Risk Factors for Poor Pain Control in Zoster-Associated Pain: A Retrospective Study

Ruifeng Sun · Ning Wang · Hai Mou · Can Gao · Lv Yu · Wenshan Li · Tiancong Li · Peiling Huang · Weijun Gong

ABSTRACT

Introduction: The objective was to investigate the risk factors for poor pain control in patients with herpes zoster (HZ)-associated neuropathic pain treated with drugs combined with nerve block therapy. Neuropathic pain commonly follows HZ. Nerve block therapy is the most commonly used clinical treatment for such pain, combining anti-inflammation and analgesia to prevent peripheral sensitization of nerve.

Methods: Using clinical practice data from a cohort study at our research center, we established a multivariate logistic regression model to investigate potential risk factors for poor control of zoster-associated pain (ZAP) treated with drugs plus nerve block therapy, including demographic characteristics, complications, laboratory tests, and characteristics of HZ attacks.

Results: Of the 429 patients with ZAP who received drugs plus nerve block therapy, 95 (22.14%) had poor pain control after treatment. The risk of poor pain control was closely related to presence of cancer (odds ratio (OR) 4.173, 95% confidence interval (CI) 1.342–12.970), numerical rating scale score on admission (OR 1.929, 95% CI 1.528–2.434), and red blood cell count (OR 0.560, 95% CI 0.328–0.954). Area under the receiver operator characteristic curve was 0.730. Goodness of fit (Hosmer–Lemeshow) was 0.874.

Conclusions: The risk of poor pain control in patients with ZAP increased as a result of certain patient characteristics and complications, especially severe pain before treatment and cancer.

Keywords: Zoster-associated pain; Nerve block therapy; Poor pain control; Risk factors; Herpes zoster
Key Summary Points

- Zoster-associated pain (ZAP) seriously affects patients’ quality of life (QoL), and poor control of ZAP leads to central sensitization and even stubborn post-herpetic neuralgia (PHN).
- The purpose of this study was to investigate risk factors for poor pain control in patients with ZAP who received drugs plus nerve block therapy.
- This study identified three independent risk factors for poor pain control in patients with ZAP treated with drugs plus nerve block therapy.
- To a certain extent, it can guide clinicians to make the most appropriate pain treatment decisions.

INTRODUCTION

Herpes zoster (HZ) is caused by reactivation of latent varicella-zoster virus (VZV) that entered the sensory ganglia during varicella infection. The condition is characterized by painful unilateral herpes. Rare cases of herpes zoster can affect the bilateral side [1, 2]. Anyone who has had primary infection with VZV, which usually manifests as varicella (chickenpox), can develop HZ [3]. According to a recent study, the total incidence of HZ is 6.64 cases per 1000 person-years in China, and the incidence of HZ increases with age [4]. Worldwide, the meta-analytic incidence for middle-aged individuals (50–54 years old; 5.15/1000 person-years) is less than half that for the old (at least 85 years old; 11.27/1000 person-years) [5]. People with HZ experience unbearable neuropathic pain caused by minor stimuli and unbearable itching, and changes in sensitivity to touch. Therefore, zoster-associated pain (ZAP) seriously affects patients’ quality of life (QoL), and poor control of ZAP leads to central sensitization and even stubborn post-herpetic neuralgia (PHN) [6].

Recent cohort and case–control studies have mostly focused on the risk factors of HZ or PHN and their effects on patients’ QoL [7, 8]. No research has focused on risk factors for poor control of ZAP. The combination of drugs and nerve block therapy is the most commonly used, most economical, and most convenient treatment for ZAP [9]. Nerve block therapy helps reduce peripheral sensitization and nerve inflammation, relieve ZAP, and prevent central sensitization [10, 11]. The purpose of this study was to investigate risk factors for poor pain control in patients with ZAP who received drugs plus nerve block therapy, based on the data of patients with HZ admitted to our center since 2012, to guide clinical selection of the most effective treatment.

METHODS

Study Design and Setting

We performed a single-center retrospective study on patients with ZAP treated with drugs plus nerve block therapy. Data were collected from an HZ cohort study conducted at our center. All patients received orally administered drugs (gabapentin/pregabalin, antiviral drugs, and nonsteroidal anti-inflammatory drugs) and nerve block therapy (corticosteroids, lidocaine, and vitamin B12). The treatment of nerve block therapy is once a week for 4 weeks. The implementers of nerve blocks have received uniform training. We divided patients into two groups based on post-treatment pain control: good pain control (GC group; numerical rating scale [NRS] ≤ 3 at discharge) and poor pain control (PC group; [NRS] > 3 at discharge) [12].

Patient Selection

We reviewed the clinical data of 429 patients with moderate or severe ZAP who received drugs plus nerve block therapy at our research center from January 2012 to March 2022.
Inclusion Criteria

Patients who met the following criteria were selected: (1) complete medical records, including general information, admission laboratory examination results, description of the disease’s general characteristics, and admission pain assessment results; (2) moderate or severe ZAP (NRS ≥ 5, affecting sleep); and (3) had received drugs plus nerve block therapy.

Exclusion Criteria

Patients who met the following criteria were excluded: (1) had received any kind of pain treatment except drugs before this hospitalization, or had received other invasive treatment during the hospitalization (e.g., nerve radiofrequency modulation and spinal-cord electrical stimulation); (2) cognitive deficits or mental disorders affecting the patient’s treatment or questionnaire evaluation and other pain-causing diseases besides HZ; and (3) those who gave up treatment and were discharged automatically.

Measures

In this study, moderate and severe ZAP refers to the diagnosis of HZ and the presence of HZ-related neuropathic pain, including acute and subacute neuropathic pain, as well as chronic sequelae of neuralgia. At the same time, the degree of pain reached moderate to severe, i.e., NRS ≥ 5. The standard was selected according to the NRS pain grading standard and the clinical experience of our research center. Clinicians have found that pain in patients with NRS ≥ 5 often significantly affects daily QoL, especially sleep quality. Usually, dedicated evaluators performed NRS assessment on the first day of admission, including the average NRS and the breakout pain NRS. The breakout pain NRS was used in this study.

Risk Factors of Interest

On the basis of previous studies and our experience, we evaluated the following possible predictive factors for poor pain control in patients with ZAP treated with drugs plus nerve block: demographic characteristics, disease-related characteristics, and laboratory indicators. Demographic risk factors included age, sex, and body mass index (BMI). Disease-related characteristics included complications (diabetes, cancer), course of disease, location of nerve block therapy, and NRS score on admission (admission NRS). Laboratory indicators included white blood cell (WBC) count, red blood cell (RBC) count, neutrophil percentage (NEU%), lymphocyte percentage (LYM%), total protein (TP), and albumin (ALB) on admission [8, 13, 14].

Statistical Analysis

We conducted a retrospective study on patients with ZAP treated with drugs plus nerve block therapy. The primary effectiveness endpoint was the NRS ≤ 3 at discharge. The outcome was effectiveness of the treatment, which was defined as either “good control” or “poor control”. Before carrying out this study, we estimated the sample size. A minimum of 130–195 patients were required on the basis of 10–15 times the possible predictive factors.

We used SPSS statistical software v22.0 (IBM Corp., Armonk, NY, USA) to process the data. The significance of the difference in continuous variables between the two groups was determined by Student’s t test and the mean (standard deviation). Measurement data that did not conform to the normal distribution were described by the Mann–Whitney U test and the median (quartile spacing). Differences between the two groups of classified variables were described by the $\chi^2$ test and frequency. The risk of poor pain control was expressed as odds ratios (ORs) and 95% confidence intervals (CIs). According to their pain control results, we divided patients into two groups; 334 patients had good pain control, while 95 had poor pain control. In this study, univariate logistic regression analysis was used to test correlations.
between all selected predictive factors and the occurrence of PHN, and multivariate logistic regression analysis (Enter, \( z = 0.05 \)) was used to analyze significant factors. Predictive model discrimination was analyzed by the area under the receiver operating characteristic curve. The model's calibration was tested with a Hosmer–Lemeshow goodness-of-fit test.

**Standard Protocol Approvals and Registrations**

This research project was approved by the Ethics Committee of Xinqiao Hospital Army Medical University (Chongqing, China; 2021 Research No. 095-01) to protect the privacy of patient data according to ethical guidelines. The report of this work was consistent with that of the HZ cohort study.

**RESULTS**

**Patient Population**

Of the 429 patients with HZ who met the inclusion criteria of this study, 95 (43 male and 52 female) had poor pain control, and the remaining 334 (157 male and 177 female) had good pain control. The average age of patients with poor pain control was 68.2 ± 10.1 years, while that of patients with good pain control was 64.4 ± 12.1 years (Table 1). All the patients with cancer involved in our study were in progressive stage, without cancer pain and received anticancer treatment during hospitalization. The results of the Mann–Whitney \( U \) and \( \chi^2 \) tests (Table 2) showed significant differences between the PC and GC groups in characteristics, such as age (\( P = 0.006 \)), admission NRS (\( P < 0.001 \)), RBC count (\( P = 0.003 \)), ALB (\( P = 0.014 \)), course of disease (\( P = 0.038 \)), and complication with cancer (\( P = 0.003 \); Figs. 1 and 2).

**Results of Univariate Logistic Regression Analyses**

Univariate logistic regression analysis showed that increasing age, longer course of disease, complication with cancer, higher admission NRS, lower RBC count, and lower ALB were risk factors for poor pain control (Table 3).
Results of Multivariate Logistic Regression Analyses

As the variance inflation factors were less than 2.0 for all six variables, there was no multi-collinearity. Multivariate logistic regression analysis showed that complication with cancer, higher admission NRS, and lower RBC count were independent risk factors for poor control of ZAP (Table 4; Fig. 3).

Performance of the Prediction Model

We generated the ROC curve for the prediction model, which showed an AUC of 0.730 (95% CI 0.670–0.790, \( P < 0.001 \)) (Fig. 4). The sensitivity, specificity, and Youden index of the model were 54%, 82%, and 36%, respectively and the model has some diagnostic value. The Hosmer–Lemeshow goodness-of-fit test statistic was 0.874, indicating the reliability of the validation set.

DISCUSSION

ZAP can adversely affect patients’ abilities to perform daily self-care tasks, reduce their QoL, and significantly increase family and socioeconomic burdens [15]. Most cohort or case–control studies have focused on the risk factors and related predictive models of PHN [16, 17], but no study has evaluated factors related to the efficacy of hospitalization in patients with ZAP. To the best of our knowledge, this study was the first to evaluate risk factors affecting the efficacy of drugs plus nerve block therapy. Our study showed that the top risk factors for poor pain control in patients with ZAP treated with drugs plus nerve block therapy were admission NRS and complication with cancer. Sex, BMI, complication with diabetes, ALB, NEU%, and LYM% had little effect on pain control.

Previous studies on risk factors of PHN suggest that advanced age, prodromal pain, severe rash, severe acute pain, eye involvement, diabetes, and severe immunodeficiency are the main factors affecting the pathogenesis of PNH [7, 18, 19]. Our logistic regression analysis showed that higher admission NRS, cancer, and lower RBC count before treatment were independent risk factors for poor pain control in patients with ZAP treated with drugs plus nerve block therapy.

Admission NRS

A meta-analysis by Forbes et al. published in *Pain* suggests that severe acute pain before treatment is a risk factor for PHN (summary rate

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**Table 2: Poor pain control-related clinical characteristics of 429 patients associated with zoster-associated pain**

| Variable                        | \( Z \) | \( \chi^2 \) | \( P \) |
|---------------------------------|-------|---------|------|
| Sex                             | –     | 0.090   | 0.764|
| Age                             | –     | 2.928   | 0.006*|
| BMI                             | –     | 1.907   | 0.385|
| Course\(^a\)                    | –     | 6.560   | 0.038*|
| Diabetes                        | –     | 2.232   | 0.135|
| Cancer                          | –     | 8.770   | 0.003*|
| Location of Nerve block therapy | –     | 0.081   | 0.775|
| Admission NRS                   | –     | 5.445   | < 0.001*|
| WBC count                       | –     | 1.438   | 0.150|
| RBC count                       | –     | 2.945   | 0.003*|
| NEU%                            | –     | 1.320   | 0.187|
| LYM%                            | –     | 1.567   | 0.117|
| TP                              | –     | 1.764   | 0.078|
| ALB                             | –     | 2.456   | 0.014*|
| GLB                             | –     | 0.153   | 0.878|

\( BMI \) body mass index, \( Admission \) NRS numerical rating scale score on admission, \( WBC \) white blood cell, \( RBC \) red blood cell, \( NEU\% \) neutrophil percentage, \( LYM\% \) lymphocyte percentage, \( TP \) total protein, \( ALB \) albumin, \( GLB \) globulin

\(^a\)Statistical significance

\(^b\)Course of herpes zoster
ratio [SRR] 2.23; 95% CI 1.71–2.92) [18]. Our study considered admission NRS an independent risk factor for poor efficacy of drugs plus nerve block in ZAP (OR 2.001; 95% CI 1.579–2.537). Higher pain score before treatment often indicated more severe HZ neuritis, more severe peripheral nerve injury, and greater proneness to pain sensitivity changes, including peripheral and central sensitization [19–21].

Complication with Cancer

The relationship between HZ and cancer has been drawing more and more attention from clinical and scientific researchers [22, 23]. Qian et al. reported a cohort study indicating that cancer was associated with an increased risk of developing HZ (adjusted hazard ratio [HR] 1.41; 95% CI 1.32–1.52), which was partially compatible with a meta-analysis showing a positive association between HZ and occult cancer [22]. Our study also found a significant correlation between cancer and increasing risk of poor pain control (OR 4.813; 95% CI 1.518–15.259). Patients with cancer have impaired immune function [24], and HZ virus spreads in the skin and even viscera, which is more likely to cause serious complications.

RBC Count

Our results showed that RBC count was closely related to the efficacy of drugs plus nerve block therapy in the treatment of ZAP and that it was significantly lower in patients with poor pain control ($P = 0.003$). We reviewed the relevant papers on this phenomenon. There are many studies on RBC count and pain [25, 26]. And there have been suggestions that RBC is not only the main undertaker of gas exchange but also the secretor of signal peptide. Hemorphins are endogenous cryptides, belonging to the family of atypical opioid peptides, released during the sequential cleavage of hemoglobin.
proteins [27]. Hemorphins bind to different opioid receptors affecting pain, perception, and behavior [28]. Neokyotorphin is an atypical analgesic neuropeptide that produces analgesic effect and increases pain threshold by inhibiting the release of \(\gamma\)-aminobutyric acid in the brain [29, 30]. The efficacy of these two molecules has been found to be complementary to that of nerve block therapy. Therefore, we infer that these two blood-derived peptides may be able to explain the correlation between RBC count and pain control. However, further research is needed to determine this relationship. Our study has limitations and there is no further collection and statistics of hemoglobin data. In our prospective cohort study and future research, we will focus on this aspect, hoping to obtain more evidence.

Increase in age has been found to be associated with a sharp increase in PHN risk [18, 31]. However, we found no significant correlation between age and pain control, nor any significant difference in sex distribution between the two groups. In addition, we found significant differences in disease course and ALB levels between the PC and GC groups. The results suggested that patients with chronic HZ pain were more likely to have poor pain control than those with acute HZ pain, which might be related to central sensitization. In addition, ALB

### Table 3 Univariate binary logistic regression analysis of poor pain control

| Variable       | Regression coefficient (\(\beta\)) | OR  | 95% CI          | \(P\) |
|----------------|-----------------------------------|-----|-----------------|-------|
| Sex            | – 0.070                           | 1.073 | 0.679–1.695    | 0.764 |
| Age            | 0.029                             | 1.029 | 1.008–1.051    | 0.006*|
| BMI            | –                                 | –    | –              | 0.397 |
| Course\(^a\)   | –                                 | –    | –              | 0.040*|
| Course (1)\(^b\)| 0.447                            | 1.564 | 0.930–2.630    | 0.092 |
| Course (2)\(^c\)| 0.745                            | 2.107 | 1.144–3.879    | 0.017*|
| Diabetes       | 0.439                             | 1.551 | 0.869–2.767    | 0.137 |
| Cancer         | 1.458                             | 4.296 | 1.516–12.172   | 0.006*|
| Admission NRS  | 0.652                             | 1.919 | 1.546–2.383    | < 0.001*|
| WBC count      | 0.062                             | 1.064 | 0.966–1.172    | 0.209 |
| RBC count      | – 0.691                           | 0.501 | 0.312–0.803    | 0.004*|
| NEU\%          | 0.014                             | 1.014 | 0.994–1.035    | 0.160 |
| LYM\%          | – 0.019                           | 0.981 | 0.958–1.004    | 0.102 |
| TP             | – 0.038                           | 0.962 | 0.926–1.000    | 0.052 |
| ALB            | – 0.081                           | 0.922 | 0.864–0.984    | 0.014*|
| GLB            | – 0.012                           | 0.988 | 0.937–1.041    | 0.644 |

\(OR\) odds ratio, \(CI\) confidence interval, \(BMI\) body mass index, \(Admission NRS\) numerical rating scale score on admission, \(WBC\) white blood cell, \(RBC\) red blood cell, \(NEU\%\) neutrophil percentage, \(LYM\%\) lymphocyte percentage, \(TP\) total protein, \(ALB\) albumin, \(GLB\) globulin

\(^a\)Course of herpes zoster

\(^b\)Subacute phase vs acute phase

\(^c\)Chronic phase vs acute phase

*Statistical significance
levels in the poor control group were low, which might be related to deficits in nutritional status, weak physical condition, and low immunity [32].

Some negative findings in our study were also interesting. Many studies have identified diabetes as a risk factor for PHN [18, 33]. However, our study showed that it was not a risk factor for poor pain control. Our analysis indicated that the nerve block used in clinical work at our center mostly acts on the spinal nerve root or nerve trunk. Diabetes often causes peripheral neuropathy, which would have little effect on pain control in this therapy.

This study addressed the lack of strong research assessing risk factors for poor control of HZ neuropathic pain. However, it has several limitations, such as whether the relevant factors

| Variable         | Regression coefficient (β) | Crude OR | 95% CI            | P     |
|------------------|-----------------------------|----------|-------------------|-------|
| Age              | 0.005                       | 1.005    | 0.981–1.029       | 0.707 |
| Course<sup>a</sup> | –                          | –        | –                 | 0.072 |
| Cancer           | 1.429                       | 4.173    | 1.342–12.970      | 0.014*|
| Admission NRS    | 0.657                       | 1.929    | 1.528–2.434       | < 0.001*|
| RBC count        | –                           | 0.560    | 0.328–0.954       | 0.033*|
| ALB              | –                           | 0.997    | 0.922–1.078       | 0.940 |

OR odds ratio, CI confidence interval, Admission NRS numerical rating scale score on admission, RBC red blood cell, TP total protein, ALB albumin

<sup>a</sup>Course of herpes zoster

*Statistical significance
discussed in this article were also risk factors for ineffectiveness of other treatments, whether some risk factors were not considered, and unsatisfactory sample size. In addition, in recent years, our center has adopted nerve radiofrequency modulation therapy or spinal-cord electrostimulation therapy for patients with poor pain control. The spinal-cord electrostimulation therapy has achieved good results, and the research results on the difference between the two treatments need to be further sorted out. In the future, we must continue to study these issues to further confirm our results.

CONCLUSIONS

This study identified three independent risk factors for poor pain control in patients with HZ neuropathic pain treated with drugs plus nerve block therapy. To a certain extent, it can guide clinicians to make the most appropriate pain treatment decisions.

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**Author Contributions.** Weijun Gong: study concept and design. Ruifeng Sun: acquisition of data, analysis and interpretation, critical revision of the manuscript for important intellectual content. Ning Wang and Hai Mou: analysis and interpretation. Can Gao and Lv Yu: acquisition of data. Wenshan Li, Tiancong Li and Peiling Huang: critical revision of the manuscript for important intellectual content, study supervision. All authors read and approved the final manuscript.

**Disclosures.** During the completion of this study, the affiliation of author Ruifeng Sun changed from Department of Pain and Rehabilitation, Xinqiao Hospital, Army Medical University, Chongqing, China to Beijing Rehabilitation Medicine Academy, Capital Medical University, Beijing, China. Ning Wang, Hai Mou, Can Gao, Lv Yu, Wenshan Li, Tiancong Li, Peiling Huang, and Weijun Gong have nothing to disclose.

**Compliance with Ethics Guidelines.** The protocol was approved by the ethics committee of Xinqiao Hospital Army Medical University, Chongqing, China (2021 Research No. 095–01).

**Data Availability.** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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