018; 218:S107-S112.

Supplement Table 1. *Univariate logistic regression analysis*.

Variables	β	S.E	Z	*P*	OR (95% CI)
Gender					
Women					1.00 (Reference)
Men	-0.09	0.30	-0.29	0.773	0.92 (0.51–1.65)
Age					
< 60 years					1.00 (Reference)
≥ 60 years	2.23	0.36	6.13	<.001	9.35 (4.57–19.10)
Dermatomal distribution of lesions					
Cranial					1.00 (Reference)
Cervical	-0.70	0.49	-1.44	0.149	0.50 (0.19–1.29)
Thoracic	-0.45	0.36	-1.26	0.208	0.64 (0.32–1.28)
Lumbosacral	-0.28	0.39	-0.72	0.473	0.76 (0.35–1.63)
TCM therapeutic engagement					
No					1.00 (Reference)
Yes	0.10	0.30	0.34	0.730	1.11 (0.62–1.98)
BMI					
BMI < 18.5					1.00 (Reference)
18.5 ≤ BMI < 24	-1.20	0.74	-1.63	0.104	0.30 (0.07–1.28)
24 ≤ BMI < 28	-0.75	0.75	-1.00	0.315	0.47 (0.11–2.04)
28 ≤ BMI	-0.69	0.84	-0.83	0.407	0.50 (0.10–2.58)
NLR					
≤ 3					1.00 (Reference)
> 3	-1.12	0.35	-3.18	0.001	0.33 (0.16–0.65)
D-dimer					
≤ 0.5mg/L					1.00 (Reference)
> 0.5mg/L	0.80	0.29	2.77	0.006	2.24 (1.27–3.95)
NRS	0.34	0.09	3.79	<.001	1.40 (1.18–1.67)
dNLR	-1.04	0.67	-1.57	0.117	0.35 (0.10–1.30)
MNR	2.26	2.91	0.78	0.438	9.54 (0.03–2847.14)
SII	-0.00	0.00	-1.41	0.159	1.00 (1.00–1.00)
HGB	-0.00	0.01	-0.08	0.940	1.00 (0.98–1.02)
PLR	-0.01	0.00	-2.16	0.031	0.99 (0.99–0.99)
MPV	0.08	0.12	0.64	0.524	1.08 (0.85–1.37)
PTA	-0.02	0.01	-1.64	0.102	0.98 (0.95–1.00)
INR	3.57	2.19	1.63	0.102	35.67 (0.49–2602.52)
MAP	0.00	0.01	0.16	0.875	1.00 (0.98–1.03)
APTT	0.06	0.04	1.52	0.129	1.06 (0.98–1.14)
TT	-0.12	0.13	-0.98	0.329	0.88 (0.69–1.13)
FDP	0.08	0.09	0.84	0.403	1.08 (0.90–1.29)
Fib	-0.04	0.18	-0.20	0.842	0.96 (0.68–1.38)

Abbreviations: S.E., standard error; OR, odds ratio; CI, confidence interval; TCM, Traditional Chinese Medicine; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; NRS, Numerical Rating Scale; dNLR, derived neutrophil to lymphocyte ratio; MNR, monocyte to neutrophil ratio; SII, systemic immune inflammation index; HGB, hemoglobin; PLR, platelet to lymphocyte ratio; MPV, mean platelet volume; PTA, prothrombin activity; INR, international normalized ratio; MAP, mean arterial pressure; APTT, activated partial thromboplastin time; TT, thrombin time; Fib, fibrinogen; FDP, fibrinogen degradation products.