Observational Study

Predictive Value of Blood Glucose Coefficient of Variation for Prognoses in Patients with Diabetes Mellitus-Associated Herpes Zoster

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Background: Herpes zoster (HZ) and diabetes mellitus (DM) are common diseases in middle-aged and older adults aged 50 years or more, and the prevalence of DM-associated HZ is gradually increasing. Several studies have confirmed that DM is a significant risk factor for postherpetic neuralgia (PHN). However, few studies have investigated the correlation between blood glucose-related indices and prognoses in patients with DM-associated HZ. The purpose of this study was to investigate the effect of blood glucose-related indices on the prognoses of these patients.

Objectives: The purpose of this study was to observe the potential value of blood glucose-related indices in predicting prognoses in patients with DM-associated HZ.

Study Design: A retrospective, observational study.

Setting: The study was carried out in the Pain Department of the First Hospital Affiliated to Jiaxing College in Jiaxing, China.

Methods: Patients with DM-associated HZ admitted to the First Hospital of Jiaxing between October 2019 and February 2022 were enrolled. The patients were divided into PHN and non-PHN groups. Demographic data, including gender, age, period of first clinical visit, site of involvement, history of DM, DM-related complications, comorbidities, and treatment were collected. Simultaneously, blood glucose-related data, including blood glucose level at admission (GLUadm), blood glucose level difference (GLUdif), and blood glucose coefficient of variation (GLUcv) were collected. Univariate and multivariate logistic regression analyses were performed to analyze factors affecting prognosis. A receiver operating characteristic (ROC) curve was constructed to assess the value of GLUcv in predicting prognosis.

Results: Overall, 136 patients were included. Among them, 65 and 71 were in the PHN and non-PHN groups, respectively. Univariate analysis showed that gender ($x^2 = 2.023$, $P = 0.044$), history of DM ($x^2 = 3.850$, $P < 0.001$), DM-related complications ($x^2 = 3.238$, $P = 0.016$), comorbidities ($x^2 = 2.439$, $P = 0.019$), and GLUcv ($x^2 = 3.576$, $P < 0.001$) were associated with PHN. Multivariate logistic regression analysis showed that a history of DM ≥ 10 years (OR = 4.096, 95% CI: 1.759–10.082, $P = 0.001$), comorbidities (OR = 2.680, 95% CI: 1.143–6.567, $P = 0.026$), and GLUcv ≥ 30.56 (OR = 5.234, 95% CI: 2.325–12.603, $P = 0.001$) were independent factors. The ROC curve revealed that GLUcv had a high predictive value for PHN (AUC = 0.714, $P < 0.001$).

Limitations: The nonrandomized, single-center, retrospective design and small sample size are major limitations of this study.

Conclusions: GLUcv has a high predictive value for the prognoses of patients with DM-associated HZ. The higher the GLUcv value, the likelier the patient is to have a poor prognosis.

Key words: blood glucose, coefficient of variation, herpes zoster, diabetes mellitus

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Herpes zoster (HZ) is caused by the reactivation of the latent varicella-zoster virus in the human sensory ganglia (1). HZ's main manifestation is a cluster of herpes on the skin accompanied by severe pain at the corresponding site, with an incidence of approximately 4–4.5/1000 person-years (2). Postherpetic neuralgia (PHN) refers to pain in the herpes area that persists for more than 3 months after the herpes rash has subsided or scabbed (3). PHN has an incidence of 2.6%–67.3%. Specific manifestations include pain similar to that of acupuncture, burning, or electric shock (4,5). Long-term chronic pain leads to anxiety, depression, and even suicidal thoughts, placing a heavy burden on the patient's family and on society (6).

Diabetes mellitus (DM) is one of the most common chronic noncommunicable diseases, caused mainly by insufficient insulin secretion due to damage to the islet β-cells or other reasons that result in decreased insulin sensitivity (7). Some studies have predicted that the overall prevalence rate of DM will be approximately 5.4% by 2025 and that the affected population will be primarily in developing countries (8). DM patients with weak resistance, abnormal cellular immunity and macrophage function, decreased immune function, and reduced ability to resist various reactions acquire HZ more easily. In these patients, the clinical symptoms are more severe and persistent and are likelier to leave sequelae (9-11).

HZ and DM are common diseases in middle-aged and older adults aged 50 years or more (12), and the prevalence of DM-associated HZ is gradually increasing. Several studies have confirmed that DM is a significant risk factor for PHN (6,13). However, few studies have investigated the correlation between blood glucose-related indices and prognoses in patients with DM-associated HZ. Therefore, this study aimed to investigate the effect of blood glucose-related indices on the prognoses of these patients.

Methods

Patients

All patients with DM-associated HZ who were admitted to the First Hospital of Jiaxing were retrospectively enrolled between October 2019 and February 2022. Based on the inclusion and exclusion criteria, 136 patients were finally enrolled in the final study. The patient selection process is shown in Fig. 1.

Inclusion criteria: 1) meeting the diagnostic criteria for HZ; 2) course of HZ < 3 months; 3) meeting the diagnostic criteria for DM; 4) age 18–85 years; and 5) moderate-to-severe pain with a numerical rating scale (NRS) score > 3.

Exclusion criteria: 1) discontinuation of treatment or incomplete clinical data; 2) refusal of regular blood glucose monitoring during hospitalization; 3) complications caused by other neuropathic pain disorders; and 4) refusal to provide clinical data and information.

Observation Indicators

Demographic data, including each patient's gender, age, period of first clinical visit, site of involvement, history of DM, DM-related complications, comorbidities, and treatment, were collected. Simultaneously, blood glucose-related data, including blood glucose level at admission (GLUadm), blood glucose level difference (GLUdif), and blood glucose coefficient of variation (GLUcv) were also collected.

The sites of involvement included the head and face (considered the same site), trunk, and limbs. Some cases showed multiple-site involvement. DM-related complications included diabetic nephropathy, diabetic ophthalmopathy, diabetic neuropathy, and so on. Comorbidities included hypertension and coronary artery disease. Treatments included pulsed radiofrequency, nerve blocks, or a combination of both.

The following formulae were used for calculation: GLUdif = highest blood glucose level – lowest blood glucose level; GLUcv = standard deviation of blood glucose × 100/average blood glucose level.

Follow-up

After discharge, patients were followed up on once a month for 3 months. After 3 months, the patients were classified into PHN and non-PHN groups based on PHN occurrence. PHN was defined as having a poor prognosis.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics® software version 26.0 (IBM). All data were tested for normality using the Shapiro–Wilk test and histograms. Normally distributed continuous data are presented as mean ± standard deviation (SD), non-normally distributed continuous data are presented as medians and interquartile ranges (IQRs), and categorical data are presented as numbers and percentages (%). Analysis of variance was used to compare groups to one another, and the least significant difference t test was used for post hoc analysis. Independent t tests were used for comparing normally distributed continu-

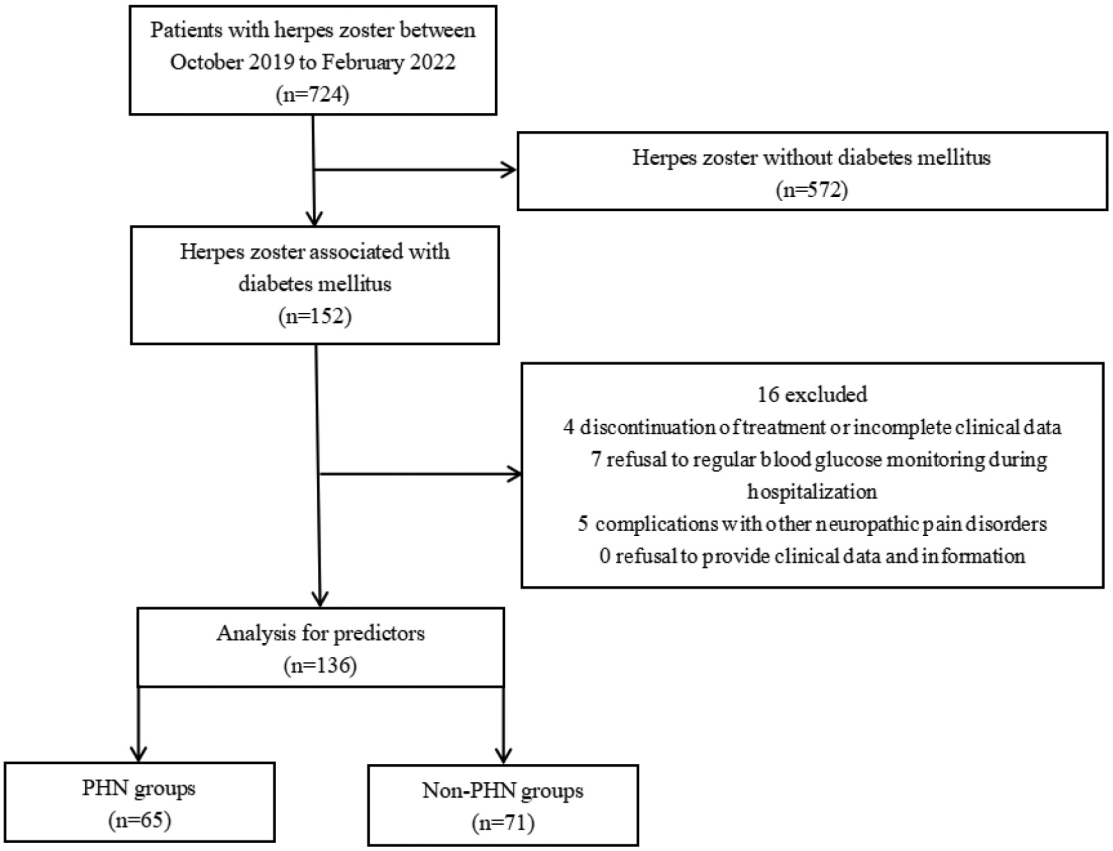

Fig. 1. *Flow of patients through this retrospective study. Ultimately, 136 patients were enrolled who suffered from DM-associated HZ..*
PHN: postherpetic neuralgia.

ous data, Mann–Whitney U tests were used for non-normally distributed continuous data, and chi-square tests were used for categorical data. Demographic and blood glucose-related data were included in the univariate analysis, and independent variables ($P < 0.05$) were included in the multivariate logistic regression analysis. Multivariate logistic regression analysis was used to analyze the independent factors influencing PHN in patients with DM-associated HZ. The value of GLUcv in predicting the occurrence of PHN in patients with DM-associated HZ was evaluated using a receiver operating characteristic (ROC) curve, and the area under the curve (AUC) was calculated. Statistical significance was set at $P < 0.05$.

Results

Demographic Data of Groups

Overall, 136 patients with DM-associated HZ were enrolled in this study. Of these, 65 (47.79%) and 71 (52.21%) were in the PHN and non-PHN groups, respectively. There were no significant differences between the groups in age, period of first clinical visit, site of involvement, and treatment ($P > 0.05$). There were significant differences between the groups in gender, history of DM, complications of DM, and comorbidities ($P < 0.05$). The details are shown in Table 1.

Blood Glucose-Related Data

The groups had no significant differences in GLUadm or GLUdif ($P > 0.05$). GLUcv was significantly higher in the PHN group than in the non-PHN group ($P < 0.05$). Details are shown in Table 2.

Univariate Analysis

The occurrence of PHN was used as the dependent variable (0 = non-PHN, 1 = PHN). Independent variables were informative, including gender, age, period of first clinical visit, site of involvement, history of DM, com-

Table 1. *Demographic or characteristic data of PHN group and non-PHN group.*

Demographic or Characteristic	PHN (n = 65)	Non-PHN (n = 71)	t / x^2 / Z	*P*
Gender			4.111	0.043
Female	29 (44.62)	44 (61.97)		
Male	36 (55.38)	27 (38.03)		
Age (years)	70.51 ± 8.82	68.37 ± 9.84	1.360	0.179
Period of first clinical visit (days)	25.00, 35.00	21.00, 16.00	-0.158	0.874
Site of involvement			0.169	0.982
head and face	12 (18.46)	12 (16.90)		
trunk	40 (61.54)	43 (60.56)		
limbs	10 (15.38)	12 (16.90)		
multiple-site	3 (4.62)	4 (5.63)		
History of DM (years)	10.00, 6.50	5.00, 6.00	-2.723	0.006
Complications of DM			6.200	0.013
No	48 (73.85)	64 (90.14)		
Yes	17 (26.15)	7 (9.86)		
Comorbidities			5.636	0.018
No	15 (23.08)	30 (42.25)		
Yes	50 (76.92)	41 (57.75)		
Treatment			1.062	0.588
PRF	32 (49.23)	35 (49.30)		
NB	15 (23.08)	12 (16.90)		
PRF + NB	18 (27.69)	24 (33.80)		

Results are expressed as mean ± SD, percentages, or as medians (IQR); *P* values were compared by independent t test, χ^2 test, or Mann-Whitney U test as appropriate. Abbreviations: PHN: postherpetic neuralgia; DM: diabetes mellitus; PRF: pulsed radiofrequency; NB: nerve block.

Table 2. *Blood glucose-related data of PHN group and non-PHN group.*

Blood Glucose-Related Data	PHN (n = 65)	Non-PHN (n = 71)	t	*P*
GLUadm	8.66 ± 3.00	8.36 ± 3.29	0.174	0.862
GLUdif	18.22 ± 4.39	17.30 ± 4.57	1.323	0.191
GLUcv	34.02 ± 8.49	27.40 ± 8.07	4.350	0.000

Abbreviations: PHN: postherpetic neuralgia; DM: diabetes mellitus; GLUadm: blood glucose level at admission; GLUdif: blood glucose level difference; GLUcv: blood glucose coefficient of variation.

plications of DM, comorbidities, treatment, GLUadm, GLUdif, and GLUcv. The median GLUadm, GLUdif, and GLUcv values in the PHN patients and the non-PHN patients were 8.50, 18.22, and 30.56, respectively. Based on the medians of the aforementioned continuous variables, the patients were divided into two groups: the up group and the down group.

Univariate analysis showed that gender (x^2 = 2.023, *P* = 0.044), history of DM (x^2 = 3.850, *P* < 0.001), complications of DM (x^2 = 3.238, *P* = 0.016), comorbidities (x^2 = 2.439, *P* = 0.019), and GLUcv (x^2 = 3.576, *P* < 0.001) were factors associated with PHN. Age, period of first clinical visit, site of involvement, treatment, GLUadm, and GLUdif were not factors associated with PHN (*P* > 0.05). Details are shown in Table 3.

Multivariate Logistic Regression Analysis

The multivariate logistic regression analysis considered the occurrence of PHN as a dependent variable and factors with *P* < 0.05 in the univariate analyses as independent variables. Multivariate logistic regression was performed using a stepwise method. The results showed that a history of DM ≥ 10 years (odds ratio [OR] = 4.096, 95% confidence interval [CI]: 1.759–10.082, *P* = 0.001), comorbidities (OR = 2.680, 95% CI: 1.143–6.567, *P* = 0.026), and GLUcv ≥ 30.56 (OR = 5.234, 95% CI: 2.325–12.603, *P* < 0.001) were the independent factors influencing PHN. Details are shown in Table 4.

ROC Curves

PHN occurrences were used as a state variable, and

Table 3. *Univariate analysis of PHN in patients with HZ associated with DM.*

	Odds Ratio (95% CI)	*P*
Gender		0.044
Female	1.000	
Male	2.023 (1.025-4.046)	
Age (years)		0.307
< 70	1.000	
≥ 70	0.539 (0.725-2.808)	
Period of first clinical visit (days)		0.876
< 30	1.000	
≥ 30	1.055 (0.538-2.073)	
Site of involvement		
head and face	1.000	
trunk	0.930 (0.372-2.325)	0.876
limbs	0.833 (0.258-2.664)	0.758
multiple-site	0.750 (0.125-4.123)	0.740
History of DM (years)		0.000
< 10	1.000	
≥ 10	3.850 (1.848-8.322)	
Complications of DM		0.016
No	1.000	
Yes	3.238 (1.288-8.948)	
Comorbidities		0.019
No	1.000	
Yes	2.439 (1.173-5.237)	
Treatment		
PRF	1.000	
NB	1.367 (0.558-3.404)	0.495
PRF + NB	0.820 (0.374-1.780)	0.617
GLUadm		0.959
< 8.50	1.000	
≥ 8.50	1.018 (0.508-2.038)	
GLUdif		0.327
< 18.22	1.000	
≥ 18.22	1.404 (0.713-2.781)	
GLUcv		0.000
< 30.56	1.000	
≥ 30.56	3.576 (1.782-7.362)	

Abbreviations: PHN: postherpetic neuralgia; HZ: herpes zoster; DM: diabetes mellitus; PRF: pulsed radiofrequency; NB: nerve block. GLUadm: blood glucose level at admission; GLUdif: blood glucose level difference; GLUcv: blood glucose coefficient of variation.

the AUC of GLUcv was calculated. ROC curve analysis revealed that GLUcv had a high predictive value for PHN (AUC = 0.714, $P < 0.001$), with a cutoff value of 30.95, sensitivity of 63.1%, and specificity of 70.4%. The details are shown in Table 5 and Fig. 2.

Table 4. *Multivariable logistic regression of PHN in patients with HZ associated with DM.*

	Odds Ratio (95% CI)	*P*
Gender		0.331
Female	1.000	
Male	1.492 (0.664-3.359)	
History of DM (years)		0.001
< 10	1.000	
≥ 10	4.096 (1.759-10.082)	
Complications of DM		0.143
No	1.000	
Yes	2.352 (0.771-7.761)	
Comorbidities		0.026
No	1.000	
Yes	2.680 (1.143-6.567)	
GLUcv		0.000
< 30.56	1.000	
≥ 30.56	5.234 (2.325-12.603)	

Abbreviations: PHN: postherpetic neuralgia; HZ: herpes zoster; DM: diabetes mellitus; GLUcv: blood glucose coefficient of variation.

Discussion

PHN is usually associated with a poor prognosis in patients with HZ. To begin with, PHN is a serious complication caused by viral infections. Approximately 10-25% of patients experience pain that lasts for more than one year. Long-term chronic pain leads to anxiety, depression, and even suicidal thoughts, which place a heavy burden on society and on the patients' families. Johnson and Mallick pointed out that even with standardized treatment, fewer than half of the patients with PHN benefit (14,15). For these reasons, clinical work should focus on identifying HZ patients who may have PHN and on intervening early to prevent PHN from occurring. Suaya et al (16) noted that after they adjusted for gender, age, and related factors, patients with DM had a 45% higher risk of developing HZ and an 18% higher risk of developing PHN than patients without DM, meaning that people with DM were likelier to develop HZ and have a poor prognosis. Therefore, more clinical attention should be focused on HZ patients with DM so physicians can detect risk factors for poor prognoses early and implement measures to improve them.

Several studies have shown that DM is an independent risk factor for poor prognoses in patients with HZ,

Table 5. *ROC curve distribution of GLUcv for PHN in patients with DM-associated HZ.*

	AUC	95% CI	*P*
GLUcv	0.714	0.629-0.800	0.000

Abbreviations: ROC: receiver operating characteristic; AUC: area under curve; CI: confidence interval; PHN: postherpetic neuralgia; HZ: herpes zoster; DM: diabetes mellitus; GLUcv: blood glucose coefficient of variation.

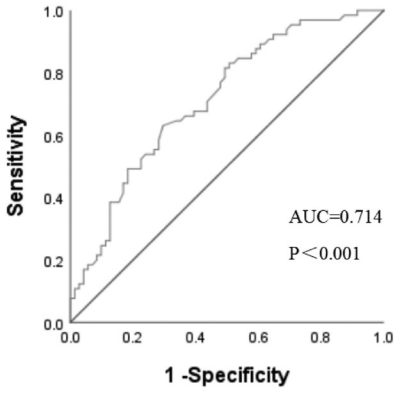

Fig. 2. *ROC curve distribution of GLUcv for PHN in patients with DM-associated HZ.*
ROC: receiver operating characteristic; AUC: area under curve; PHN: postherpetic neuralgia; HZ: herpes zoster; DM: diabetes mellitus; GLUcv: blood glucose coefficient of variation.

which may be related to the pathophysiological mechanism of DM. Katsuda et al (17) observed that persistent hyperglycemia in patients with DM can activate a polyol bypass, thereby damaging cellular functions, which can easily lead to PHN. Geerlings et al reported that the innate immune response of polymorphonuclear cells and mononuclear macrophages in patients with DM is lower than in healthy patients (18). Therefore, PHN is likelier to occur in patients with DM.

This study included 136 patients with DM-associated HZ and found that in the demographic data, history of DM and comorbidities were risk factors for PHN. Patients with long histories of DM were likelier to have poor prognoses, especially those diagnosed with DM for more than 10 years, and the incidence of PHN was 4.096 times higher than in patients with disease histories of fewer than 10 years. This pattern may be related to microangiopathy caused by long-term DM. In patients with long-term DM, the microvascular network is severely damaged, neurons respond to stress, and the varicella-zoster virus proliferates in large numbers, increasing the risk of PHN (19,20). In this study, DM complications were not risk factors for PHN. Some patients with DM might have been in the early stages of complications, which would thus not have been detected in time. The incidence of diabetic complications is underestimated, leading to a lack of objectivity and precision in the results. Comorbidities are also a risk factor for PHN in these patients, which is consistent with the findings of Srivastava et al (21) and may be related to these patients' abnormal immune function and poor nerve repair.

Furthermore, some studies have reported that women are likelier to develop PHN than men are (22), which is inconsistent with the results of this study and may be due to the specific patients in this study with complications of DM. Men are likelier to develop diabetes than women due to poorer eating habits and greater stress. The gender of the patient did not significantly affect the prognosis of DM-associated HZ. This study also assumes that age, period of first clinical visit, and site of involvement are not essential factors that influence PHN. This assumption may be due to the particular habits of patients with DM. Most of the patients who are older (>= 50 years old) and visit a doctor within 3 months may have had a peripheral nerve injury leading to PHN, regardless of the period of the first clinical visit and the site of involvement. Nerve blocks and pulsed radiofrequency are effective in relieving early HZ neuralgia. This study found no significant differences in the effects of these treatments on the prognoses.

In our study, of all the blood glucose-related data, GLUcv was a risk factor for PHN in the patients. Blood glucose variability refers to the degree of fluctuation in blood glucose over a period, which exists independently of a single blood glucose level and can better reflect the dynamic changes in blood glucose levels (23). GLUcv is a commonly used index that reflects the degree of fluctuation in blood glucose levels (24,25). The higher the value of GLUcv, the greater the fluctuation of patients' blood glucose. Existing literature reports that irregular blood glucose fluctuations lead to "hyperglycemic memory" (26,27). That is, abnormal blood glucose fluctuations trigger an expression of proinflammatory cytokines that continues even after blood glucose levels return to normal. These persistent proinflammatory cytokines are involved in HZ neuroinflammation and lead to increased sensitivity in the body's nociceptive receptors. This process may explain why patients with high blood glucose fluctuations still have neuralgia 3 months after HZ is healed.

Furthermore, based on the ROC curve, GLUcv was

found to have a high predictive value for the occurrence of PHN in patients with DM-associated HZ, with a cutoff value of 30.95. Severe fluctuation of blood glucose during hospitalization triggers the expression of proinflammatory cytokine genes and is involved in the neuroinflammatory response of HZ, resulting in a poor prognosis. The above cutoff values can be used as a clinical reference, and blood glucose can be actively monitored after hospitalization in patients with DM-associated HZ. In such patients, we should not only pay attention to the change in the absolute blood glucose level but also actively control the fluctuation of blood glucose. Therefore, lowering GLUcv to a value below 30.95 is essential to improve the prognosis.

Limitations

There are some limitations to this study: First, the study was retrospective and lacked some important original data, such as glycosylated hemoglobin and C-peptide levels, so the conclusion may involve bias. Furthermore, due to the small sample size, other risk factors that may affect the prognosis of HZ, such as the NRS score, the duration of pain, the lesion area, and a family history of DM, could not be included in univariate and multivariate regression analyses. Finally, the lack of objective detection methods made it impossible to determine whether the patients' neuralgia was a sequela of HZ or caused by diabetic peripheral neuropathy.

Conclusion

In conclusion, the history of DM, comorbidities, and GLUcv are factors that independently influence PHN in patients with DM-associated HZ. GLUcv has a relatively high predictive value for the prognoses of such patients. The higher the GLUcv value, the likelier the patient with DM-associated HZ is to have a poor prognosis.

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