*Neurology Asia 2025; 30(4) : 1135 – 1142*

# Age-sex interaction on the development of postherpetic neuralgia among shingles patients with moderate and severe pain levels

[1]Lulu Yan *MD*, [2]Xiaoping Shen *MD*, [2]Dan Li *MD*, [2]Dehou Yu *MD*, [1]Hongguang Lu *MD PhD*

*[1]Clinical Medicine, Suzhou Medical College of Soochow University, Suzhou, Jiangsu, China; [2]Department of Dermatology, Affiliated Hospital of Guizhou Medical University, Guiyang City, Guizhou Province, China.*

## *Abstract*

*Background:* Herpes zoster (HZ), commonly known as shingles, can lead to postherpetic neuralgia (PHN), a chronic neuropathic pain condition that significantly impacts patients' quality of life. Age is a well-established risk factor for PHN, with incidence increasing among older individuals. However, the role of sex in PHN development remains unclear, with conflicting evidence regarding its influence. This study investigates the interaction between age, sex, and PHN risk among shingles patients with moderate to severe pain levels. *Methods:* A retrospective cohort study was conducted using electronic medical records from hospitalized HZ patients between 2018 and 2021. PHN was defined as persistent pain lasting ≥3 months post-HZ onset. Statistical analyses, including logistic regression and generalized additive models, were employed to assess risk factors. *Results:* Results showed that age was a significant predictor of PHN, particularly among patients with moderate to severe pain. In male patients, PHN risk increased linearly with age, whereas in female patients, a nonlinear relationship was observed, with a peak in risk between 60 and 70 years. Pain severity and comorbidities were also associated with PHN development. The observed sex differences may be influenced by variations in pain perception and healthcare-seeking behaviors, with older women receiving antiviral treatment earlier.
*Conclusion:* These findings highlight the importance of considering age-sex interactions when assessing PHN risk. Early intervention, particularly in patients experiencing severe acute pain, may help mitigate PHN development. Further research is needed to refine targeted prevention strategies.

*Keywords:* Postherpetic neuralgia, herpes zoster, age-sex interaction, neuropathic pain, risk factors

## INTRODUCTION

Herpes zoster (HZ), more commonly known as shingles, occurs due to the reactivation of the varicella-zoster virus, leading to a painful rash accompanied by blisters. One of the most significant complications of HZ is postherpetic neuralgia (PHN), a condition characterized by persistent nerve pain even after the skin lesions have healed. PHN is known to considerably impact patients' quality of life and remains a major challenge in clinical practice.[1,2]

Age is a well-documented risk factor for both HZ and PHN. The incidence of HZ rises with age, and older adults are particularly vulnerable to PHN.[3,4] A systematic review and meta-analysis reported that the relative risk of developing PHN increases per decade, with estimates ranging from 1.22 to 3.11. However, while most studies indicate a continuous rise in PHN risk with age, some findings suggest that patients older than 80 years may experience a decline in PHN incidence.[5,6]

The influence of sex on PHN susceptibility remains a topic of debate. Study by Amicizia *et al*. suggests that older men with HZ are at greater risk of developing PHN compared to younger men, yet this pattern is not as clear in women.[7] Conversely, findings by Muñoz Quiles *et al*. do not indicate a strong correlation between gender and PHN risk.[8] While some studies argue that sex has little impact, others propose that women may be slightly more prone to developing persistent pain.[9,10]

In addition to demographic factors, the clinical presentation of HZ influences the likelihood of

*Address correspondence to:* Hongguang Lu (PhD), Clinical Medicine, Suzhou Medical College of Soochow University, No. 1 Shizi Street, Suzhou, Jiangsu, 215006, P.R. China, e.mail: hongguanglu@hotmail.com

Date of Submission: 28 April 2025; Date of Acceptance: 14 September 2025

https://doi.org/10.54029/2025dzt

PHN development. Severe pain during the acute phase, an extensive rash, and prodromal pain have been linked to an increased risk of prolonged neuralgia.[11,12] Notably, individuals experiencing intense pain at the onset of HZ have a higher probability of developing persistent neuropathic pain following recovery.[13]

Further studies have highlighted additional risk factors for PHN. Large cohort studies have demonstrated that individuals with severe immunosuppressive conditions, such as leukemia and lymphoma, face a heightened risk of developing PHN. Chronic conditions, including asthma and diabetes, have also been associated with a greater likelihood of PHN occurrence. Moreover, lifestyle factors such as smoking and extreme body weight—whether underweight or obese—have been identified as contributing factors.[14]

Given these complexities, it is essential to explore the interaction between age, sex, clinical characteristics, and comorbidities in the development of PHN. A more detailed understanding of these factors may help refine prevention strategies and enhance clinical management. Therefore, we conducted a retrospective study to investigate the role of age-sex interaction in PHN development among shingles patients with varying pain levels, utilizing diverse statistical methodologies.

## METHODS

### *Study design and data collection*

This retrospective cohort study was conducted using the electronic medical record system data of inpatients at the Affiliated Hospital of Guizhou Medical University. We identified eligible patients by searching for the keywords "shingles," "Zoster," and "Herpes Zoster" within the hospital database, covering a period from October 1, 2018, to September 30, 2021. Patients were included if they had a primary diagnosis of herpes zoster (HZ), meaning HZ was the primary reason for hospitalization.

### *Definition of postherpetic neuralgia (PHN)*

PHN was defined as pain persisting for ≥3 months following the onset of the HZ rash. Pain intensity was assessed using the Numeric Rating Scale (NRS), where patients rated their pain from 0 (no pain) to 10 (worst possible pain). For the purposes of our analysis, scores of 0–3 were defined as mild or no pain, while scores of 4–10 were categorized as moderate to severe pain.[15] Patients were categorized into different pain levels based on their initial assessment.

### *Inclusion and exclusion criteria*

Patients were included in the study if they had a confirmed diagnosis of HZ documented in their medical records, were hospitalized during the study period, and had available data on pain assessment and follow-up. Exclusion criteria included incomplete or missing follow-up information, presence of chronic pain conditions unrelated to HZ, and immunocompromised status due to factors such as chemotherapy, organ transplantation, or autoimmune diseases requiring immunosuppressive therapy. Additionally, patients with central nervous system (CNS) complications related to HZ, such as herpes zoster encephalitis or meningitis, were excluded, as these conditions are not typically associated with the development of PHN.

The primary independent variables included age, sex, pain grading, ophthalmic zoster, comorbidities, interval between onset and antiviral therapy, and glucocorticoid use. Age was treated as both a continuous variable and categorized into groups for subgroup analysis. Sex was recorded as a categorical variable (male/female) to assess potential differences in PHN occurrence. Pain grading was determined using the NRS, classifying patients into mild, moderate, and severe pain levels Although information on the site of zoster involvement was available for some patients, it was not consistently recorded in a standardized format across the dataset. Therefore, dermatome-level classifications (e.g., thoracic, lumbar) were not included in the multivariable models. However, ophthalmic (trigeminal) zoster was included as a binary variable.

Comorbidities were recorded as categorical variables, reflecting additional medical conditions that could influence PHN development. The interval between onset and antiviral therapy was measured as a continuous variable, capturing the time from rash onset to antiviral treatment initiation. Glucocorticoid use was recorded as a binary variable to evaluate its potential impact on PHN occurrence. The primary outcome variable was PHN, defined as persistent pain lasting ≥3 months after rash onset, analyzed as a binary outcome (PHN present vs. absent). To control for confounding factors, multivariable-adjusted models were implemented, incorporating sex, ophthalmic zoster, comorbidities, pain grading, interval between onset and antiviral therapy, and glucocorticoid use. Additionally, a generalized

additive model (GAM) was employed to explore potential nonlinear relationships between age and PHN.

*Statistical analysis*

Descriptive statistics were used to summarize the baseline characteristics of inpatients with and without a PHN diagnosis. Continuous variables were reported as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. The Mann-Whitney U test was used to compare continuous variables, while the chi-square test was applied to compare categorical data. To evaluate the association between age and PHN, multiple logistic regression models were constructed. Both unadjusted and multivariable-adjusted models were analyzed. The adjusted models accounted for potential confounding factors, including sex, ophthalmic zoster, comorbidities, interval between onset and antiviral therapy, glucocorticoid use, and pain grading. A generalized additive model was also used to explore potential nonlinear relationships between age and PHN occurrence.

All statistical analyses were performed using R software (http://www.R-project.org, R Foundation)[16] and Empowers tats (http://www.empowerstats.com, X & Y Solutions, Inc, MA, USA).[17] A two-sided P-value of <0.05 was considered statistically significant.

*Ethical considerations*

This study was approved by the institutional review board at the Affiliated Hospital of Guizhou Medical University. Patient confidentiality was maintained, and data were anonymized before analysis.

## RESULTS

A total of 614 patients were hospitalized with herpes zoster at the Affiliated Hospital of Guizhou Medical University, of whom 516 completed follow-ups. Among these 516 HZ patients, 148 (67 males and 81 females) developed PHN, with an average age of 64.7 years. Of these, 17 patients (11.5%) were younger than 50 years, 23 (15.5%) were between 50 and 60 years, 55 (37.2%) were between 60 and 70 years, 35 (23.6%) were between 70 and 80 years, and 18 (12.2%) were over 80 years old (Table 1).

**Table 1: Baseline characteristics of inpatients with herpes zoster (N =516)**

| Characteristic | Postherpetic neuralgia | | *P*-value |
|---|---|---|---|
| | No | Yes | |
| No. of participants | 368 | 148 | |
| Age, years, mean (SD) | 58.4 ± 18.2 | 64.7 ± 12.6 | <0.001 |
| Age, years, (groups) | | | <0.001 |
| <50 | 105 (28.5%) | 17 (11.5%) | |
| ≥50, <60 | 69 (18.8%) | 23 (15.5%) | |
| ≥60, <70 | 83 (22.6%) | 55 (37.2%) | |
| ≥70, <80 | 59 (16.0%) | 35 (23.6%) | |
| ≥80 | 52 (14.1%) | 18 (12.2%) | |
| Sex | | | 0.524 |
| Male | 178 (48.4%) | 67 (45.3%) | |
| Female | 190 (51.6%) | 81 (54.7%) | |
| Ophthalmic zoster | | | 0.116 |
| No | 312(84.8%) | 117(79.1%) | |
| Yes | 56(15.2%) | 31(20.9%) | |
| Pain grading | | | <0.001 |
| None or mild pain (0-3 points) | 146(39.7%) | 18(12.2%) | |
| Moderate or severe pain (4-10 points) | 222(60.3%) | 130(87.8%) | |
| Comorbidities | | | 0.032 |
| No | 180(48.9%) | 57(38.5%) | |
| Yes | 188(51.1%) | 91(61.5%) | |
| Interval between onset and antiviral therapy, days | | | 0.556 |
| ≤7 | 304(82.6%) | 119(80.4%) | |
| >7 | 64(17.4%) | 29(19.6%) | |
| Glucocorticoid use | | | 0.480 |
| No | 253(68.8%) | 97(65.5%) | |
| Yes | 115(31.2%) | 51(34.5%) | |

*Age-sex interaction in the development of PHN*

Univariate regression analysis of the relationship between various factors and PHN showed that age (P<0.001), pain grading (P<0.001), and comorbidities (P=0.033) were significantly associated with PHN (Table 2). However, no significant correlation was observed between PHN and other variables, including sex, ophthalmic zoster, the interval between onset and antiviral therapy, and glucocorticoid use.

To further explore whether the association between different age groups and PHN is consistent across various subgroups of variables, we conducted a subgroup analysis based on different age groups (Table 3). No significant interactions were found across all strata (P = 0.44-0.67), except for pain grading (P=0.03), indicating that pain levels in HZ patients are associated with PHN. Moreover, among HZ patients with no pain or mild pain, PHN occurrence did not increase with age, whereas in patients with moderate to severe pain, PHN incidence increased with age.

Next, multiple regression analysis was conducted on HZ patients with moderate to severe pain in both genders. The results indicated that male patients had an increased risk of PHN with age, with statistically significant differences (age ≥60, <70: OR 5.5, 95% CI [1.6, 18.8], P=0.007; age ≥70, <80: OR 12.4, 95% CI [3.2, 48.2], P<0.001; age ≥80: OR 5.0, 95% CI [1.2, 21.0], P=0.026; Table 4). However, in female patients, while age was also a risk factor for PHN, statistical significance was observed only in those aged 60 to 70 years (OR 6.5, 95% CI [2.2, 19.5], P<0.001; Table 5).

Additionally, a generalized additive model was applied to patients with moderate to severe HZ pain. As shown in Figure 1, a threshold nonlinear correlation between age and PHN was found in female patients (green dashed line), whereas a linear correlation between age and PHN was observed in male patients (solid red line).

**Table 2: Univariate analysis for postherpetic neuralgia**

| Covariate | Statistics | OR (95%CI) | *P*-value |
|---|---|---|---|
| Age, years, mean (SD) | 60.2±17.0 | 1.0(1.0, 1.0) | <0.001 |
| Age, years, (groups) | | | |
| <50 | 122(23.6%) | 1.0 | |
| ≥50, <60 | 92(17.8%) | 2.1(1.0,4.1) | 0.042 |
| ≥60, <70 | 138(26.7%) | 4.1(2.2,7.6) | <0.001 |
| ≥70, <80 | 94(18.2%) | 3.7(1.9,7.1) | <0.001 |
| ≥80 | 70(13.6%) | 2.1(1.0,4.5) | 0.045 |
| Sex | | | 0.524 |
| Male | 245(47.5%) | 1.0 | |
| Female | 271(52.5%) | 1.1(0.8,1.7) | |
| Ophthalmic zoster | | | 0.117 |
| No | 429(83.1%) | 1.0 | |
| Yes | 87(16.9%) | 1.5(0.9,2.4) | |
| Pain grading | | | <0.001 |
| None or mild pain (0-3 points) | 164(31.8%) | 1.0 | |
| Moderate or severe pain (4-10 points) | 352(68.2%) | 4.7(2.8,8.1) | |
| Comorbidities | | | 0.033 |
| No | 237(45.9%) | 1.0 | |
| Yes | 279(54.1%) | 1.5(1.0,2.3) | |
| Interval between onset and antiviral therapy, days | | | 0.556 |
| ≤7 | 423(82.0%) | 1.0 | |
| >7 | 93(18.0%) | 1.2(0.7,1.9) | |
| Glucocorticoid use | | | 0.480 |
| No | 350(67.8%) | 1.0 | |
| Yes | 166(32.2%) | 1.2(0.8,1.7) | |

**Table 3: Effect size of age on postherpetic neuralgia in hospitalized patients in each subgroup**

| Variable | Different age groups(year) | | | | | | *P* for interaction |
|---|---|---|---|---|---|---|---|
| | No. of participants | <50 Ref | >=50, <60 OR (95%CI)[a] | >=60, <70 OR (95%CI)[a] | >=70, <80 OR (95%CI)[a] | >=80 OR (95%CI)[a] | |
| Sex | | | | | | | 0.45 |
| Male | 245 | 1.0 | 1.3 (0.4, 4.1) | 2.3 (0.9, 5.8) | 5.1 (1.8, 14.1) | 1.9 (0.6, 6.0) | |
| Female | 271 | 1.0 | 1.9 (0.7, 5.2) | 5.0 (1.9, 13.0) | 1.9 (0.6, 5.5) | 2.0 (0.6, 6.4) | |
| Ophthalmic zoster | | | | | | | 0.67 |
| No | 429 | 1.0 | 2.0 (0.9, 4.7) | 3.7 (1.8, 7.8) | 3.5 (1.5, 7.9) | 1.8 (0.7, 4.6) | |
| Yes | 87 | 1.0 | 1.2 (0.2, 6.9) | 4.0 (0.7, 21.4) | 2.8 (0.4, 17.3) | 2.1 (0.3, 15.0) | |
| Pain grading | | | | | | | 0.03 |
| None or mild pain (0-3 points) | 164 | 1.0 | 0.4 (0.1, 2.4) | 1.5 (0.4, 5.9) | 1.4 (0.3, 6.0) | 0.2 (0.0, 1.5) | |
| Moderate or severe pain (4-10 points) | 352 | 1.0 | 2.4 (1.0, 5.8) | 5.0 (2.3, 11.1) | 4.1 (1.7, 9.6) | 3.6 (1.4, 9.3) | |
| Comorbidities | | | | | | | 0.44 |
| No | 237 | 1.0 | 1.4 (0.5, 3.6) | 2.4 (1.0, 5.7) | 2.2 (0.7, 6.6) | 1.7 (0.5, 5.9) | |
| Yes | 279 | 1.0 | 1.9 (0.6, 6.5) | 4.6 (1.5, 13.7) | 3.8 (1.3, 11.7) | 2.2 (0.7, 7.3) | |
| Interval between onset and antiviral therapy, days | | | | | | | 0.50 |
| ≤7 | 423 | 1.0 | 1.7 (0.8, 3.8) | 3.0 (1.5, 6.0) | 3.0 (1.4, 6.4) | 1.9 (0.8, 4.4) | |
| >7 | 93 | 1.0 | 1.9 (0.1, 37.8) | 12.0 (0.6, 259.3) | 9.0 (0.4, 219.9) | 1.2 (0.0, 48.2) | |
| Glucocorticoid use | | | | | | | 0.55 |
| No | 350 | 1.0 | 1.9 (0.7, 5.2) | 3.3 (1.4, 8.1) | 3.3 (1.3, 8.4) | 2.0 (0.7, 5.5) | |
| Yes | 166 | 1.0 | 1.4 (0.4, 4.5) | 5.6 (1.9, 16.5) | 2.3 (0.7, 7.7) | 1.5 (0.3, 7.0) | |

a: Each stratification adjusted for all the factors (Sex, Ophthalmic zoster, pain grading, Comorbidities, Interval between onset and antiviral therapy, Glucocorticoid use) except the stratification factor itself. CI, confidence interval; OR, odds ratio.

**Table 4: The relationship between age and postherpetic neuralgia in different models in the male patients with moderate and severe pain**

| Variable | Crude Model | | Model I[a] | | Model I[b] | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *P*-value | OR (95%CI) | *P*-value | OR (95%CI) | *P*-value |
| Age, years | 1.0(1.0,1.0) | 0.001 | 1.0(1.0, 1.1) | <0.001 | 1.0(1.0, 1.1) | 0.001 |
| Age, years, (subgroups) | | | | | | |
| <50 | 1.0 | | 1.0 | | 1.0 | |
| ≥50, <60 | 2.5(0.6,9.9) | 0.184 | 3.1(0.8, 12.3) | 0.115 | 3.0(0.8, 12.2) | 0.119 |
| ≥60, <70 | 4.6(1.4, 15.4) | 0.012 | 5.6(1.6, 18.9) | 0.006 | 5.5(1.6, 18.8) | 0.007 |
| ≥70, <80 | 9.3(2.6,32.6) | <0.001 | 12.8(3.4,48.2) | <0.001 | 12.4(3.2,48.2) | <0.001 |
| ≥80 | 4.3(1.1, 17.3) | 0.037 | 5.2(1.3,21.2) | 0.022 | 5.0(1.2,21.0) | 0.026 |

Abbreviations: CI, confidence interval.
a:Model Iadjusted for Ophthalmic zoster, Interval between onset and antiviral therapy, Glucocorticoid use.
b:Model adjusted for Ophthalmic zoster, pain grading, Comorbidities, Interval between onset and antiviral therapy, Glucocorticoid use.

## DISCUSSION

PHN is one of the most severe complications of HZ, significantly impacting the quality of life for patients.[1,2] It is well-established that the incidence of PHN increases with age[3,18], making age an essential risk factor, especially for individuals over the age of 50. However, findings regarding this association have not been entirely consistent. For example, while Muñoz Quiles *et al*. reported a continuous increase in PHN incidence with age, Sun *et al*. observed the highest incidence in the 55 to 64 age group, with a subsequent decline in older patients.[3,4] This pattern is similar to the one identified in our study, where PHN incidence was highest among patients aged 60 to 70 years (Table 1).

Furthermore, prior research has emphasized that the severity of pain at the onset of HZ is an important predictor for the development of PHN.[5,6] In our analysis, univariate regression revealed that age, pain severity, and comorbidities were significant risk factors for PHN (Table 2). To further understand how pain severity interacts with age and sex in relation to PHN, we performed a subgroup analysis. The results showed that PHN risk did not increase with age in patients with mild pain. However, among those experiencing moderate to severe pain, the risk of PHN rose significantly with age (Table 3).

To investigate the relationship between age, sex, and PHN in more detail, we conducted multiple regression analyses, focusing on male and female patients with moderate to severe pain. Our findings indicated a clear association between increasing age and PHN risk in men (Table 4). However, in

**Table 5: The relationship between age and postherpetic neuralgia in different models in the female patients with moderate and severe pain**

| Variable | Crude Model | | Model I[a] | | Model I[b] | |
|---|---|---|---|---|---|---|
| | OR (95%CI) | *P*-value | OR (95%CI) | *P*-value | OR (95%CI) | *P*-value |
| Age, years | 1.0(1.0,1.0) | 0.025 | 1.0(1.0, 1.1) | 0.009 | 1.0(1.0, 1.1) | 0.021 |
| Age, years (subgroups) | | | | | | |
| <50 | 1.0 | | 1.0 | | 1.0 | |
| ≥50, <60 | 2.3(0.8,6.5) | 0.119 | 2.4(0.8, 7.4) | 0.135 | 2.2(0.7, 6.9) | 0.174 |
| ≥60, <70 | 4.9(1.9, 13.0) | 0.001 | 7.2(2.4, 21.2) | <0.001 | 6.5(2.2, 19.5) | <0.001 |
| ≥70, <80 | 1.9(0.7,5.8) | 0.228 | 2.4(0.8,7.7) | 0.133 | 2.1(0.6,6.8) | 0.239 |
| ≥80 | 2.8(0.9, 9.2) | 0.080 | 4.2(1.2,15.1) | 0.026 | 3.7(1.0,13.5) | 0.051 |

Abbreviations: CI, confidence interval.
a: Model I adjusted for Ophthalmic zoster, Interval between onset and antiviral therapy, Glucocorticoid use.
b: Model II adjusted for Ophthalmic zoster, Pain grading, Comorbidities, Interval between onset and antiviral therapy, Glucocorticoid use.

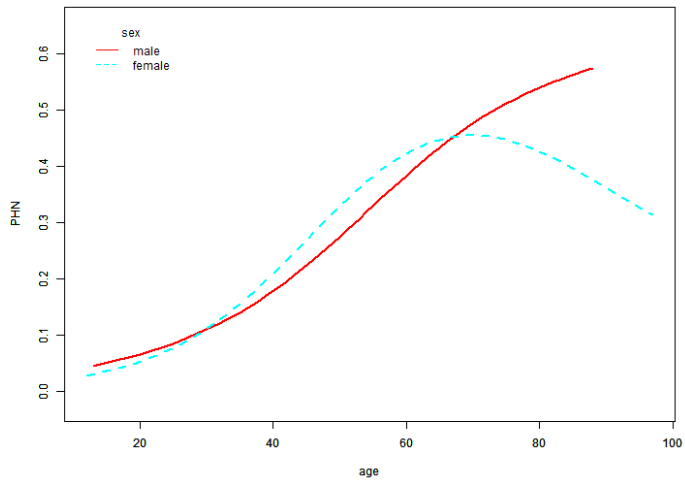


Figure 1. Association between age and PHN in different sex with moderate and severe pain. A threshold, nonlinear association between age and PHN was found in a generalized additive model (GAM) of female patients (Green dashed line). A linear correlation between age and PHN was found in the generalized additive model (GAM) of male patients (Solid red line). All adjusted for Ophthalmic zoster, comorbidities, Interval between onset and antiviral therapy, Glucocorticoid use.

female patients, a statistically significant increase in PHN risk with age was observed only in the 60 to 70-year age group (Table 5).

Previous studies have highlighted an age-sex interaction, particularly in men, where PHN incidence increases with age, but no consistent trend is seen among women.[7,19] Our results align with these observations. However, other studies suggest that PHN is more common in women, with incidence increasing with age in both sexes(3, 8). These studies often considered fewer variables, such as age and sex, without accounting for pain severity, which could have influenced their findings. To further validate the relationship between age, sex, and PHN, we employed a generalized additive model. Our analysis revealed a linear correlation between age and PHN risk in men, while a threshold nonlinear pattern was observed in women(20). One explanation for this difference could be that men and women perceive and respond to pain differently, with women generally demonstrating greater pain sensitivity.[9,10] This could lead older women to seek medical care more promptly after the onset of HZ, resulting in earlier antiviral treatment, which may reduce the risk of PHN. Our data support this theory, showing that women aged 70 to 80 years received antiviral treatment earlier than their male counterparts in the same age group (Table S1).

Since there are currently no highly effective treatments for PHN, prevention remains crucial. In our study, we found that in HZ patients with moderate to severe acute pain, PHN incidence increased progressively with age. The nonlinear relationship between age, sex, and PHN could be influenced by earlier antiviral treatment among female patients, underscoring the importance of early intervention to reduce PHN risk, especially in those with moderate to severe pain.

This study offers valuable insights into the age-sex interaction in PHN development using a large, hospital-based dataset and advanced statistical techniques. It examines key risk factors and provides important clinical implications. However, the retrospective nature of the study may introduce bias, and the exclusion of outpatient cases limits the generalizability of the findings. Additionally, the study did not explore sociodemographic factors or the biological mechanisms behind sex differences in PHN. Another limitation of our study is the lack of standardized and complete data regarding the dermatome location of zoster involvement. This prevented us from adjusting for rash site as a potential confounder, which may influence pain severity and PHN risk.

Despite these limitations, the research emphasizes the importance of early intervention, particularly for patients with severe pain, and lays the foundation for future investigations.

In conclusion, this study enhances our understanding of the role of age and sex in PHN development, employing robust statistical methods and a comprehensive dataset. PHN is more common among older individuals, particularly those experiencing moderate to severe neuropathic pain at the onset of HZ. Sex

may also play a role in PHN incidence, with a nonlinear pattern of age-related PHN in women, possibly due to differences in pain perception and healthcare-seeking behavior. Further prospective studies involving a broader patient population and additional risk factors would help reinforce these findings.

## DISCLOSURE

Data availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of interest: None

## REFERENCES


1. Zhang W, He Z, Li P, *et al*. The necessity for popularizing varicella-zoster virus vaccine programs worldwide: An age-period-cohort analysis for the Global Burden of Disease study 2019. *J Infect Public Health* 2023;16(7):1093-101. https:// doi.org/10.1016/j.jiph.2023.05.016.
2. Shen Y, Lin P. Association between frailty and postherpetic neuralgia in the older adult with herpes zoster. *Front Public Health* 2025;13:1511898. https://doi.org/10.3389/fpubh.2025.1511898.
3. Yang F, Yu S, Fan B, *et al*. The epidemiology of herpes zoster and postherpetic neuralgia in China: results from a cross-sectional study. *Pain Ther* 2019;8:249-59. https://doi.org/10.1007/s40122-019-0127-z.
4. Serpell M, Gater A, Carroll S, Abetz-Webb L, Mannan A, Johnson R. Burden of post-herpetic neuralgia in a sample of UK residents aged 50 years or older: findings from the Zoster Quality of Life (ZQOL) study. *Health Qual Life Outcomes* 2014;12:1-4. https://doi.hqlo.com/content/12/1/92.
5. Lu WH, Lin CW, Wang CY, Chen LK, Hsiao FY. Epidemiology and long-term disease burden of herpes zoster and postherpetic neuralgia in Taiwan: a population-based, propensity score-matched cohort study. *BMC Public Health* 2018;18:1-9. https://doi.org/10.1186/s12889-018-5247-6.
6. Gross GE, Eisert L, Doerr HW, *et al*. S2k guidelines for the diagnosis and treatment of herpes zoster and postherpetic neuralgia. JDDG: *J Dtsch Dermatol Ges* 2020;18(1):55-78. https://doi.org/10.1111/ddg.14013.
7. Sun X, Wei Z, Lin H, Jit M, Li Z, Fu C. Incidence and disease burden of herpes zoster in the population aged ≥50 years in China: data from an integrated health care network. *J Infect* 2021;82(2):253-60. https://doi.org/10.1016/j.jinf.2020.12.013.
8. Forbes HJ, Thomas SL, Smeeth L, *et al*. A systematic review and meta-analysis of risk factors for postherpetic neuralgia. *Pain* 2016;157(1):30-54. https://doi.org/10.1097/j.pain.0000000000000307.
9. Amicizia D, Domnich A, Arata L, *et al*. The role of age-sex interaction in the development of post-herpetic neuralgia. *Hum Vaccin Immunother* 2017;13(2):376-8. https://doi.org/10.1080/21645515.2017.1264799
10. Zhuang J, Liu T, Hu J. Herpes zoster after botulinum toxin combined with hyaluronic acid injection. *J Craniofac Surg* 2023;34(5):1503-6. DOI: 10.1097/SCS.0000000000009359
11. Muñoz-Quiles C, López-Lacort M, Orrico-Sánchez A, Díez-Domingo J. Letter to the editor regarding "The role of age-sex interaction in the development of post-herpetic neuralgia". *Hum Vaccin Immunother* 2018;14(4):906-8. https://doi.org/10.1080/21645515.2017.1417715.
12. Domínguez-Casas LC, Lasa-Teja C, Ferraz-Amaro I, Castañeda S, Blanco R. Increased risk of herpes zoster in rheumatoid arthritis not only due to JAK inhibitors—Study of 392 patients from single university center. *J Clin Med* 2024;13(11):3121. https://doi.org/10.3390/jcm13113121.
13. Drolet M, Brisson M, Schmader K, *et al*. Predictors of postherpetic neuralgia among patients with herpes zoster: a prospective study. *J Pain* 2010;11(11):1211-21. https://doi.org/10.1016/j.jpain.2010.02.020
14. 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(1):94-102. https://doi.org/10.1212/WNL.0000000000002808.
15. Niv D, Maltsman-Tseikhin A. Postherpetic neuralgia: The never-ending challenge. *Pain Pract* 2005;5(4):327-40. https://doi.org/10.1111/j.1533-2500.2005.00035.x.
16. The R Foundation: Duke University, Durham, NC, USA; [Available from: http://www.R-project.org, https://doi.org/10.4324/9780203499894.
17. EmpowerStats USA2011 [Available from: https://www.empowerstats.net/en/.
18. Matthews S, De Maria A, Passamonti M, *et al*. The economic burden and impact on quality of life of herpes zoster and postherpetic neuralgia in individuals aged 50 years or older in Italy. *Open Forum Infect Dis* 2019;6(2): ofz007. https://doi.org/10.1093/ofid/ofz007.
19. Wang L, Li A, Lan Z, Xu S, He R, Jiang Z. The association between age and acute pain sensitivity in patients with Herpes Zoster. *Sci Rep* 2025;15(1):5495. https://doi.org/10.1038/s41598-025-88618-9.
20. Bartley EJ, Fillingim RB. Sex differences in pain: A brief review of clinical and experimental findings. *Survey Anesthesiol* 2016;60(4):175-6. https://doi.org/10.1093/bja/aet127.

**Table S1: The interval between onset and antiviral treatment in patients of different genders at different age stages**

| Variable | Male | | Female | | *P*-value |
|---|---|---|---|---|---|
| | Interval between onset and antiviral therapy(day) ≤7 | Interval between onset and antiviral therapy(day) >7 | Interval between onset and antiviral therapy(day) ≤7 | Interval between onset and antiviral therapy(day) >7 | |
| Age, years, (subgroups) | | | | | |
| <50 | 37(100.0%) | 0(0.0%) | 42(91.3%) | 4(8.7%) | 0.07 |
| ≥50, <60 | 24(77.4%) | 7(22.6%) | 31(66.0%) | 16(34.0%) | 0.28 |
| ≥60, <70 | 43(76.8%) | 13(23.2%) | 47(73.4%) | 17(26.6%) | 0.67 |
| ≥70, <80 | 25(62.5%) | 15(37.5%) | 35(85.4%) | 6(14.6%) | 0.02 |
| ≥80 | 20(83.3%) | 4(16.7%) | 22(81.5%) | 5(18.5%) | 0.86 |