ORIGINAL RESEARCH

Retrospective Clinical Observation of Correlation between Galectin-3 and Early Herpes Zoster Neuralgia and Post-herpetic Neuralgia

Wei Wang, MM; Xixi Liu, MD

ABSTRACT

Background • Herpes Zoster Neuralgia (HZN) and Post-Herpetic Neuralgia (PHN) are neuropathic pain conditions following Varicella Zoster Virus infection. PHN primarily affects individuals aged 60 and above and the pervasive and severe neuropathic pain in PHN leads to significant emotional and psychological distress in approximately 80%-90% of patients, precipitating a decline in their overall quality of life and that of their families. Galectin-3, a pro-inflammatory factor, is implicated in inflammatory responses, potentially influencing neuronal damage and pain signal transmission.

Objective • This study aims to evaluate the clinical relevance of serum Galectin-3 in HZN and PHN patients, alongside other contributing factors.

Methods • We retrospectively analyzed data collected from 40 HZN patients, 40 non-HZN patients, and 20 healthy controls in our hospital between 2015 and 2017. Variables included demographic data, clinical characteristics, and inflammatory markers. Statistical analyses comprised t-tests, ANOVA, chi-square tests, and multivariate logistic regression. A Receiver Operating Characteristic (ROC) curve was constructed to evaluate Galectin-3's predictive value for PHN.

Results • PHN patients showed significantly higher ages, NRS scores, and prevalence of shingles in the head and neck region compared to Non-PHN and Non-HZN groups ($P < .05$). Elevated levels of IL-6 (66.33±8.93 pg/mL) and Galectin-3 (2.44±0.29 ng/mL) were observed in HZN patients. Galectin-3 emerged as a significant risk factor for PHN development ($P < .05$), while other factors such as age, shingles location, IL-6, and T lymphocyte subsets did not show a significant impact.

Conclusion • Galectin-3 may serve as a predictive biomarker for PHN development, offering insights into its pathophysiology and potential therapeutic targets. Patients with elevated Galectin-3 levels might benefit from specific targeted therapies or interventions aimed at reducing Galectin-3 levels and mitigating its effects. (*Altern Ther Health Med.* 2024;30(10):465-471).

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INTRODUCTION

Herpes zoster, a dermatological condition marked by acute inflammation and resulting from the varicella-zoster virus (VZV), exhibits an incidence rate ranging between 2.9 to 19.5 cases per 1000 individuals.[1] The incidence of herpes zoster is influenced by various factors such as age, sex, immune status, and vaccination.[2] Among these factors, age is the most certain and widely recognized risk factor, with the incidence of HZ increasing with age. Immunosuppressed states, such as weakened immune system function or the use of immunosuppressive drugs, also increase the risk of developing herpes zoster. Additionally, vaccination can reduce the incidence of herpes zoster, particularly with the widespread use of varicella and herpes zoster vaccines. Manifesting predominantly on the face or one side of the body, herpes zoster precipitates neurological afflictions, leading to severe neuropathic pain syndromes, with symptoms persisting for months or years, thus gravely diminishing patient quality of life due to VZV's neurotropism. Herpes zoster neuralgia (HZN) typically presents during the acute phase, whereas post-herpetic neuralgia (PHN), common sequelae, is characterized by enduring, intense pain. While pain from herpes zoster typically resolves within 2 to 4 weeks, PHN denotes pain persisting beyond 4 to 9 weeks. Neuropathic pain caused by PHN has a significant impact on patients' daily life and health, and may lead to persistent pain, fatigue, sleep disturbances, anxiety, and depression.[3] The pathogenesis of acute pain and its progression to PHN involves intricate interactions among the virus, immune, and nervous systems,

the VZV can remain latent in nerve ganglia and be reactivated when the immune system is weakened, leading to inflammation and nerve damage, which triggers abnormal activation of pain pathways.[4-6]

Symptoms of mechanical allodynia and thermal hyperalgesia distinguish PHN. Advanced neuroimaging studies have uncovered abnormalities in brain structures and functions associated with sensory and emotional processing.[7] Alterations in gray matter volume and intrinsic functional connectivity in specific brain regions are intricately associated with the evolution of PHN from herpes zoster.[8] Currently, PHN represents a challenging, intractable pain condition predominantly afflicting middle-aged and elderly individuals. The pain, ranging from moderate to severe, is characterized by its heterogeneity and protracted duration, often lasting several months to years, even decades. The pervasive and severe pain in PHN leads to significant emotional and psychological distress in approximately 80%-90% of patients, precipitating a decline in their overall quality of life and that of their families. Despite its prevalence, the etiology of PHN remains enigmatic and efficacious treatment strategies continue to be a global challenge.

Galectin-3, a ubiquitous endogenous β-galactoside-binding lectin in humans,[9] stands as the sole chimeric member within the galectin family, comprising three distinct domains: (1) a highly conserved N-terminal domain with 12 amino acid residues, pivotal for galectin-3 secretion; (2) a proline-glycine-tyrosine tandem repeat domain, serving as a substrate for matrix metalloproteinases; (3) a C-terminal carbohydrate recognition domain (CRD) consisting of 140 amino acid residues, capable of binding glycosyl groups.[10,11] Galectin-3 has garnered escalating interest in recent research, playing an integral role in various biological processes, including immune and inflammatory responses, cell proliferation, differentiation, and apoptosis. Its substantial research value has made galectin-3 a prominent marker in disease progression and prognostic evaluations.[12-15] Therefore, as a multifunctional biomarker, Galectin-3 may play an important role in the pathogenesis of HZN and PHN. However, the role of Galectin-3 in HZN and PHN has been relatively unexplored.

This study aims to evaluate the clinical relevance of serum galectin-3 levels in patients with HZN and PHN and as well as to analyze additional factors contributing to the onset of HZN and PHN.

MATERIALS AND METHODS

Recruitment of Clinical Participants

The study categorized participants into three distinct cohorts: the Herpes Zoster Neuralgia (HZN) group, comprising forty patients admitted between 2015 and 2017 and diagnosed with HZN; the Non-HZN group, consisting of forty patients without herpes zoster neuralgia; and the Control group, encompassing twenty healthy individuals. Following hospital discharge, the HZN group underwent a month-long follow-up, during which they were subdivided into the Post-Herpetic Neuralgia (PHN) group for patients still experiencing pain after one month and the Non-PHN group, for those without pain.

Inclusion criteria for the HZN group entailed a documented history of VZV infection, presentation of cutaneous manifestations such as erythematous patches, vesicles, or ulcers accompanied by pain and pruritus, typically following a nerve distribution; first-time hospital visitation; age between 30 and 80 years; cognizance and agreement with the study's objectives, alongside voluntary participation consent. We selected patients within the age range of 30 to 80 years because PHN is more likely to occur in this age group. This allowed us to obtain an adequate sample size for reliable statistical analysis and to ensure that the results have clinical relevance. We included variables such as gender and other factors because they may be associated with the development and outcomes of the disease under study. By collecting this information, we aimed to gain a more comprehensive understanding of the characteristics of the study population and conduct further analysis. Exclusion criteria included incomplete patient data, concurrent neuralgia from other etiologies, prior self-administered or hospital-provided antiviral or neurotrophic treatments, disease course exceeding ten days, severe cardiopulmonary or renal pathologies, chronic steroid or immunosuppressant use, ongoing malignant tumor therapy, and any other contraindications to steroid use.

The HZN group received routine pharmacotherapy and nerve blockade tailored to individual patient conditions by clinical physicians. This investigation received approval from the Wenling Hospital of Traditional Chinese Medicine's Medical Ethics Committee, and informed consent was obtained from each participant.

Demographic Data Collection

Comprehensive clinical data encompassing gender, age, cephalic and cervical herpes zoster manifestations, standardized treatment initiation within 72 hours of onset, complications, Numeric Rating Scale (NRS) scores, and lesion extent in HZN patients were meticulously recorded. The NRS scores ranged from 0 to 10 (0: No pain; 1-3: Mild pain, can be tolerated; 4-6: Moderate pain, interferes with normal activities; 7-9: Severe pain, seriously affects daily life; 10: Most intense pain, unbearable). Lesion area was assessed as a percentage relative to the individual's palm size, where the palm represented 1% of the total body surface area, and lesions were categorized as small (<3%), medium (3%–5%), or large (>5%).

Galectin-3 and IL-6 Quantification

A 5 ml venous blood sample was extracted from each patient's elbow, left to settle for 30 minutes, and then centrifuged at 1,000 rpm for 15 minutes. The supernatant serum was collected and stored at -80°C. Serum Galectin-3 levels were measured using a commercial enzyme-linked immunosorbent assay (ELISA) kit (ZK-H1734, 0.3-10 ng/

mL, Shenzhen Zikang Biological Technology Co., Ltd.). The process involved adding 100 µL of HRP-labeled detection antibody to 50 µL of the sample, sealing the wells, and incubating at 37°C for 60 minutes. Following a thorough washing procedure, 50 µL each of substrates A and B were added and incubated in darkness at 37°C for 15 minutes, followed by 50 µL of stop solution. The optical density (OD) at 450 nm wavelength was measured within 15 minutes, and a standard curve was drawn from the standard sample OD values to determine Galectin-3 levels in the test samples. We followed the quality control measures provided by the manufacturer, including the use of quality control samples and standard curves.

Similarly, serum IL-6 levels were quantified using an ELISA, in accordance with the ZK-HZ238 kit protocol (4.69-500pg/mL, Shenzhen Zikang Biological Technology Co., Ltd.), utilizing two monoclonal antibodies recognizing distinct IL-6 epitopes for sample binding and enzyme-linked colorimetric reaction. We adhered to the manufacturer's recommended quality control measures, which involved utilizing quality control samples and standard curves as part of our assay protocol.

T Lymphocyte Subset Analysis

Peripheral blood lymphocyte subset expression levels of CD3+, CD4+, and CD8+ were analyzed via flow cytometry (Coulter, Beckman Company, USA). The assay involved adding 2 µL PE-Cy7 anti-mouse CD8 Antibody (BD), 1 µL PE anti-mouse CD4 Antibody (eBio), and 2 µL FITC anti-mouse CD8 Antibody (eBio) to 100 µL of anticoagulated blood. The mixture was incubated in darkness for 30 minutes, followed by red blood cell lysis and subsequent centrifugation steps. The final cell pellet was resuspended in 500 µL of PBS for flow cytometric analysis. We validate the accuracy of our analysis by using positive and negative samples, exclude cell debris and dead cells using gating strategies, and determine the gating position for the formal antibody staining using isotype controls.

Statistical Analysis

Data analysis was conducted using SPSS 19.0 (SPSS Inc., Chicago, IL). Normally distributed continuous data were expressed as mean ± standard deviation ($\bar{x} \pm s$), and inter-group comparisons were conducted using the *t* test or one-way ANOVA. Categorical data, such as gender and comorbidities, were presented as percentages or absolute numbers, with the chi-square test employed for group comparisons. We employed a multivariate logistic regression model to evaluate the relationship between Galectin-3, IL-6, CD3+, CD4+, CD8+, and CD4+/CD8+ and the incidence of HZN and PHN. Additionally, we utilized Receiver Operating Characteristic (ROC) curve analysis to assess the predictive capacity of Galectin-3 and IL-6 levels regarding the occurrence of HZN and PHN. $P < .05$ was deemed statistically significant.

RESULTS

Demographic Data Interpretation

The demographic characteristics of 40 HZN patients, 40 Non-HZN patients, and 20 healthy controls were statistically analyzed. Age and gender were included as demographic variables because they were important factors in the occurrence of PHN. Age was an independent risk factor for PHN, with the incidence of PHN increasing as age advances. Gender was also considered a factor in the development of PHN, with females being more susceptible to PHN than males. Including age and gender in the analysis helped control for the influence of these factors on the relationship between PHN and Galectin-3. This allowed for a more accurate assessment of the significance of Galectin-3 as a primary risk factor for PHN, independent of factors such as age and gender. Therefore, age and gender were included as demographic variables in the study to comprehensively evaluate the risk factors for PHN and the role of Galectin-3. However, our findings revealed no significant disparities in age and gender among these groups: the HZN, the Non-HZN, and the Control group (Table 1). The mean age was 65.05±9.91 in the HZN group, 62.93±4.92 in the Non-HZN group, and 63.50±5.81 in the healthy control group.

The HZN cohort was further dichotomized into PHN and Non-PHN subgroups based on the persistence of severe pain one-month post-shingles recovery. Notably, the PHN subgroup exhibited a significantly higher mean age, NRS scores and a higher incidence of shingles on the head and neck compared to both the Non-PHN and Non-HZN groups ($P < .05$) (Table 1). The Non-HZN group showed a significantly lower prevalence of comorbid diseases compared to the PHN group ($P < .05$); however, no significant differences were observed in comorbid diseases between the Non-PHN and PHN groups ($P > .05$). Gender, lesion surface area, and initiation of standard treatment within 72 hours post-onset of shingles did not demonstrate significant differences across the groups ($P > .05$) (Table 1).

Table 1. Data analysis of demography

Variable	HZN (n = 40)		Non-HZN (n = 40)	F/χ^2	*P* value
	PHN (n = 15)	Non-PHN (n = 25)			
age	69.93±8.98	61.56±7.44	62.93±4.92	5.008	.01
gender					
male	7 (46.67%)	13 (52)	21 (52.5)	2.385	.30
female	8 (53.33)	12 (48)	19 (47.5)		
NRS score	7.00±0.65	4.28±0.94	4.35±0.53	11.12	<.01
surface area of the skin					
<3%	4(26.67)	7(28)	8(20)	7.16	.13
3%-5%	7(46.66)	11(44)	19(47.5)		
>5%	4(26.67)	7(28)	13(32.5)		
shingles on the head and neck					
yes	10(66.67)	8(32)	12(30)	10.08	<.01
no	5(33.33)	17(68)	28(70)		
standardized treatment within 72 hours of shingles onset					
Yes	4(26.67)	8(32)	9(22.5)	3.17	.20
No	11(73.33)	17(68)	31(77.5)		
combined disease					
Yes	13(86.67)	20(80)	24(60)	6.17	.046
No	2(13.33)	5(20)	16(40)		

Table 2. Comparison of IL-6, Galectin-3, CD3+, CD4+, CD8+, and CD4+/CD8+ among HZN group, Non-HZN group and the Control group

Variable	HZN (n = 40)	Non-HZN (n = 40)	Control (n = 20)	F/χ^2	*P* value
IL-6	66.33±8.93	35.15±3.13	7.25±1.16	702.84	<.01
Galectin-3	2.44±0.29	2.20±0.14	2.02±0.13	34.64	<.01
percentage of CD3+	73.56%±6.01%	68.5%±4.8%	80.3%±3.5%	73.15	<.01
percentage of CD4+	48.1%±1.56	42.5%±3.8%	55.6%±2.9%	110.39	<.01
percentage of CD8+	24.98%±0.04%	23.8%±2.5%	18.7%±1.9%	171.19	<.01
The ratio of CD4+/CD8+	1.82±0.2	1.7±0.2	2.9±0.3	14.84	<.01

Table 3. Comparison of IL-6, Galectin-3, CD3+, CD4+, CD8+, and CD4+/CD8+ among PHN group and Non-PHN group

Variable	PHN (n = 15)	Non-PHN (n = 25)	F/χ^2	*P* value
IL-6	76±4.12	60.52±5.11	60.63	<.01
Galectin-3	2.79±0.13	2.23±0.10	142.02	<.01
percentage of CD3+	70.2%±5.6%	75.8%±6.2%	14.11	<.01
percentage of CD4+	44.8%±4.2%	50.2%±5.1%	28.13	<.01
percentage of CD8+	25.4%±3.8%	27.6%±3.2%	3.07	.09
The ratio of CD4+/CD8+	1.9±0.3	1.8±0.2	0.03	<.05

Comparative Analysis of IL-6, Galectin-3, and T Lymphocyte Subsets

Elevated levels of IL-6 and Galectin-3 were found in HZN patients compared to both Non-HZN and Control groups ($P < .01$), as shown in Figure 1. The Non-HZN group also presented significantly higher IL-6 levels than the Control group ($P < .01$). However, Galectin-3 levels did not show a significant difference between the Non-HZN and Control groups (Table 2). These observations suggest a potential predictive role of Galectin-3 in HZN occurrence.

CD3+, CD4+, CD8+, and CD4+/CD8+ were commonly used markers for T lymphocyte subsets. The differences observed in the proportions of these subsets may have potential implications for the pathogenesis and treatment of herpes zoster neuralgia (HZN). Changes in the proportion of CD4+ may be associated with immune dysregulation in HZN, affecting the body's control of the virus and inflammatory response. CD8+ were essential components of cellular immune responses and were primarily responsible for killing infected cells. Variations in the proportion of CD8+ may be related to immune responses and viral clearance in HZN. The CD4+/CD8+ ratio was an indicator used to assess immune system function and balance. Changes in this ratio may reflect immune system activity and imbalance, which could be relevant to the pathological process and immune regulation in HZN. T lymphocyte subset analysis indicated that the Control group had significantly higher proportions of CD3+, CD4+, and CD4+/CD8+ T lymphocytes compared to the HZN and Non-HZN groups ($P < .01$) (Figure 1, Table 2). No significant differences were observed in CD8+ proportions between the HZN and Non-HZN groups, though both were significantly higher than the Control group ($P < .01$) (Figure 1, Table 2).

These results underscore a potential association between elevated IL-6 and Galectin-3 levels and the development of HZN. Moreover, alterations in T lymphocyte subsets may also contribute to HZN pathogenesis, offering new insights for its prevention and treatment.

Figure 1. Comparison of IL-6, Galectin-3, CD3+, CD4+, CD8+ and the ratio of CD4+/CD8+ among the HZN group, Non-HZN group and Control group.

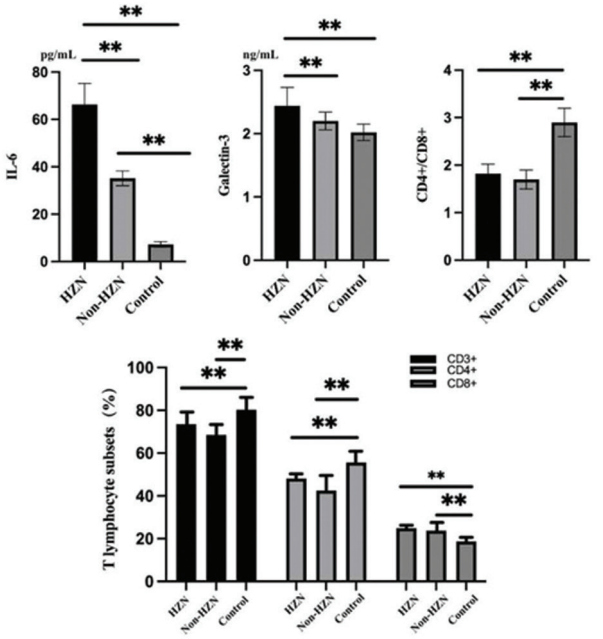
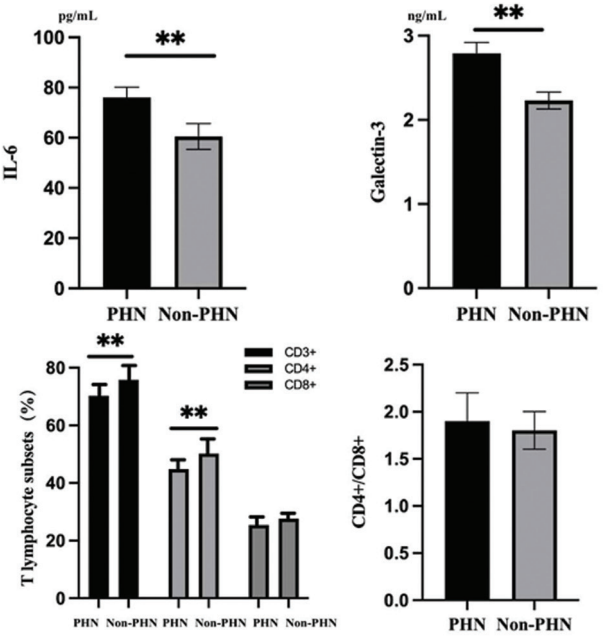


Figure 2 Comparison of IL-6, Galectin-3, CD3+, CD4+, CD8+ and the ratio of CD4+/CD8+ among PHN group and Non-PHN group.



Comparative Analysis in PHN and Non-PHN Groups

Elevated levels of IL-6 (76±4.12 pg/ml vs 60.52±5.11 pg/ml, $P < .01$)) and Galectin-3 (2.79±0.13 vs 2.23±0.10, $P < .01$) were observed in the PHN group compared to the Non-PHN group, and significant differences in CD3+ and CD4+ T lymphocyte percentages and CD4+/CD8+ ratio ($P < .05$) were found between the two groups (Table 3). However, there was no significant difference in CD8+ percentages (Figure 2).

Galectin-3 as a Risk Factor for PHN

Multiple logistic regression analysis, with PHN occurrence as the dependent variable, identified Galectin-3 as a primary risk factor influencing PHN development, as indicated by a $P < .05$ (Table 4). This finding indicated a close association between the presence of Galectin-3 and the occurrence of PHN. Elevated levels of Galectin-3 may increase the individual's risk of developing PHN. This has important clinical implications as it provides a novel approach to predict and assess the risk of PHN. By detecting and monitoring Galectin-3 levels, doctors can identify individuals at risk of developing PHN at an earlier stage and implement appropriate interventions. This can contribute to early treatment and management of PHN, alleviating the pain and discomfort experienced by patients. However, it is important to note that this result still requires further research and validation. Other variables, including age, NRS score, shingles on the head and neck, IL-6, CD3+, and CD4+ did not significantly impact PHN occurrence ($P > .05$) (Table 4).

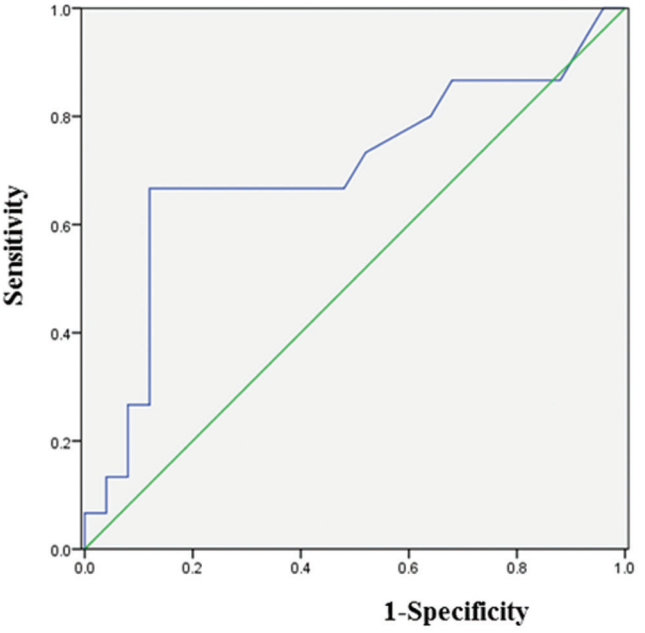
Table 4. Multiple logistic regression analysis for PHN.

Variable	B	S.E.	Wald	Exp (B)	95% CI		*P* value
					Lower limit	Upper limit	
age	0.062	0.046	1.841	1.064	0.947	1.196	.175
NRS score	0.021	0.077	0.076	1.021	0.875	1.190	.783
shingles on the head and neck	0.008	0.879	0.001	1.008	0.160	6.335	.974
IL-6	0.043	0.045	0.932	1.044	0.956	1.140	.335
Galectin-3	2.915	1.029	7.970	18.478	2.334	146.231	.005
CD3+	-0.154	0.144	1.152	0.858	0.652	1.130	.283
CD4+	-0.166	0.139	1.431	0.847	0.649	1.105	.232

ROC Analysis for Galectin-3 in PHN Prediction

The area under the curve (AUC) is a measure used to assess the accuracy of Galectin-3 as a biomarker for PHN prediction. It ranges from 0 to 1, where a value closer to 1 indicates higher accuracy in predicting PHN. Generally, an AUC value greater than 0.5 is considered to have some predictive ability, while a value closer to 1 indicates higher accuracy. Sensitivity refers to the ability to correctly identify individuals with PHN among all PHN patients. It represents the ability of Galectin-3 as a biomarker to detect individuals with PHN. Higher sensitivity means Galectin-3 can better detect PHN patients. Specificity refers to the ability to correctly identify individuals without PHN among all non-PHN patients. It represents the ability of Galectin-3 as a biomarker to exclude individuals without PHN. The Receiver Operating Characteristic (ROC) curve analysis of serum Galectin-3 levels in predicting PHN revealed an AUC of 0.7 (95% CI: 0.517 - 0.883, $P < .05$), as illustrated in Figure 3. The optimal threshold identified was 2.52 ng/ml, with a sensitivity of 66.7% and specificity of 88.0%. These findings position Galectin-3 as a viable biomarker for predicting PHN.

Figure 3 ROC curve distribution of galectin-3 for PHN. (AUC was 0.7 (95% CI: 0.517 - 0.883, $P < .05$))



DISCUSSION

Shingles, clinically known as herpes zoster, emerges as a contagious dermatological affliction caused by the reactivation of the dormant VZV within spinal or cranial nerve ganglia. This condition, apart from its characteristic skin lesions, is frequently accompanied by neuropathic pain. Age is acknowledged as a significant risk factor for PHN,[16] a finding corroborated by this study, which noted an escalation in PHN incidence with advancing age. Furthermore, the anatomical location of the herpes zoster outbreak is linked to the development of PHN. Typically, herpes zoster affecting the head and neck regions is more prone to evolve into PHN, with pain potentially intensifying post-recovery.

In contrast, limb-involved herpes zoster, regardless of the severity of pain, usually does not lead to PHN. The pathophysiological mechanisms of PHN are complex and involve multiple factors. Inflammation and nerve damage caused by viral infection are among the main mechanisms of PHN development. During viral infection, the immune system is activated and releases inflammatory mediators such as cytokines and chemokines. These inflammatory mediators can activate pain signaling pathways and cause abnormal neuronal excitation, leading to neuropathic pain. Some theories suggest a correlation between abnormal neurotransmitter release after viral infection and persistent neuropathic pain. Additionally, intracellular mechanisms such as altered neuronal metabolism and signaling pathways may also play a role.[17] Clinically, the prevention of PHN is prioritized, advocating short-term corticosteroid therapy in conjunction with early and adequate antiviral treatment, especially for individuals over 60 and those with cephalic herpes zoster, to effectively prevent the development of PHN. Prompt treatment for herpes zoster is advised, alongside bolstering immunity to prevent the condition. Vaccination against VZV is recommended for middle-aged, elderly, and high-risk individuals with underlying conditions.

T lymphocyte subsets play a crucial role in cell-mediated immunity, virus resistance, and immune regulation. The immune function relies on the total count of T lymphocytes (CD3+) and the relative composition of CD4+ and CD8+ subsets. Typically, these subsets balance each other to maintain immune equilibrium. Immune dysregulation, characterized by altered cell counts and ratios, can make individuals more susceptible to diseases. CD4+ T lymphocytes primarily modulate and enhance immune responses, while CD8+ T lymphocytes are mainly responsible for eliminating infected and neoplastic cells. The CD4+/CD8+ ratio serves as an indicative measure of immune function status. In patients with PHN, the levels of CD3+ and CD4+ were significantly lower compared to non-PHN individuals. A recent study has demonstrated that a significant decrease in peripheral blood CD3+ and CD4+ can lead to severe autoimmune disorders.[18] These findings suggest a close relationship between the decrease in T lymphocyte subsets and the occurrence of PHN. Specific T-cell immune function can prevent virus activation, which is particularly important in the elderly and immunocompromised individuals. The increased risk of PHN in older adults is also due to a reduced number of VZV-specific CD4+ lymphocytes in the serum, which is attributed to a decrease in CD4+ lymphocyte subset expression with age.[19] Studies have shown that patients with CD4+ and CD8+ deficiency are at a higher risk of herpes zoster virus infection and are relatively more prone to developing PHN.[20]

Interleukin-6 (IL-6), discovered by Weissenbach in 1980, is a multifunctional cytokine primarily produced by T cells, monocytes/macrophages, and endothelial cells. It is involved in acute inflammatory responses, human metabolism, autoimmune cell differentiation, and certain disease treatments.[21] IL-6 not only affects the immune system but also exerts extensive effects on the nervous, endocrine, and cardiovascular systems. In inflammatory responses, IL-6 increases precede other factors and have a prolonged presence, making it useful in early acute infection diagnosis. In this study, the serum levels of IL-6 in patients with PHN were significantly higher than those in non-PHN patients, suggesting that patients with high levels of IL-6 were more likely to develop PHN. IL-6 is associated with postherpetic neuralgia (PHN) and can regulate the production of inflammatory mediators and neuronal excitability, and participate in the development of neuropathic pain. IL-6 may damage the nervous system under conditions of high expression.[22] Additionally, the neuroendocrine effects of IL-6 may also impact pain perception and inflammatory responses in PHN patients.

Galectin-3 is a multifunctional protein expressed in various cell types and tissues, including endothelial cells, epithelial cells, activated microglial cells, inflammatory cells (mainly macrophages), and organs such as the spleen, stomach, colon, liver, kidney, heart, uterus, ovary, and pancreas. It plays a role in multiple biological functions, particularly in immune regulation and inflammatory responses. Previous research has highlighted Galectin-3's involvement in various physiological processes and its significant role in disease pathogenesis, particularly in inducing inflammatory responses.[23-25] In this study, elevated Galectin-3 levels were observed in the herpetic neuralgia (HZN) and postherpetic neuralgia (PHN) groups compared to others. Logistic regression analysis further identified Galectin-3 as a risk factor for PHN development. These results propose Galectin-3 as a novel biomarker for predicting PHN. The precise mechanism of Galectin-3's involvement in PHN is yet to be fully understood. Research suggests that Galectin-3 may affect the development of neuropathic pain by interacting with the ERK 1/2 signaling pathway and regulating the activation state of microglia. Galectin-3 is expressed in F4/80 and Iba1-positive cells in the spinal dorsal horn, indicating that these cells are Galectin-3 secretors.[26] Galectin-3 stimulates the expression and phosphorylation of extracellular signal-regulated kinase 1/2 (ERK 1/2) mRNA.[27,28] In neuropathic pain states, the ERK 1/2 pathway is activated in spinal dorsal horn neurons, and Galectin-3 is implicated in this activation.[29,30] Thus, the induction of herpetic pain may involve Galectin-3-mediated ERK1/2 activation. Moreover, evidence suggests that factors released by activated microglia play a crucial role in the development of neuropathic pain, indicating another potential mechanism involving Galectin-3 and microglia. These mechanisms may lead to abnormal neuronal excitability and activation of pain transmission pathways. The discovery of Galectin-3 as a potential biomarker for predicting PHN has important clinical implications and may have a significant impact on clinical practice. By measuring Galectin-3 levels, doctors can identify the risk of PHN in patients earlier and take appropriate preventive and therapeutic measures. Furthermore, further research into the role of Galectin-3 in the development of PHN may provide clues for the development of new treatment methods and drugs and guide further investigations.

This study's limitations include inherent selection and recall biases due to its retrospective nature and the insufficient sample size. These limitations may affect the generalizability of our research findings. Therefore, future studies with larger sample sizes and long-term prospective follow-up are needed to validate our observations and gain a better understanding of the roles of Galectin-3, IL-6, and T lymphocyte subgroups in the development of PHN.

CONCLUSION

This investigation underscores Galectin-3 as a predictive biomarker for PHN development, offering insights into its pathophysiology and potential therapeutic targets. Patients with elevated Galectin-3 levels might benefit from specific targeted therapies or interventions aimed at reducing Galectin-3 levels and mitigating its effects. Despite the study's constraints, these findings lay a foundational groundwork for future research and underscore the significance of early intervention and preventive strategies in managing these debilitating conditions.

AUTHOR'S CONTRIBUTION

Wei Wang is responsible for study design, data collection, preparation of manuscript, and literature search. Xixi Liu is responsible for study design, data collection, data analysis, and data interpretation.

REFERENCE

1. van Oorschot D, Vroling H, Bunge E, Diaz-Decaro J, Curran D, Yawn B. A systematic literature review of herpes zoster incidence worldwide. *Hum Vaccin Immunother*. 2021;17(6):1714-1732. doi:10.1080/21645515.2020.1847582
2. Kawai K, Gebremeskel BG, Acosta CJ. Systematic review of incidence and complications of herpes zoster: towards a global perspective. *BMJ Open*. 2014;4(6):e004833. Published 2014 Jun 10. doi:10.1136/bmjopen-2014-004833
3. Johnson RW, Rice AS. Clinical practice. Postherpetic neuralgia. *N Engl J Med*. 2014;371(16):1526-1533. doi:10.1056/NEJMcp1403062
4. Ou M, Chen J, Yang S, Xiao L, Xiong D, Wu S. Rodent models of postherpetic neuralgia: How far have we reached?. *Front Immunol*. 2023;14:1026269. Published 2023 Mar 20.
5. Philip A, Thakur R. Post herpetic neuralgia. *J Palliat Med*. 2011;14(6):765-773. doi:10.1089/jpm.2011.9685
6. Peng WW, Guo XL, Jin QQ, et al. Biological mechanism of post-herpetic neuralgia: evidence from multiple patho-psychophysiological measures. *Eur J Pain*. 2017;21(5):827-842. doi:10.1002/ejp.985
7. Wollina U, Machetanz J. Herpes zoster und postzosterische Neuralgie. [Herpes zoster and postherpetic neuralgia]. *Hautarzt*. 2016;67(8):653-665. doi:10.1007/s00105-016-3834-y
8. Tang Y, Ren C, Wang M, et al. Altered gray matter volume and functional connectivity in patients with herpes zoster and postherpetic neuralgia. *Brain Res*. 2021;1769:147608. doi:10.1016/j.brainres.2021.147608
9. Lakshminarayan R, Wunder C, Becken U, et al. Galectin-3 drives glycosphingolipid-dependent biogenesis of clathrin-independent carriers. *Nat Cell Biol*. 2014;16(6):595-606. doi:10.1038/ncb2970
10. Hayashi Y, Jia W, Kidoya H, Muramatsu F, Tsukada Y, Takakura N. Galectin-3 Inhibits Cancer Metastasis by Negatively Regulating Integrin β3 Expression. *Am J Pathol*. 2019;189(4):900-910. doi:10.1016/j.ajpath.2018.12.005
11. Song L, Tang JW, Owusu L, Sun MZ, Wu J, Zhang J. Galectin-3 in cancer. *Clin Chim Acta*. 2014;431:185-191. doi:10.1016/j.cca.2014.01.019
12. Mishra BB, Li Q, Steichen AL, et al. Galectin-3 functions as an alarmin: pathogenic role for sepsis development in murine respiratory tularemia. *PLoS One*. 2013;8(3):e59616. doi:10.1371/journal.pone.0059616
13. Erriah M, Pabreja K, Fricker M, et al. Galectin-3 enhances monocyte-derived macrophage efferocytosis of apoptotic granulocytes in asthma. *Respir Res*. 2019;20(1):1. Published 2019 Jan 3. doi:10.1186/s12931-018-0967-9
14. Agoston-Coldea L, Bheecarry K, Petra C, et al. The value of global longitudinal strain and galectin-3 for predicting cardiovascular events in patients with severe aortic stenosis. *Med Ultrason*. 2018;20(2):205-212. doi:10.11152/mu-1456
15. Li P, Liu S, Lu M, et al. Hematopoietic-Derived Galectin-3 Causes Cellular and Systemic Insulin Resistance. *Cell*. 2016;167(4):973-984.e12. doi:10.1016/j.cell.2016.10.025
16. Dai YX, Yeh FY, Shen YJ, et al. Cigarette smoking and risk of herpes zoster: a population-based cohort study in Taiwan. *Clin Exp Dermatol*. 2021;46(7):1293-1298. doi:10.1111/ced.14650
17. Stepanović A, Kolšek M, Kersnik J, Erčulj V. Prevention of post-herpetic neuralgia using transcutaneous electrical nerve stimulation. *Wien Klin Wochenschr*. 2015;127(9-10):369-374. doi:10.1007/s00508-014-0669-3
18. Cassis L, Aiello S, Noris M. Natural versus adaptive regulatory T cells. *Contrib Nephrol*. 2005;146:121-131.
19. Asanuma H, Sharp M, Maecker HT, Maino VC, Arvin AM. Frequencies of memory T cells specific for varicella-zoster virus, herpes simplex virus, and cytomegalovirus by intracellular detection of cytokine expression. *J Infect Dis*. 2000;181(3):859-866. doi:10.1086/315347
20. Domingo P, Torres OH, Ris J, Vazquez G. Herpes zoster as an immune reconstitution disease after initiation of combination antiretroviral therapy in patients with human immunodeficiency virus type-1 infection. *Am J Med*. 2001;110(8):605-609. doi:10.1016/S0002-9343(01)00703-3
21. Weissenbach M, Clahsen T, Weber C, et al. Interleukin-6 is a direct mediator of T cell migration. *Eur J Immunol*. 2004;34(10):2895-2906. doi:10.1002/eji.200425237
22. Zajkowska A, Garkowski A, Świerzbińska R, et al. Evaluation of Chosen Cytokine Levels among Patients with Herpes Zoster as Ability to Provide Immune Response. *PLoS One*. 2016;11(3):e0150301. Published 2016 Mar 2. doi:10.1371/journal.pone.0150301
23. Iacobini C, Amadio L, Oddi G, et al. Role of galectin-3 in diabetic nephropathy. *J Am Soc Nephrol*. 2003;14(8)(suppl 3):S264-S270. doi:10.1097/01.ASN.0000077402.95720.B4
24. Ahmed RA, Shebl AM, Habashy HO. Expression levels of β-catenin and galectin-3 in meningioma and their effect on brain invasion and recurrence: a tissue microarray study. *Cancer Biol Med*. 2017;14(3):319-326. doi:10.20892/j.issn.2095-3941.2017.0024
25. Nguyen MN, Su Y, Vizi D, et al. Mechanisms responsible for increased circulating levels of galectin-3 in cardiomyopathy and heart failure. *Sci Rep*. 2018;8(1):8213. doi:10.1038/s41598-018-26115-y
26. Takasaki I, Taniguchi K, Komatsu F, et al. Contribution of spinal galectin-3 to acute herpetic allodynia in mice. *Pain*. 2012;153(3):585-592. doi:10.1016/j.pain.2011.11.022
27. Mazurek N, Sun YJ, Price JE, et al. Phosphorylation of galectin-3 contributes to malignant transformation of human epithelial cells via modulation of unique sets of genes. *Cancer Res*. 2005;65(23):10767-10775. doi:10.1158/0008-5472.CAN-04-3333
28. Maeda N, Kawada N, Seki S, et al. Stimulation of proliferation of rat hepatic stellate cells by galectin-1 and galectin-3 through different intracellular signaling pathways. *J Biol Chem*. 2003;278(21):18938-18944. doi:10.1074/jbc.M209673200
29. Ji RR, Gereau RW IV, Malcangio M, Strichartz GR. MAP kinase and pain. *Brain Res Brain Res Rev*. 2009;60(1):135-148. doi:10.1016/j.brainresrev.2008.12.011
30. Shalom-Feuerstein R, Cooks T, Raz A, Kloog Y. Galectin-3 regulates a molecular switch from N-Ras to K-Ras usage in human breast carcinoma cells. *Cancer Res*. 2005;65(16):7292-7300. doi:10.1158/0008-5472.CAN-05-0775